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# Review article: evidence-based dietary advice for patients with inflammatory bowel disease

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## SUMMARY

### Background
The therapeutic effect of enteral nutrition in Crohn's disease (CD) and the epidemiological associations between diet and inflammatory bowel disease (IBD) implicate diet in IBD causation. There is little evidence, however, to support specific dietary changes and patients often receive contradictory advice.

### Aim
To review the literature on the impacts of diet on IBD causation and activity to produce guidance based on 'best available evidence'.

### Method
Review of Medline, Embase and Cochrane databases from 1975 to 2012 using MeSH headings 'crohn's disease' 'ulcerative colitis' 'enteral' 'diet' 'nutrition' 'fatty acid' and 'food additives'.

### Results
Enteral nutrition with a formula-defined feed is effective treatment for CD, but approximately 50% of patients relapse within 6 months of return to normal diet. There is no direct evidence of benefit from any other specific dietary modification in CD, but indirect evidence supports recommendation of a low intake of animal fat, insoluble fibre and processed fatty foods containing emulsifiers. Foods tolerated in sustained remission may not be tolerated following relapse. Some evidence supports vitamin D supplementation. In ulcerative colitis (UC), evidence is weaker, but high intakes of meat and margarine correlate with increased UC incidence and high meat intake also correlates with increased likelihood of relapse.

### Conclusions
There is little evidence from interventional studies to support specific dietary recommendations. Nevertheless, people with IBD deserve advice based on 'best available evidence' rather than no advice at all, although dietary intake should not be inappropriately restrictive. Further interventional studies of dietary manipulation are urgently required.

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## INTRODUCTION

Our knowledge of the genetic factors involved in inflammatory bowel disease (IBD) causation has increased remarkably, but environmental factors are at least as important in Crohn's disease (CD) and more important still in causation of ulcerative colitis (UC). Thus, an identical twin of an individual with CD has approximately 27% chance of developing CD, whilst an identical twin of an individual with UC has 15% chance of developing UC[1] and only about 22% of IBD patients have one or more other affected family members.[2] Moreover, the incidence of IBD has increased rapidly over the last 50 years, clearly due to some changing environmental factor or factors.

Smoking is the only environmental risk factor clearly established as harmful for CD, but there is little or no correlation between changes in smoking habits and the markedly increased CD (and UC) incidence seen recently in westernised countries. Alternative hypotheses to explain this increased IBD incidence include greater hygiene and greater use of antibiotics in infancy.[3] There is also considerable epidemiological evidence showing correlations between incidence of both CD and UC and various dietary components.

The strongest evidence for associations between diet and IBD pathogenesis comes from interventional studies. There have been many studies showing that clinical remission and mucosal healing can be achieved in CD by a switch from normal diet to a formula-defined enteral feed, but the mechanisms for this response are not well understood. Theories put forward include changes in nature or quantity of the gut bacteria, improved nutritional status, reduced allergenicity of gut contents, avoidance of food additives or provision of an anti-inflammatory factor such as transforming growth factor (TGF) beta.[4]

Evidence from interventional studies for an impact of diet on UC is much weaker and for neither disease is there convincing evidence from interventional studies to implicate any specific foodstuffs. Clinicians might therefore reasonably conclude that evidence is insufficient to allow any dietary recommendations to be given to patients other than to have a 'well-balanced diet' that ensures adequate nutrition. Alternatively, and we believe more appropriately, we should do our best to interpret available evidence from epidemiological as well as interventional studies to provide 'best evidence-based dietary advice' that will at least inform patients of the current state of knowledge without leading to inappropriately strict dietary restriction. Without such advice, many patients will resort to even less well evidence-based and often inappropriately restrictive diets.

This review examines the evidence linking diet to IBD causation or activity and concludes with suggestions of practical dietary advice for people with IBD based on the evidence available. It does not aim to cover the special needs of patients with short bowel syndrome or correction of micronutrient deficiencies occurring as a consequence of IBD, which are reviewed elsewhere.[5, 6]

## METHODS

A review of the published literature on diet and IBD was performed using the Medline, Embase and Cochrane databases from 1975 to September 2012 using the MeSH headings individually and in combination 'Crohn's disease' 'Ulcerative colitis' 'diet' 'nutrition' and 'enteral' 'fatty acid' and 'food additives'.

### Evidence from interventional studies

*Intravenous feeding and 'bowel rest'.* Total parenteral (intravenous) nutrition (TPN) with complete 'bowel rest' was shown by Ostro *et al.* to be effective in the primary management of complicated CD.[7] In a retrospective study of 100 patients who were otherwise refractory to conventional medical management, 90 received complete nutrient replacement and 10 received protein-sparing therapy. In 77 patients, a clinical remission was achieved. The location of the intestinal involvement did not influence the remission rate: 73% in those with small bowel disease only, 78% in those with combined small and large bowel disease and 100% in six with isolated colonic disease.

In UC, however, controlled trials of intravenous feeding and bowel rest showed no influence on the response of severe acute disease to corticosteroids (Table 1).[8, 9] This has strongly influenced clinicians towards the conclusion that diet has little impact on UC, but it needs to be remembered that these were short-term studies in patients with established severe disease. It is reasonable to speculate that diet might still play a subtler, longer term, role in UC pathogenesis.

