

Chapter 2

Dietary Risk Factors for the Onset and Relapse of Inflammatory Bowel Disease

Andrew R. Hart and Simon S.M. Chan

Introduction

The aetiology of Crohn's disease (CD) and ulcerative colitis (UC), and the factors that influence disease relapse are largely unknown. Identifying the relevant exposures is vital, so that measures may be instituted to prevent inflammatory bowel disease (IBD) in high-risk groups, and interventions recommended to help patients remain in clinical remission. Diet is an obvious exposure to investigate as there are plausible biological mechanisms for how this may be involved in both the pathogenesis and natural history. The potential biological mechanisms will be discussed in the following sections, but diet can affect: the composition of the gut microbiota, have direct toxic actions on intestinal cells and influence the local mucosal inflammatory mechanisms. A role for diet in IBD pathogenesis is supported by the results from ecological epidemiological studies. The incidence of both CD and UC is higher in Western than Eastern countries, which may reflect variations in dietary patterns [1]. In the East, the increasing adoption of westernised diets could be contributing to the rising incidence there. In Europe, where there are differences in patterns of food consumption across the continent, the incidence in northern European countries, compared to those in the south, is 80 % higher for CD and 40 % higher for UC [2]. Migrants to new countries adopt the incidence pattern of their host nation [3]. Finally, the dramatic increases in incidence in IBD, particularly during the latter part of the twentieth century [1] may hypothetically be explained by

A.R. Hart, M.B. Ch.B., M.D., F.R.C.P. • S.S.M. Chan, M.B. B.Chir., Ph.D., M.R.C.P. (✉)
University of East Anglia, Bob Champion Research and Education Building,
James Watson Road, Norwich Research Park, Norwich, Norfolk NR4 7TJ, UK

Department of Gastroenterology, Norfolk and Norwich University Hospital, NHS Foundation
Trust, Colney Lane, Norwich, Norfolk NR4 7UY, UK
e-mail: a.hart@uea.ac.uk; simon.chan@doctors.org.uk

Table 2.1 Summary of the evidence for foods in the aetiology of IBD

Nutrient/food group	Evidence to date	Suggestions for future work
Fatty acids	PUFAs are precursors of inflammatory and anti-inflammatory mediators affect the gut microbiota and influence obesity. Epidemiological evidence from two cohort studies suggest a beneficial effect of a low n-6/n-3 PUFA ratio in UC, but the findings are inconsistent for UC	Cohort studies to investigate the effects of particular PUFAs and to consider if there are interactions between different groups
Vitamin D	In vitro studies have demonstrated the anti-inflammatory effects of vitamin D via modulating toll-like receptor activation and antibacterial responses. Descriptive epidemiological studies report a north–south gradient in incidence which may reflect variations in sunlight exposure. Data from the US cohort study showing inverse associations between predicted total vitamin D status and CD, and dietary vitamin D and UC	Investigation of vitamin D status and dietary intake in other cohort studies
Fibre	Fibre is converted to short-chain fatty acids, such as butyrate, which is the energy source for colonocytes and have immunomodulatory properties including inhibition of <i>NF-KB</i> . The two cohort investigations report no associations between dietary fibre and UC. The US work found inverse associations between fibre from fruit and CD	Investigation of fibre intake from different sources in CD in other cohort studies
Sulphur, iron and zinc	Toxic effects on the mucosa including sulphur inhibiting butyrate metabolism and pro-oxidant effects of iron. Conversely, zinc appears to be required for maintenance of intestinal barrier integrity and down-regulation of pro-inflammatory cytokines	Observational epidemiological work to justify any clinical interventions

dietary changes. This chapter will review the current evidence on how food and its components may be involved in both the aetiology of IBD and affect the natural history of established disease in patients and suggest what further research is required for clarification (Table 2.1).