*Enteral nutrition.* The Cochrane review on the use of sole enteral nutrition to induce remission in CD concludes that 'the effectiveness of enteral nutrition for the induction of remission in CD is evident from the remission rates' (up to 84%).[10] The review is, however, usually interpreted negatively by clinicians as it shows better

**Table 1 |** Controlled trials of nutritional therapy in IBD*

| Intervention | *N* | Type of trial | Primary endpoint(s) | Result | *P* value | Ref |
|---|---|---|---|---|---|---|
| **Crohn's disease** | | | | | | |
| Enteral nutrition vs. placebo for maintenance (no acute therapy trials performed) | | | | | | |
| 50% calories as enteral feed vs. normal food | 51 adults | Randomised controlled maintenance | Relapse (CDAI >200) over 2 years | 50% enteral: 9/26<br>Control: 16/25 | 0.05<br>Favours enteral | 13 |
| Elemental feeding at night and low-fat diet during day vs. normal food<br>Extension of same trial | 40 adults<br>Same 40 patients | Nonrandomised controlled<br>Maintenance<br>As above | Clinical relapse over 1 year<br>Relapse requiring biologics or surgery over 5 years | EN: 5/20<br>Control: 13/20<br>EN: 2/20<br>Control: 9/20 | 0.03<br>Favours elemental<br>0.03<br>Favours elemental | 97, 98 |
| Omega3 fatty acids (fish oil) vs. placebo for maintenance | | | | | | |
| Enteric coated fish oil capsules containing 1.8–3.3 g/day eicosopentaenoic acid (EPA) and 0.8–1.8 g/day docosahexaenoic acid (DHA) compared with placebo | 1039 pts in six studies (including 38 children in one study) | Cochrane meta-analysis 2009 | Remission at 1 year (absence of relapse defined varyingly between studies) | RR 0.77 (0.61, 0.98)<br>Favours fish oil but significant heterogeneity noted between studies | 0.03<br>Favours fish oil | 99 |
| Enteral nutrition vs. corticosteroids – as acute therapy | | | | | | |
| Various enteral nutrition formulae as sole feed compared with conventional (varying) corticosteroid therapy | 352 patients in seven studies (including 37 children in one study) | Cochrane meta-analysis 2007 | Remission varyingly defined by CDAI, PCDAI or Van Hees Index after 4–10 weeks of therapy | OR 0.33 (0.21, 0.53)<br>Favours steroid [but high-quality studies only: OR 1.18 (0.37, 3.70)] | <0.00001<br>Favours steroid | 10 |
| Elemental vs. polymeric enteral nutrition as acute therapy | | | | | | |
| Various enteral nutrition formulae as sole feed comparing elemental (amino-acid-based feeds) with polymeric (whole protein) | 334 adults in 10 studies | Cochrane meta-analysis 2007 | Remission varyingly defined by CDAI, or Van Hees Index after 10 days – 6 weeks of therapy | OR 1.10 (0.69, 1.75), i.e. elemental = polymeric | NS | 10 |
| Elemental feeding vs. polymeric | 34 children | Randomised double-blind | Remission (PCDAI <11) after 6 weeks | Elemental: 14/15<br>Polymeric 15/19 | NS | 100 |
| Low-fat vs. high-fat enteral nutrition as acute therapy | | | | | | |
| Various enteral nutrition formulae as sole feed comparing low-fat (<20 g fat/1000 kcal) vs. high-fat (>20 g fat/1000 kcal) | 209 adults in seven studies | Cochrane meta-analysis 2007 | Remission varyingly defined by CDAI, or Van Hees Index after 4–6 weeks of therapy | OR 1.13 (0.63, 2.01) | NS | 10 |
| Low% Long-chain triglyceride (LCT) vs. high LCT enteral nutrition as acute therapy | | | | | | |
| Various enteral nutrition formulae as sole feed comparing low LCT (<10% of total energy) vs. high LCT (>10% of total energy) | 210 adults in six studies | Cochrane meta-analysis 2007 | Remission varyingly defined by CDAI, or Van Hees Index after 4–6 weeks of therapy | OR 1.39 (0.78, 2.48) | NS | 10 |



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**Table 1 |** (Continued)

| Intervention | *N* | Type of trial | Primary endpoint(s) | Result | *P* value | Ref |
|---|---|---|---|---|---|---|
| n6-rich enteral nutrition vs. non n6-rich enteral nutrition as acute therapy | | | | | | |
| Enteral nutrition formulae as sole feed comparing n-6 rich feed to n-6 low feed | 127 pts in two studies including 84 children in one study | Cochrane meta-analysis 2007 | Remission varyingly defined by CDAI, or Van Hees Index after 4 weeks of therapy | OR 1.59 (0.26, 9.83) | NS | 10 |
| Fructo-oligosaccharide (prebiotic) supplementation vs. placebo as acute therapy | | | | | | |
| Supplementation with oral fructo-oligosaccharide (prebiotic) 15 g/day maltodextrin (placebo) | 103 adults | Randomised double-blind | Response (reduction in CDAI of at least 70 by 4 weeks) | Active: 12/54 Placebo: 19/49 | $P = 0.067$ (trend favouring placebo) | 54 |
| **Ulcerative colitis** | | | | | | |
| Intravenous nutrition and bowel rest vs. placebo as acute therapy | | | | | | |
| IV feeding vs. normal food as adjunct to steroids | Acute colitis: 27 UC 9 CD All adults | Randomised, controlled | Colectomy | Control: 6/17 IV feeding: 9/19 | NS | 8 |
| IV feeding vs. normal food as adjunct to steroids | Acute severe colitis: 27 UC 16 CD All adults | Randomised controlled | Colectomy or death | UC: Control: 6/12 (1 death) IV feeding: 10/15 (1 death) CD: no colectomy or death | NS | 9 |
| n3 fatty acid (fish oil) supplementation vs. placebo as maintenance | | | | | | |
| Fish oil supplementation as liquid or capsules containing 3.2–5.0 g/day EPA and 1.2–2.1 g/day DHA vs. placebo (variously olive oil/maize oil) | 148 adult pts in three studies | Cochrane meta-analysis 2007 | Relapse (various clinical and endoscopic parameters over 1–2 years of treatment) | OR 1.02 (0.51, 2.03)For placebo vs. n3 | 0.96 | 101 |
| Curcumin supplementation vs. placebo as maintenance | | | | | | |
| Curcumin orally 2 g/day for 6 months | 89 adult patients in one study | Cochrane meta-analysis 2012 | Relapse | 4% relapse curcumin vs. 18% placebo RR 0.24 (0.05–1.09) | 0.06 | 27 |
| Avoidance of dairy products as acute therapy and maintenance | | | | | | |
| Milk-free diet (avoiding cheese but butter allowed) compared with normal diet and also with dairy-free and gluten-free | 77 adults | Randomised open-label | Remission (absence of relapse defined by symptoms plus endoscopy) over 1 year | 10/26 Milk-free; 5/24 normal diet; 8/27 milk- and gluten-free | 0.19 for milk-free vs. normal '1 in five benefited' | 34 |

* Only trials where clear criteria for remission/relapse/response were specified are included. For interventions where a Cochrane review has been performed, we have cited data from the most recent Cochrane meta-analysis plus controlled trials published subsequent to that analysis.

efficacy for corticosteroids than enteral nutrition when compared on an intention-to-treat basis – across the seven included studies, the overall remission rate was 49% for enteral nutrition and 75% for corticosteroids. (Table 1) However, efficacy is equivalent when the comparison is made per protocol (only about 2/3 of adult patients tolerate enteral nutrition sufficiently to complete a 3-week course); moreover, equivalent efficacy was also seen when only the 'highest quality' studies were analysed – showing remission rates of 79% for enteral nutrition and 64% for corticosteroids. Different enteral feeds were used in the various studies and it is unclear whether some of the differences in efficacy may have reflected real differences resulting from the different feed

constituents, thus making meta-analysis across the different feeds of uncertain validity. There is also reasonable evidence that maintenance treatment with enteral nutrition, e.g. given as 50% of calorie intake, is effective.[11, 12] This includes a randomised controlled trial in which 51 patients with CD in recently established remission (achieved by various means including corticosteroids, enteral nutrition or surgery) were randomised, 26 to receive half their calorie intake as enteral nutrition and 25 to a free diet. Over a mean follow-up of 11.6 months, the relapse rate was 34.6% in the 'half enteral' group compared with 64.0% in those receiving the free diet (HR 0.40; 95% CI 0.16–0.98).[13]

Evidence taken exclusively from paediatric studies gives even stronger support for the role of enteral nutrition, showing equivalent efficacy with corticosteroids and better improvements in growth and mucosal healing.[14–19] A recent worldwide survey of 35 paediatric IBD centres demonstrated wide variation in the use of enteral nutrition in CD.[20] The duration of exclusive enteral nutrition was most commonly 6–8 weeks and 90% used polymeric formulas. The reintroduction of food after exclusive enteral nutrition varied greatly: the most common recommendations were for an initial low-fibre diet (26%) or the gradual re-introduction of normal food as the formula volume decreased (52%). Enteral nutrition taken orally, usually with a flavouring such as Nesquick,[21] is as effective as continuous feeding via a naso-gastric tube.[22]

It has been suggested that the efficacy of enteral nutrition is greater for CD involving the small bowel than the colon[23]; however, many of the studies do not differentiate between locations of CD and improvements have also been reported for patients with primarily colonic disease. A major problem that prevents wider use of enteral nutrition as primary therapy for CD is the high relapse rate, approximately 50% within 6 months, when patients return to their normal diet.[21]

The mechanism by which enteral nutrition benefits CD is unclear. Possible mechanisms include low residue resulting in reduced gut microbiota, perhaps particularly in the distal small intestine; avoidance of long-chain fat which, if taken up by macrophages, impairs their function; avoidance of other harmful components of 'normal' food – these might include food additives such as emulsifiers or nano-particles; addition of anti-inflammatory substances such as TGFbeta, present in milk-derived feeds where casein is the main protein source.

It was initially thought that whole proteins or peptides, being potentially antigenic, might need exclusion, but subgroup analyses performed to evaluate the different types of elemental (amino-acid-based) and non-elemental diets (semi-elemental – peptide-based and polymeric – whole protein-based, usually with casein as the protein source) have shown no significant difference in their efficacy.[10] Amino-acid-based feeds have a lower energy density, are more hyperosmolar and may have a lower adherence rate so polymeric feeds are generally now preferred.

Although an earlier meta-analysis suggested an inverse correlation between percentage of energy in enteral nutrition feeds given as long-chain fat and efficacy for inducing remission in CD,[24] the more recent Cochrane analysis covered seven trials including 209 patients treated with enteral nutrition of differing fat content (low fat: <20 g/1000 kcal vs. high fat: >20 g/1000 kcal) and showed no significant difference in efficacy, OR (1.13, 95% CI 0.63–2.01) for low fat vs. high fat. There was also no consistent difference when comparing feeds with high omega-3 vs. high omega-6 fatty acid content.[10]

*Conclusion:*

(i) CD – Enteral nutrition as sole feed can induce clinical remission and mucosal healing. It possibly works better when the small intestine is involved. Enteral nutrition given as 50% of calories is effective in maintaining remission. Whole protein ('polymeric') feeds work as well as amino-acid-based feeds and are generally less hyperosmolar and easier to flavour. Mechanisms of action are unclear. Use of TPN is associated with higher costs and significant risks including line sepsis unless carefully managed and should be restricted to patients who for some reason, e.g. obstruction or short bowel, cannot take adequate nutrition enterally.

(ii) UC – There is no evidence that bowel rest by either enteral nutrition or intravenous feeding is effective therapy for active UC, although nutritional support is appropriate if the patient is malnourished.

*Dietary supplementation with Omega 3 fatty acids.* CD: Earlier positive results for supplementation with omega-3 (n-3) fatty acids (fish oil) have not been consistently reproduced and although a recent meta-analysis of six published trials shows a small benefit for maintenance supplementation (RR of relapse 0.77, 95% CI 0.61–0.98), the studies were significantly heterogenous (consistency index $I^2$ = 58.4%, $P$ for heterogeneity = 0.03) and two well-performed studies with a relatively large sample size showed no benefit.[25] There remains controversy around

this with some investigators suggesting that negative studies may have resulted from use of unsatisfactory omega-3 preparations with variable bioactivity, thus impacting on the results.

UC: Meta-analysis of three trials of maintenance with omega-3 fatty acid supplementation in UC showed no significant benefit (RR for relapse 1.02, 95% CI 0.51–2.03).[25] A systematic review has also been performed of studies that assessed omega-3 fatty acid supplementation as treatment for active UC, but there is considerable heterogeneity between the trials and the data are inconclusive.[26] Further studies using enteric coated capsules may be justified.