Methodology to Investigate Diet

The ideal methodology to investigate if diet influences the aetiology of incident IBD and clinical outcomes in patients is to adopt randomised controlled trials of either dietary supplementations or exclusions. However, for investigating aetiology and diet, randomised controlled trials are unethical and non-pragmatic. The practical difficulties are that hundreds of thousands of initially well people

would need to be recruited and then followed up for many years for adequate numbers to develop IBD to ensure that the trial had sufficient power. Asking well people to continuously modify their diet over many years is unrealistic, and it is unethical to encourage participants to eat foods which may be deleterious. Therefore, to study IBD aetiology, non-interventional observational investigations are required, where participants' habitual diet is recorded and compared between those with and without IBD. The two types of observational study design available are retrospective case-control studies and prospective cohort investigations. The latter are more scientifically robust for nutritional epidemiological work, as they reduce both selection and recall biases for diet which are associated with case-control work. In a cohort study, many thousands of well people complete information on their habitual diet and are then followed up over many years to identify those who develop IBD. As participants are recording their current diet at recruitment, there is less recall bias for eating habits, than in case-control work, where patients have difficulties accurately recalling their diet months or years before the onset of their symptoms. Furthermore, in prospective studies as both future cases and those who remain as controls are recruited from the same baseline population then selection bias is minimised. Whilst cohort studies are more time consuming and expensive to conduct than case-control work, they are the preferred methodology for investigating diet and IBD aetiology. To date, two such studies exist: EPIC-IBD (European Prospective Investigation into Cancer and Nutrition) in a cohort of 401,326 men and women in eight European countries and secondly the US Nurses' Health Study (NHS) of 238,386 female nurses.

For studying dietary modifications and the subsequent clinical outcomes in patients with established disease, randomised controlled clinical trials are possible as sufficient numbers of patients can be recruited. An approach to deciding which foods to investigate can be based on firstly plausible mechanisms and secondly surveys of patients who report foods which they feel may exacerbate their symptoms. In a survey of 244 French patients with IBD, 40 % identified food as a risk factor for precipitating relapse, and 47.5 % reported that the disease had changed the pleasure of eating [4]. In a cohort study from the USA, diet was measured with both semi-quantitative food frequency questionnaires and open-ended questions [5]. Foods reported to frequently worsen symptoms included: vegetables, spicy foods, fruit, nuts, milk, red meat, soda, popcorn, dairy, alcohol, high-fibre foods, coffee and beans and those which improved symptoms included: yogurt, rice and bananas.

When investigating aetiology or treatments, whether the findings in individual studies are indeed casual need to be considered in the context of The Bradford Hill Criteria [6]. These state that causality is implied if: there are plausible biological mechanisms for any findings, the effect sizes are large with dose-response effects, there are consistent findings across many studies, co-variables are considered and the data on exposures are recorded before the onset of symptoms. The sections below summarise the prospective cohort studies which have investigated diet in the aetiology of IBD and also the few randomised controlled clinical trials of dietary

interventions in patients with UC and CD. Whether the findings are causal will be discussed in the context of the Bradford Hill Criteria, and where appropriate we suggest what further research or clarification is required.

Hypothesis Generating Studies

One approach to studying dietary factors in IBD aetiology is to investigate if there are any associations with many nutrients, namely a hypothesis-free approach. Although this may generate several false-positive findings, any associations detected may stimulate further work to explore potential biological mechanisms for nutrients to investigate in greater detail. As discussed above, the preferred aetiological methodology for this are prospective cohort investigations. Such data were first reported from the EPIC-IBD study in 2008 where in a subcohort of EPIC, 260,686 initially well men and women were followed up for a median time of 3.8 years during which 139 participants developed incident UC [7]. A total of 18 nutrients, vitamins and minerals were studied and no associations were detected, apart from a borderline significant positive association with an increasing percentage energy intake from total polyunsaturated fatty acids (PUFAs) (trend across quartiles OR = 1.19, 95 % CI = 0.99–1.43, $P = 0.07$). These macronutrients may influence the inflammatory process, and this association led to further work investigating PUFAs [8–11], which is discussed in the following section. A similar exploratory analysis for many nutrients has not yet been conducted for EPIC participants who subsequently developed Crohn's disease. In the US Nurses' Health Study, such a global nutrient analysis has not yet been reported, although the effects of particular food groups including dietary fat [12], fibre [13] and vitamin D [14] have been published. The EPIC-IBD study investigated dietary carbohydrate intake and the risk of CD and UC and reported no associations with either total sugar, carbohydrate or starch intakes [15]. Conversely, several previous case-control investigations had documented positive associations between a high sugar intake and the development of CD [16–19], although the definitions of sugar varied in different investigations. However, the positive links in the latter study design may be due to recall bias, where subjects with CD reported their current rather than their pre-symptomatic diet that included soluble sugars which they could tolerate. This potential recall bias for sugar intake emphasises the importance of prospective cohort studies for investigating diet and the risk of IBD. The aetiological prospective epidemiological studies investigating specific dietary hypothesis in both cohort investigations are now discussed.