*Conclusion:* Despite theoretical evidence that omega-3 fatty acids might be beneficial in CD and UC, current evidence is weak.

*Dietary supplementation with curcumin.* Curcumin is a natural phenol found in turmeric and has had a long history of use in traditional herbal remedies. *In vitro* studies have demonstrated a variety of potentially beneficial effects including antioxidant activity and suppression of NFkappaB activation. A placebo-controlled maintenance trial of curcumin 2 g/day for 6 months showed a trend towards a reduced relapse rate (4% vs. 18%, RR 0.24, $P = 0.06$) and a significantly reduced endoscopic score.[27]

*Conclusion:* Curcumin shows promise as a dietary supplement as adjunctive therapy for UC maintenance, but data are currently inconclusive and a further large-scale trial is needed.

*Dietary component modification. Sugar and fibre:* Intervention studies do not support avoidance of sugar or increased intake of fibre (nonstarch polysaccharide) in CD. A controlled trial of maintenance with a high-fibre, low refined sugar diet increased CD symptoms and was associated with a high withdrawal rate.[28] A separate trial that assessed reduction in sugar intake without altering fibre was also negative.[29] It should be noted that insoluble fibre, with its potential for causing obstruction at CD strictures, and soluble fibre, which should have little risk for obstruction, might have quite different effects on IBD and further studies are needed to assess this.

*Nanoparticles:* It has been suggested that very small insoluble particles consumed in the diet may have a harmful effect. A typical example might be titanium oxide – an insoluble white powder used not only in white paint but also in substantial quantities in foods such as mayonnaise as a whitener. Because of their very high ratio of surface area to weight, such 'nanoparticles' can act as haptens – for example enhancing by several orders of magnitude the cytokine response of lymphocytes to bacterial lipopolysaccharide.[30] They are also taken up by M (microfold) cells overlying Peyer's patches, accumulate in gut macrophages, and can impair macrophage phagocytic activity.[31] Western diets regularly expose the gastrointestinal tract to large quantities ($>10^{12}$/day) of man-made, submicron-sized, particles derived from food additives and excipients. An initial small trial showed benefit of a particle exclusion diet in CD,[32] but a larger controlled trial performed by the same investigators was negative.[33] Further larger scale trials are probably still warranted.

*Milk and dairy products:* An early clinical trial (77 patients) showed that about one in five patients with UC benefited from removal of milk and cheese from the diet,[34] but this has never been repeated and further trials are needed.

*Lactose:* Hypolactasia is commonly present in IBD, but double-blind challenge with 240 mL of milk in non-IBD patients with proven hypolactasia did not cause significant symptoms[35] and therefore, strict lactose exclusion, even though widely practised, is not usually necessary.

*Avoidance of various specific dietary components.* In an extended study of staged cumulative re-introduction of dietary components in a patient with stricturing small bowel CD, various foods (bread, lamb, potatoes, oranges, sugar, meats, dairy products, flour, rice) were tolerated without problems until relapse, accompanied by elevation of serum C-reactive protein (CRP), occurred when green vegetables were introduced.[21] Following re-induction of remission with a 3-week period of enteral feeding, a return to the same low-residue diet taken prior to introduction of green vegetables repeatedly ($\times 2$) resulted in immediate relapse accompanied by elevation of serum CRP. This implied that the low-residue diet that had been well tolerated when the patient was in remission was no longer tolerated following recent relapse. It seems plausible that the initial relapse had resulted in mucosal ulcers and that once ulcers had developed, intolerance set in to foods that had previously been well tolerated.

Promising results have been reported with an approach in which CD patients re-introduce specific

foods one by one and then leave out those that they find problematic, thus generating an individually tailored exclusion diet. A controlled trial was performed in which patients who had entered remission with elemental enteral nutrition were randomised to either tapering corticosteroids or exclusion diet and showed better long-term maintenance with the exclusion diet.[36] Foods which most commonly caused problems and were therefore omitted included wheat, dairy products and yeasts.

*Conclusions:* Strong statistical associations exist between diet and IBD, particularly CD and a high intake of refined carbohydrate (see later); however, interventional studies of sugar exclusion and a combination of high-fibre, low-sugar diet have been negative. Because of the increased symptoms seen in the trial of high fibre, low refined sugar, coupled with the knowledge that most patients with small intestinal CD are likely to develop stricturing at some time in their course, it seems appropriate to recommend a low intake of foods that are high in insoluble fibre. Evidence from a single detailed case study suggests that a diet that is well tolerated when a patient is in long-standing remission may not be tolerated following recent relapse. A single controlled trial suggested good results for maintenance of remission in CD with an exclusion diet with wheat, dairy product and yeasts, the most common foods excluded. There is insufficient evidence at present to recommend a particle-free diet.

Early studies showing possible benefit in UC from milk and dairy product exclusion need repeating. Hypolactasia, although common, is probably overestimated as a cause of symptoms.

*Vitamin and mineral supplementation. Vitamin D and calcium:* There is a resurgence of interest in the possible role of vitamin D deficiency in various conditions, including CD, that are commoner or more severe in northern Europe where diminished sunlight exposure is associated with vitamin D deficiency.[37] Vitamin D is important for the function of the innate immune system and vitamin D deficiency is linked with increased susceptibility to tuberculosis.[38] The actions of Vitamin D are relevant to all the potential pathogenic mechanisms of CD that have been highlighted by the genome-wide association studies, i.e. mucosal barrier function, innate immunity and immune regulation.[39]

Low serum concentrations of Vitamin D have been reported in 63% of patients with CD,[40] but caution is needed in interpreting this as 25-OH vitamin D acts as a negative acute phase reactant and serum concentrations may be an unreliable guide to vitamin D deficiency.[41] Prediction of vitamin D deficiency from diet and lifestyle in a prospective cohort study of 72 719 women (age, 40–73 years) enrolled in the Nurses' Health Study showed that those predicted to have vitamin D levels in the top quartile compared with those in the bottom quartile had a significantly reduced risk for CD [Hazard Ratio 0.54 (95% CI 0.30–0.99)] and a nonsignificantly reduced risk for UC HR 0.65 (0.34–1.25).[42] A randomised placebo-controlled trial of maintenance supplementation with 1200 IU/day of vitamin D in 94 patients with CD, regardless of vitamin D status on entry, showed a reduction in relapse rate (from 29% to 13%) that very nearly reached significance ($P = 0.06$).[43] The vitamin D supplement dose of 1200 IU was relatively low and 2000 IU/day has been shown to be safe i.e. without risk of hypercalcaemia.[44]

Patients with IBD have up to 40% increased risk of fractures compared with the general population[45] and osteoporosis is common, particularly in patients who have received corticosteroids. Routine vitamin D supplementation is therefore not unreasonable even though clear evidence of its efficacy is lacking for prevention of disease relapse or osteoporosis.

It is common for people with IBD to believe that they are intolerant to dairy foods and this may lead to an inadequate intake of calcium. The daily recommendation for calcium intake in IBD is 1000 mg.[46] However, calcium supplementation has come under scrutiny recently with some studies linking it to arterial calcification and a meta-analysis of data from 11 921 participants in 11 randomised controlled trials (not including IBD) showed that calcium supplements (≥500 mg/day) were associated with increased risk for myocardial infarction (RR 1.27, 95% CI 1.01–1.59) and smaller, nonsignificant, increases in the risk of stroke and mortality.[47]

*Vitamins C and E.* Oxidative stress has been suggested to play a role in tissue damage in IBD.[48] The nutritional antioxidants, including vitamins C and E, are attractive therapeutics because they are inexpensive and have relatively little toxicity. However, vitamin C can be pro-oxidant under certain conditions, and systemically altering the redox state may have unexpectedly negative effects on the inflammatory response.[49] Clinical studies of vitamin C and E supplementation in CD have shown effects on biomarkers of oxidative stress, but have not so far been shown to have significant clinical efficacy.[50]

*Conclusions:* Vitamin D deficiency may contribute to the cause and progression of IBD, particularly CD. Further trials of vitamin D supplementation are under way in both UC and CD, but meanwhile, low-dose vitamin D supplementation seems reasonable in all patients with CD.

### Prebiotics

There is growing evidence for impressive associations between IBD and an alteration in the gut microbiota, particularly an increase in mucosa-associated *Escherichia coli* and reduction in CD of faecal *Faecalibacterium prauznitzii*. Evidence for the pro-inflammatory and immune-regulatory effects of the microbiota is also increasing[51]; however, given the complexity of the gut microbiota, this research is still in its early stages. Dietary research has centred on the use of food components, termed 'prebiotics' that enhance the growth of beneficial bacteria, in particular bifidobacteria and lactobacilli, which can be immunoregulatory.[52] The most tested prebiotics are the fructose-oligosaccharides (FOS) and galacto-oligosaccharides. Dietary supplementation with FOS increases faecal bifidobacteria that induce immunoregulatory dendritic cell responses. There has been a rapidly growing literature reporting impressive effects of various prebiotics in animal models of colitis, but, so far, very little evidence of efficacy in human IBD. A pilot study in CD suggested that FOS may be of benefit[53]; however, a subsequent randomised controlled trial showed no benefit and even some worsening of symptoms.[54]

A trial of the prebiotic psyllium showed no benefit in UC, although possible benefit was seen when it was given together with a probiotic.[55] The non-absorbed disaccharide, lactulose, has also been shown to have no benefit in either CD or UC.[56]

*Conclusions.* Dietary supplementation with prebiotics has not so far been shown to benefit CD or UC.

### Fermentable Oligo-, di-, monosaccharides and polyols

A recent development in the treatment of irritable bowel syndrome (IBS) has been the low fermentable Oligo-, di-, monosaccharides and polyols (FODMAP) diet. This involves the restriction of FODMAPs, i.e. a diet that is low in foods such as wheat, onions, beans, many fruits and sorbitol. Controlled trials show benefit in the treatment of IBS[57] and an uncontrolled study of 52 patients with CD and 20 with UC reported symptomatic improvement.[58] It is thought that reducing passage of fermentable fibre into the caecum results in less distension, discomfort or diarrhoea. Controlled trials are needed in IBD and care needs to be taken that patients following this diet do not restrict their fruit and vegetable intakes too severely. It is worth noting that most/all prebiotics are FODMAPs.

*Conclusions.* A low-FODMAP diet may be worth trying in patients with IBD who have 'IBS-type' symptoms such as bloating or watery diarrhoea that have persisted despite appropriate treatments for underlying active IBD or bile salt malabsorption.

Key data from the published interventional studies are summarised in Table 1.

### Evidence from epidemiological studies

There has been approximately fourfold rise in IBD incidence in Western Europe over the last 40 years and a fourfold increase in Japan in 15 years.[59, 60] Although possible explanations for the increase could include increased hygiene in infancy and greater exposure to antibiotics, there is also circumstantial evidence to implicate dietary changes. Shoda *et al.* studied the correlation between dietary changes and the incidence of CD in Japan from 1966 to 1985.[61] By univariate analysis, the increased incidence of CD was strongly correlated ($P < 0.001$) with increased intake of total fat ($r = 0.919$), animal fat ($r = 0.880$), n-6 polyunsaturated fatty acids (PUFAs; $r = 0.883$), animal protein ($r = 0.908$), milk protein ($r = 0.924$) and the ratio of n-6 to n-3 fatty acid intake ($r = 0.792$). There was weaker correlation with intake of total protein ($r = 0.482$, $P < 0.05$). There was no correlation with intake of fish protein ($r = 0.055$, $P > 0.1$) and inverse correlation with intake of vegetable protein ($r = -0.941$, $P < 0.001$). Multivariate analysis showed that increased intake of animal protein was the strongest independent factor. A separate study from Japan identified consumption of margarine as a significant risk factor ($P$ for trend = 0.005) for development of UC.[62] An Italian study also showed high consumption of margarine to be strongly associated with risk for UC [OR 21.37 (2.32–196.6)], but not CD.[63]

Case–control studies of dietary intake in patients with CD have largely been based on retrospective recall of pre-illness diet and need to be interpreted with caution. Nevertheless, a systematic review that included 19 studies reporting pre-illness diet in IBD showed a very consistent reporting of high pre-illness intake of refined sugar amongst patients with CD.[64] Sugar does not, however, seem to be the harmful factor (see earlier for negative results of intervention studies) and may be associating with some other causative factor(s).