Fatty Acids

The different PUFAs chiefly omega-6 (n-6 PUFAs) and omega-3 (n-3 PUFAs) are characterised by the position of the double bond on their long aliphatic tail. The synthesis of both groups is limited in humans and dietary intakes are the main

sources. Significant quantities of n-6 PUFAs are found in red meat, certain cooking oils (e.g. sunflower and corn oils) and some margarines. Similarly, foods rich in n-3 PUFAs are oily fish, rape-seed oil and soya bean oil. In Western countries, the ratio of n-6/n-3 dietary PUFA intakes is higher in comparison to those people living in developing countries, and there is emerging evidence that these macronutrients may play a role in IBD aetiology. The pathophysiological effects of PUFAs may hypothetically be via a variety of mechanisms that affect inflammatory processes in different ways. Firstly, both n-6 and n-3 PUFAs are precursors to a large range of key mediators involved in modulating the intensity and duration of inflammatory responses [20]. Lipid mediators derived from n-6 PUFAs are converted via the arachidonic acid pathway to substrates for the enzymes cyclooxygenase and lipoxygenase which leads to the production of prostaglandins and leukotrienes with pro-inflammatory effects. Conversely, the same enzymes metabolise n-3 PUFAs to lipid mediators with biologically less potent inflammatory properties than those derived from n-6 PUFAs. Competitive inhibition may exist between n-6 and n-3 metabolism as a consequence of dietary intakes which affects the relative production of the different prostaglandins and leukotrienes. More recently, n-3 PUFAs are reported to give rise to a novel class of lipid mediators that limit the inflammatory process [21]. A second possible mechanism of PUFAs is diets containing differing proportions of fatty acids may shape the composition of the gut microbiota to one that predisposes to the development or relapse of IBD. The nature of the diet affects the composition of the gut microbiota and the metabolites they produce, which may have diverse effects on host immune and inflammatory responses [22]. Thirdly, excess intakes of fat can lead to obesity which itself is associated with increased markers of bowel inflammation and intestinal permeability, both hallmarks of IBD [23]. Finally, n-3 PUFAs can act directly on inflammatory cells to inhibit key transcription factors such as PPAR γ and NF κ B, required for the intracellular signalling cascade that activates inflammation [24]. However, the effects of these fatty acids may be dependent on having a background of susceptible genetics as a study in children reported that those who consumed a higher ratio of n-6:n-3 and were carriers of specific single nucleotide polymorphisms in the genes *CYP4F3* and *FADS2* had an increased susceptibility to paediatric Crohn's disease [25].

There are several epidemiological studies which report that PUFAs are associated with IBD aetiology, although the evidence is more compelling for UC than CD. In the EPIC-IBD study, the highest quintile for dietary intakes of the n-6 PUFA linoleic acid, as measured by food frequency questionnaires (FFQs) were associated with an increased odds of developing UC (OR=2.49, 95 % CI=1.23–5.07) [10]. Conversely, the same EPIC-IBD nested case–control study reported that the highest quintile for dietary intakes of docosahexaenoic acid, an n-3 PUFA, were associated with a decreased odds of developing UC (OR=0.32, 95 % CI=0.06–0.97) [10]. In addition to FFQs, a subcohort of the EPIC-IBD study from Denmark has used biomarker measurements of n-6 PUFA intakes from gluteal fat biopsies, which provide a more accurate assessment of longer term dietary intake compared to FFQs [9]. In this particular study, an association with increased arachidonic acid intake, an n-6 PUFA, measured from gluteal fat biopsies and odds of developing UC was reported