The same systematic review found a positive association between subsequent risk for CD and a high intake of saturated fats, monounsaturated fatty acids, total PUFAs, total omega-3 fatty acids, omega-6 fatty acids, mono- and disaccharides, and meat and low intake of dietary fibre and fruits.[64] Increased subsequent risk for UC was associated with high intakes of total fats, total PUFAs, omega-6 fatty acids, and a low vegetable intake. Again, it needs to be noted (see earlier) that interventional studies have not so far supported a causative role for total fat in CD. The association between CD and low illness intake of fibre also needs to be treated with caution. The negative results from the intervention study of increased fibre intake noted earlier suggest the possibility that pre-illness low intake of fibre might reflect increasing symptoms with insoluble fibre noticed by patients prior to diagnosis.

A study of the influence of environmental factors on development of IBD in twins showed that a high intake of processed meat conveyed a high risk for both CD – OR 7.9 (2.15–38.12) in monozygous twins, OR 10.75 (4.82–25.55) in dizygous twins and UC – OR 5.69 (1.89–19.48) in monozygous twins and OR 18.11 (7.34–50.85) in dizygous twins.[65]

Prospective cohort studies are generally more powerful than retrospective case–control studies and intriguing data have come from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. This was designed to investigate the relationships between diet, nutritional status, lifestyle and environmental factors and the incidence of cancer and other chronic diseases. This recruited 203 193 people in 10 European countries. A nested case–control study was performed within the EPIC cohort. This included 126 cases with subsequent development of UC who were matched with 504 controls. Multivariate analysis showed that the highest quartile of intake of linoleic acid, an n-6 PUFA present particularly in red meat (beef and pork) corn and sunflower oils and margarine, associated with an increased risk of UC (OR = 2.49, 95% CI 1.23–5.07, $P = 0.01$) when adjusted for age at recruitment, gender, centre, energy intake and cigarette smoking.[66, 67]

Another very large prospective cohort study involving 67 581 women aged 40–65 in France showed a similar association between high animal protein intake (meat or fish but not eggs or dairy products) and IBD, particularly UC: hazard ratio for top tertile vs. bottom tertile 3.29 (1.34–8.04, $P = 0.005$).[68]

It is curious that no study seems to have reported whether or not UC develops in vegetarians – the EPIC UC cohort did not include any.

A high red meat intake has also been associated with increased risk of relapse in UC. A prospective cohort study was performed in 191 UC patients in remission who were followed up for 1 year to determine the effect of their dietary intake on relapse. Nutrient intake was assessed using a food frequency questionnaire and categorised into tertiles.[69] Fifty-two per cent of patients relapsed. Consumption of meat, OR 3.2 (95% CI 1.3–7.8), particularly red and processed meat, OR 5.19 (95% CI 2.1–12.9), protein, OR 3.00 (95% CI 1.25–7.19), and alcohol, OR 2.71 (95% CI 1.1–6.67) in the top tertile of intake increased the likelihood of relapse compared with the bottom tertile of intake. High sulphur, OR 2.76 (95% CI 1.19–6.4) or sulphate, OR 2.6 (95% CI 1.08–6.3) intakes were also associated with relapse and might be another mechanism for the association with high intake of red meat.

*Conclusions.*

(i) CD – Epidemiological studies suggest a strong association between high pre-illness intakes of refined sugar, meat and animal fat, and low intake of fibre with increased incidence of CD. A diet that is low in sugar and high in fibre has not, however, been shown to be of benefit.

(ii) UC – Fewer epidemiological studies have been performed into the role of diet in UC, but these include two large cohort studies that both show strong correlations between high pre-illness intakes of meat and risk of UC and no reports that we can find of UC occurring in vegetarians.

Key data from the published prospective cohort studies are shown in Table 2.

## Evidence from experimental studies

Many studies have reported the impact of dietary components on animal and other laboratory models of gut inflammation, but these need interpreting with care as positive results have often not been borne out when tested in patients. In this section, we review evidence from animal and laboratory studies regarding dietary components that have not yet been tested in human intervention studies.

*Harmful effects of dietary components.* Perhaps not surprisingly, relatively few studies have tested dietary components for their possible harmful effects in comparison with those seeking to identify therapeutic dietary components.

*'Western diet':* A 'westernised' meat-containing high-fat diet has been shown to exacerbate dextran sulphate coli-

**Table 2 |** Prospective cohort studies of diet and inflammatory bowel disease

| Location | *N* | Duration | Endpoint | Results | *P* value | Reference |
|---|---|---|---|---|---|---|
| **Dietary factors associated with disease incidence** | | | | | | |
| Five European countries | 203 193 (men and women aged 20–80) | Median 4 years | Onset of UC | 126 developed UC<br>Linoleic acid highest quartile OR 2.49 (1.23–5.07)<br>Attributable risk 30% | *P* = 0.01 (P0.02 for trend across all quartiles) | 67 |
| France | 67 581 (women aged 40–65) | Mean 10.4 years | Onset of IBD | 30 developed CD and 43 developed UC<br>Animal protein intake: UC HR 3.29 (1.34–8.04) for highest tertile<br>CD HR 2.70 (0.69–10.52) | UC P 0.005<br>CD NS | 68 |
| **Dietary factors associated with disease relapse** | | | | | | |
| UK | 191 UC adult patients in remission | 1 year | Relapse of UC | Red meat OR 3.2 (1.3–7.8)<br>Red and processed meat OR 5.19 (2.1–12.9)<br>Protein OR 3.00 (1.25–7.19)<br>Alcohol OR 2.71 (1.1–6.67)<br>Sulphur OR 2.76 (1.19–6.4)<br>All for top tertile | Meat 0.027<br>Red and proc meat 0.001<br>Alcohol 0.017<br>Sulphur 0.039 | 69 |

tis.[70] This provides some support for the epidemiological evidence that a high red meat and linoleic acid intake correlates with increased risk for UC.