(P_{trend} per 0.1 % unit increase in arachidonic acid concentration=0.0001). The US prospective Nurses' Health Study cohort has also found associations between PUFAs and the risk of developing IBD having observed that participants in the highest quintile of n3/n6 PUFA ratio intake had a decreased risk of developing UC (HR=0.69, 95 % CI=0.49–0.98, P for trend=0.03) [13]. No associations were seen for the intakes of the n-6 PUFAs, arachidonic acid and linoleic acid or the total intake of long-chain n-3 PUFAs (docosapentaenoic acid, eicosapentaenoic acid and docosahexaenoic acid). For CD only the EPIC-IBD study has reported an association between PUFAs and CD aetiology, with participants in the highest quintile of docosahexaenoic acid intake having a decreased odds for CD (OR=0.06, 95 % CI=0.01–0.72) [11]. The dissimilarities in the n-3 PUFA results with the Nurses' Health Study Cohort may be due to differences in the reporting of individual n-3 PUFAs as opposed to total n-3 PUFAs. The only consistent finding from the two cohort studies was that no associations were seen for n-6 PUFAs and the development of CD. Clarification of the inconsistencies of the role of all PUFAs in UC aetiology, and n-3 PUFAs in CD are required by providing more precise estimates of the intakes from biomarker studies.

In the clinical setting, there is currently no evidence to support the use of actual PUFA *dietary modifications* in preventing the relapse of either UC or CD in patients. Most clinical trials have assessed fish oil *supplements*, rich in n-3 PUFAs with the results having shown no benefits. These trials in UC and CD are summarised in Cochrane reviews [26, 27], although the conclusions are limited by heterogeneity in study design and in several the small sample sizes. To date, *large* randomised controlled clinical trials (EPIC-1 and EPIC-2) investigating fish oils for the maintenance of disease remission have been performed in CD only [28]. Each of these enrolled over 350 CD patients in remission who were randomised to receive either placebo or gelatin capsules containing fish oils. The Kaplan–Meier analyses showed no differences in the time to relapse between these interventions in either study (EPIC-1, $p=0.30$; EPIC-2, $p=0.48$). Similar large trials need to be conducted in patients with UC.

Vitamin D

Vitamin D is a hormone with a broad range of biological activities that are mediated via signalling of the vitamin D receptor (VDR), which belongs to the nuclear hormone receptor superfamily. Cells of the immune system including T cells and antigen-presenting cells all express VDR as do intestinal epithelial cells. Whilst the role of VDR signalling in the gut has not been fully elucidated, there are plausible biological mechanisms for how vitamin D may prevent IBD via modulating innate and adaptive immune responses between toll-like receptors (TLR) and the TLR-induced antibacterial responses. Other potential protective mechanisms include a synergistic interaction with NF- κ B inducing expression of B-defensin [29] which facilitates autophagy in macrophages [30] and preventing the production of TNF α

in monocytes [31]. Vitamin D has further effects on both B and T cells [32], including tolerance to self-antigens and inhibition of IL-2 production required for lymphocyte proliferation. Deficiency of vitamin D, which is derived predominantly from exposure to sunlight and in smaller amounts from diet, may therefore predispose to IBD through over activation of the immune system or lack of a response to foreign antigens. These anti-inflammatory mechanisms are supported by animal work reporting mice lacking VDR are more susceptible to dextran sodium sulphate colitis which may be due to disruption in epithelial junctions [33].