*Emulsifiers and detergents:* Emulsifiers are detergents that are often added to modern processed foods to keep fats in suspension.[71] Studies by our group have shown that permitted food emulsifiers such as polysorbate 80 can, even at very low concentrations that may plausibly exist in the distal ileum of someone consuming a western diet, markedly increase bacterial translocation across intestinal cells in culture and across *ex vivo* cultures of human Peyer's patches.[72] We have also shown a correlation between the marked increase in IBD in some countries and increased *per capita* consumption of food emulsifiers.[73] We have speculated that differing efficacy of different polymeric feeds used in CD might reflect differing emulsifier content, but it has proved very difficult to assess this as formulations of the feeds have changed over the years and information is not complete regarding the feeds used in many of the published trials. The natural cell membrane component, phosphatidyl choline, an emulsifier which can be given in enteric coated form, has conversely been shown to enhance mucosal barrier function and to ameliorate UC,[74] although ingestion of phosphatidyl choline has been shown, following its metabolism by the intestinal microbiota to the pro-atherogenic metabolite trimethylamine-N-oxide, to associate with increased cardiovascular mortality.[75] Detergents used in washing of dishes and cutlery are another potential source of exposure and in a questionnaire-based study of 512 healthy controls (median age 67) on Merseyside, we found that approximately one-third used detergent to wash dishes and cutlery and then left them to dry without any rinsing (R. Evans and J. M. Rhodes, unpublished data).

*Beneficial effects of dietary components. Prebiotics:* Many studies have demonstrated protective effects of various prebiotics on experimental colitis.[76] They include fructo-oligosaccharides, galacto-oligosaccharides and fermented barley fibre. Postulated mechanisms include generation, following fermentation by the microbiota, of the short-chain fatty acid butyrate that is an energy source for the colonic mucosa, and also the encouragement of probiotic bacteria. Their use in human CD has so far been disappointing (see earlier), but they have yet to be fully assessed in UC.

*Soluble plant fibres as 'contrabiotics':* Many bacteria adhere to epithelial cells using mechanisms that include lectin-carbohydrate interactions. The complex oligosaccharides that are present in soluble plant fibres may bind bacterial or epithelial lectins because of their structural similarity to glycolipid or glycoprotein receptors. We have shown that various soluble plant fibres are able to block interaction with epithelia *in vitro* for a wide range of pathogenic bacteria and also for the mucosally associated *E. coli* that are found in increased numbers in CD and, to a lesser extent, in UC. We have suggested the term 'con-

trabiotic' for soluble plant fibres that block epithelial adherence of potentially pathogenic bacteria.[77] Various plant fibres can do this, but we have found that soluble plantain (banana, Musa spp.) fibre is the most consistently effective.[78] Soluble plantain fibre blocks adherence and M cell translocation of *E. coli*, Salmonella spp. and Shigella spp. *in vitro* and *ex vivo* in cultured Peyer's patches.[73] Juice from boiled green bananas, which is likely to contain similar contrabiotic soluble fibre, has been shown to ameliorate infective diarrhoea.[79] A trial is currently being conducted into the use of soluble plantain fibre in the maintenance of remission in CD.

*Other effects of dietary components on the gut microbiota:* There is a complex interaction between diet and the human gut microbiota which is only beginning to be understood. It has been suggested that 'enterotypes' can be defined based on the relative predominance of Bacteroides, Prevotella, and Ruminoccous respectively in human faecal samples, although it is becoming apparent that the distinctions between enterotypes are not sharp, but graded.[80] In healthy individuals, different long-term diets correlate with different enterotypes – thus a predominant Bacteroides enterotype is associated with a high animal protein, high saturated fat 'Western' diet whilst a predominant Prevotella enterotype has been shown to be associated with a high-carbohydrate 'agrarian' diet.[81] A 10-day dietary intervention reported as part of the same study showed that short-term change to high-fat/low-fibre or low-fat/high-fibre diet produced rapid but fairly modest changes in the microbiota and no sustained switch in enterotype. Similar associations between Bacteroides enterotype and Western diet, Prevotella enterotype and African diet have been reported in a study comparing European children with children in Burkina Faso.[82] Such correlations between diet and microbiota also exist across mammalian species.[83]

The relevance of these interactions between diet and microbiota on intestinal inflammation has been studied in animal models of IBD. In addition to the extensive literature on the protective effects of prebiotics (see earlier), an intriguing study has shown that Interleukin-10 knockout mice fed a diet high in saturated (milk-derived) fat had an increased spontaneous rate of colitis (from 25% to 30% to over 60% over 6 months), which was also more severe and more extensive. This was associated with expansion of a sulphite-reducing organism *Bilophila wadsworthia*, apparently as a consequence of promotion of taurine-conjugation of hepatic bile acids, thus increasing the availability of organic sulphur.[84]

The impact of sole enteral nutrition used in CD therapy on the microbiota has been studied by several groups. A study investigating changes in five key groups of bacteria showed marked changes during enteral nutrition in children with CD. Greater changes in the *Bacteroides–Prevotella* group correlated with greater therapeutic response.[85] Another study reported similarly marked changes in microbiota in children with CD receiving enteral nutrition, using a gradient gel electrophoresis technique (TGGE) to profile bacterial DNA.[86] Shiga *et al.*, using polymerase chain reaction profiling of faecal microbiota, showed less impressive changes with enteral nutrition with post-treatment CD samples still showing different profiles from healthy control samples.[87] Enteral nutrition has been reported actually to reduce the prevalence of the anti-inflammatory, and presumably beneficial, *Faecalibacterium prausnitzii* in healthy subjects.[88] More rigorous studies using 'state-of-the-art' pan-microbiome technology to assess the effects of enteral nutrition on the CD microbiota are awaited, although there has been a very interesting single patient study reported. Ileal mucosal samples were taken from a 14-year-old boy at diagnosis of active CD and after disease remission was achieved using enteral nutrition and compared with an ileal sample from a control 15-year old with a gut polyp. The gut microbiome of the ileal samples was examined using 16S rRNA 'next-generation' sequencing. Before therapy, there were more abundant Proteobacteria and less abundant Bacteroidetes as well as a general reduction in diversity compared with the control. These changes all disappeared after induction of remission with enteral nutrition.[89] Larger studies of this nature are clearly needed. The problem will still remain of trying to determine whether the changes seen in the microbiota have caused the improvement in the CD or occurred as a result of the improvement. There is a substantial literature now showing that gut inflammation itself brings about some of the changes in microbiota (reduced diversity, increase in Protobacteria) that are seen in CD.[77]

*Antioxidants, curcumin, olive oil and various other putative beneficial dietary components.* A wide range of likely antioxidants has been tested, often with positive results, in experimental colitis. These include bilberry (blueberry) and tea extracts.[90, 91] They have yet to shown to be beneficial in human IBD and trials of antioxidant vitamins in IBD have so far proved disappointing (see earlier).

Curcumin, a common component of curries, has been shown to inhibit NFkappaB activation and to improve

experimental trinitrobenzene sulphonic acid-induced colitis in mice[92, 93] and has shown promise in a trial of maintenance in UC (see earlier).

Inflammatory bowel disease seems to be relatively mild around the Mediterranean and there has been considerable speculation that there might be a protective effect of olive oil. Recent attention has focussed on the polyphenols that are particularly plentiful in the sediment of virgin olive oil. Promising results have been shown with suppression of NFkappaB activation and dextran sulphate-induced colitis in mice.[94, 95]

*Conclusions:* Caution needs to be taken when extrapolating from laboratory studies based on cell lines or animal models as interventions, which seem promising in these models, have a fairly poor track record of confirmation in human IBD. At most, the models can be used as initial proof of concept for hypotheses. Some of the materials that look promising in these models (curcumin, olive oil, and plantain fibre for example) are at least likely to be harmless. Emulsifiers are detergents and, in view of the evidence that they can increase bacterial translocation, processed foods with a high emulsifier content may be better avoided by patients with IBD unless human challenge studies can be performed to establish safety.

## Dietary guidance

Taking into account the evidence presented above, noting the caution necessary in extrapolating from epidemiological correlations and laboratory studies, we would suggest that the following represents reasonable dietary advice for patients with IBD:

### *Dietary guidance for patients with CD.*

(i) In about two-thirds of patients, remission of CD may be achieved, usually over about 3 weeks, by stopping all normal food and taking a formula-defined liquid diet ('enteral nutrition'), with appropriate flavouring, as the sole feed. This is of course fairly tedious and will usually only be the first choice treatment for a minority of adults, but may more commonly be first choice treatment for children and adolescents.

(ii) Unfortunately, about 50% of patients treated by enteral nutrition relapse within 6 months of return to a normal diet.

(iii) The mechanisms by which enteral nutrition benefits CD are unclear and no specific food exclusion or inclusion has yet been proven definitively to benefit patients

(iv) The following advice is therefore based on a combination of evidence from interventional studies together with more indirect (and therefore probably less reliable) evidence based on statistical associations between risk of CD and diets in individuals and across countries.

This evidence suggests that it may be reasonable to have a diet that –

*Is low in animal fat* – guidelines suggest that a low-fat intake is approximately 30% of energy requirements, which equates to 90 g fat for someone who has an intake of 2500 kcal/day.

*Avoids foods that are high in insoluble fibre* – stringy or fibrous vegetables such as green beans, corn on the cob (whole maize), tomato skins, orange pith, potato skins and wheat bran.

*Avoids processed fatty foods* – often high in fat and usually contain emulsifiers – these are detergents that alter the behaviour of the intestinal lining – exposure to dish-washing detergents should also be minimised by careful rinsing.

*Includes supplementary vitamin D* – up to 1200 IU/day.

*Dairy products if tolerated can be consumed* to help ensure adequate calcium intakes.

### *Dietary guidance for patients with UC.*

(i) Short-term use of total bowel rest with intravenous feeding has proved ineffective in active UC and therefore, the general conclusion has been that diet has little role in causation of UC.

(ii) There is, however, evidence from several studies that risk for UC, and risk of relapse in patients who have UC, is increased in those with a high intake of red meat or margarine.

(iii) One small study showed that about one in five patients benefited from exclusion of milk and cheese. This study has yet to be repeated and strict avoidance of dairy products is not justified.

(iv) Lactose intolerance has probably been overemphasised as a clinical problem. Half the world's population does not retain the intestinal enzyme (lactase) necessary for lactose absorption into adult life, and a double-blind controlled trial failed to show correlation of symptoms with ingestion of 240 mL of lactose-containing milk in people with proven lactase deficiency.

This evidence suggests that it may be reasonable to have a diet that –

*Is low in meat* – particularly red meat and processed meats, e.g. restricting their intake to no more than once per week

*Avoids margarine*. There is weak evidence that olive oil might be protective.

*Strict avoidance of dairy products and/or lactose is not justified* on the basis of current evidence.

*Conclusions.* There are some clear signals that diet is relevant to IBD pathogenesis, yet frustratingly little good evidence from interventional studies. Published guidance provided by professional bodies varies considerably between different sources and is often based on consensus of opinion rather than evidence.[96] The guidance provided here attempts to give advice that is supported by the best available evidence and not inappropriately restrictive. We have compared this with other guidance provided by 'best hit' internet sites in supplementary Tables 1 and 2. There is a clear need for greater priority to be given to the conduct of high-quality interventional studies of dietary manipulation in IBD so that we can obtain a much clearer understanding of the associations between diet and IBD.

## AUTHORSHIP

*Guarantor of the article*: Jonathan Rhodes.

*Author contributions*: Both authors contributed to writing the manuscript and literature review.

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