There is supportive evidence for a role for vitamin D deficiency in the aetiology of IBD from descriptive, aetiological and genetic epidemiological studies. There is a north–south gradient in IBD incidence in both the USA [34] and Europe [2], which may reflect differences in exposure to sunlight. Furthermore, there may be a link between polymorphisms in the VDR gene on chromosome 12 and the development of IBD [35, 36]. The US Nurses' Health Study has investigated a validated score predictive of plasma vitamin D status and the subsequent risk of CD and UC in their cohort of 72,719 women aged 40–73 years recruited in 1986 and followed up to 2008 [14]. The predicted vitamin D status was based on a combination of variables including: dietary intake and supplements, body mass index, racial origin, exposure to sunlight and regional ultraviolet radiation intensity [14]. During the follow-up of 1,492,811 person-years, there were 122 documented incident cases of CD and 123 of UC. For CD, there was a significant inverse association for total predicted vitamin D status (highest vs. lowest quartile $HR=0.54$, 95 % $CI=0.30–0.99$, $P_{trend}=0.02$), but none for UC. However, for vitamin D intake from dietary and supplement sources, there were statistically non-significant inverse associations with CD, but an inverse trend across quartiles for UC ($P_{trend}=0.04$). The reasons for the discrepancies between vitamin D sources for the two forms of IBD are unknown, but the possibilities include firstly varying biological properties of vitamin D derived from different sources and secondly residual confounding. The latter are other factors associated with vitamin D status, which themselves influence the development of IBD. In the first report from the EPIC-IBD study, no association was found for dietary vitamin D intake and UC (excluding supplement use) [7]. In the clinical setting, as far as we are aware there are no randomised controlled trials of foods rich in vitamin D in the treatment of either the relapse or maintenance of remission in patients with IBD. The results from such trials would be difficult to interpret as foods rich in vitamin D also contain n-3 PUFAs, the latter which could also have therapeutic benefits. Furthermore, the relevance of such work could be questionable as exposure to sunlight is a major source of vitamin D. There is only one controlled trial assessing dietary supplements of vitamin D, which randomised 104 patients with CD in remission to receive either 1200 IU of oral vitamin D3 plus 1200 mg of calcium daily, or 1200 mg calcium alone, as a maintenance therapy for 1 year [37]. There were fewer relapses during follow-up in the test group compared to controls (13 % vs. 29 %, $P=0.06$). We believe there is no similar work in UC, and these plus confirmatory clinical trials in CD are needed to confirm if there any therapeutic benefits of vitamin D supplementation.

In summary, there is emerging but as yet insufficient evidence to state vitamin D is involved in either preventing the development of IBD or has any therapeutic properties. Laboratory and animal studies have reported many biological mechanisms for how vitamin D may have beneficial effects on the immune system and protect against the development of intestinal inflammation. To fulfil the Bradford Hill Criteria as to whether vitamin D deficiency is important, confirmatory prospective cohort studies are required to confirm the results reported in the US Nurses' Health Study and further clinical trials in patients.

Fibre

Dietary fibre may protect against the development of IBD, through several mechanisms, through its conversion to the short-chain fatty acids (SCFAs) acetate, butyrate and propionate. Butyrate is the main energy source for colonocytes and is associated with the maintenance of the intestinal epithelium, whilst SCFAs have immunomodulatory roles including inhibition of the transcription factor NF- κ B [38]. The fermentation of fibre is dependent on the gut microbiota, including *Bacteroidetes* species, which some studies report are deficient in patients with IBD [39]. The intake of total dietary fibre, and that from different food sources, was recorded in FFQs completed every 4 years, in the US Nurses' Health Study of 170,776 women with 3,317,425 person-years of follow-up over 26 years [13]. In this report, there were 269 incident cases of CD diagnosed and 338 cases of UC. For UC, there were no associations with either total dietary fibre intake or that from any specific food groups. However, for CD the highest quintile of energy-adjusted cumulative average dietary fibre intake, namely 24.3 g/day, was associated with a 41 % reduction in risk compared with the lowest quintile (HR=0.59, 95 % CI=0.39–0.90). This reduction was largely due to the fibre content from fruits (highest vs. lowest quintile HR=0.57, 95 % CI=0.38–0.85), with no associations detected for fibre from either: vegetables, cereals or legumes. The dose–effect relationship across quintiles ($P=0.02$) for fruit fibre adds support for a causal association. In the EPIC-IBD study, no associations were reported for total fibre intake (OR trend across quartiles=1.03, 95 % CI=0.84–1.25) and the odds of developing UC, although fibre intake from specific foods nor fibre in CD have yet been investigated [7]. To date, no clinical trials have investigated dietary fibre as a treatment for IBD. In summary, although there are biological mechanisms for fibre deficiency in IBD, these are not fully supported by the epidemiological evidence. To clarify if there is a causal association in CD, further prospective aetiological data are required and evidence from randomised controlled clinical trials of fibre supplements in patients.

Sulphur, Iron and Zinc

Excess dietary sulphur may be involved in the aetiology of IBD as it is converted to hydrogen sulphide which may be deleterious to the colon through inhibiting butyrate oxidation, the principal energy source for colonocytes [40]. The mineral is obtained

from several sources: namely sulphated amino acids (cysteine and methionine in red meat, cheese, whole milk, eggs, fish and nuts), and inorganic sulphur present firstly in Brassica vegetables, (cauliflower, cabbage, broccoli and sprouts) and secondly in preservatives in processed foods (breads, beers, sausages and dried fruit). Excess hydrogen sulphide is present in the faeces of patients with ulcerative colitis [41] and is the principal by-product of sulphate-reducing bacteria. These obligate anaerobic flagellated organisms are present in higher numbers in the faeces of patients with ulcerative colitis than in healthy controls [42]. However, faecal flora cultures do not accurately reflect bacteria colonising both the intestinal mucous gel layer and tissues themselves. Tissue colonisation was investigated by using FISH (fluorescent in situ hybridisation) to determine the presence of sulphate-reducing bacteria microbial composition in specimens resected from patients with IBD. In a small study, whose findings need confirmation from larger work, such bacteria were not detected in control tissues, but were in 3 of 12 patients with UC and 1 of 8 patients with colonic CD, but none in ileal specimens [43]. To the best of our knowledge, there are no epidemiological studies which have assessed if dietary sulphur is involved in the aetiology of either UC or CD. However, the effect of dietary sulphur intake was investigated, as measured by food-frequency questionnaires, in 183 patients with known UC in remission and their subsequent rates of relapse [44]. During the 1-year follow-up period, 52 % of patients relapsed and for those in the top tertile of sulphur intake, compared to the lowest, the odds ratio for relapse was nearly trebled (OR=2.76, 95 % CI=1.19–6.40) and for sulphate intake (OR=2.61, 95 % CI=1.08–6.30). For red and processed meat intakes which contain sulphur, higher intakes were associated with more than a fivefold chance of relapse (OR=5.19, 95 % CI=2.09–12.9). To advance our knowledge of whether sulphur is important, validated dietary questionnaires need to be developed to measure dietary sulphur intake and randomised controlled clinical trials performed in patients of a diet low in sulphur.

For dietary iron, there are plausible mechanisms for a potential role in aetiology and relapse due to the mineral's pro-oxidant properties resulting in tissue damage to: proteins, DNA and lipids. Iron may induce oxidant activity in the intestinal mucosa by enhancing the conversion of hydrogen peroxide to the highly reactive hydroxyl-free radical. Of note the aminosalicylate drugs used to treat IBD possess antioxidant properties [45]. In vitro work on colonic biopsies from patients with UC and normal control subjects, reported the amounts of mucosal reactive oxygen species, as measured by luminol-amplified chemiluminescence, were significant lowered by the iron-chelating agent desferrioxamine in inactive and active disease, respectively [46]. To date, the cohort investigations have not currently assessed dietary iron in either UC or CD, although the positive associations in work on relapse in UC with red meat intake could plausibly involve haem [44]. Clarification of any possible mechanisms of iron and data from observational work are required to fully justify randomised controlled trials of iron-chelating therapies.

The micronutrient zinc also has strong biological plausibility in the development and risk of IBD relapse. At present, this is limited to in vitro work and animal models of colitis reporting that zinc is required to maintain the integrity of the intestinal mucosal barrier and down-regulation of pro-inflammatory cytokines [47–49]. Notably zinc deficiency is associated with severity of colitis in animal models [50].

To date, there are no published cohort studies investigating the association between zinc and IBD aetiology or relapse. However, unpublished work from the US prospective Nurses' Health Study cohort suggests that intakes of zinc are inversely associated with the risk of developing CD but not UC.

Conclusions

There are many plausible mechanisms for how several dietary constituents, namely PUFAs, vitamin D, fibre, sulphur, iron and zinc may influence the development of UC and CD. The effects of specific nutrients needs to be further studied in both the European and US follow-up studies, which currently does not exist for all nutrients, to see if the findings are consistent. Dietary interventions in patients cannot be recommended at present. Interventional studies would require representative patient groups, a precise dietary modification to be determined and involve a sufficiently large sample size. Work investigating diet needs to progress as it is eminently modifiable if it is found to be associated with both the development and natural history of IBD.

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