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Title: Research Gaps in Diet and Nutrition in Inflammatory Bowel Disease. A Topical Review by D-ECCO Working Group (Dietitians of ECCO)

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Authors' contributions

All authors drafted the individual sections of the manuscript which were grouped under three thematic areas by AL, ML, RSB. KG collated the individual sections and produced the first complete draft with the assistance of RSB. KW critically edited the manuscript. RSB & KG were the project coordinators. All authors and the Governing Board of ECCO approved the final version for submission.

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Abstract

Although the current doctrine of IBD pathogenesis proposes an interaction between environmental factors with gut microbiota in genetically-susceptible individuals, dietary exposures have attracted recent interest and are, at least in part, likely to explain the rapid rise in disease incidence and prevalence. The D-ECCO working group along with other ECCO experts with expertise in nutrition, microbiology, physiology and medicine reviewed the evidence investigating the role of diet and nutritional therapy in the onset, perpetuation and management of IBD. A narrative topical review is presented where evidence pertinent to the topic is summarized collectively under three main thematic domains: i) the role of diet as an environmental factor in IBD aetiology; ii) the role of diet as induction and maintenance therapy in IBD; and iii) assessment of nutritional status and supportive nutritional therapy in IBD. A summary of research gaps for each of these thematic domains is proposed which is anticipated to be agenda setting for future research in the area of diet and nutrition in IBD.

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Introduction

The current dogma of inflammatory bowel disease (IBD) pathogenesis involves a complex, yet elusive, interaction between environmental factors and the gut microbiota in people who are genetically predisposed. However, the rapid rise in global prevalence of both ulcerative colitis (UC) and Crohn's disease (CD) cannot be attributed to human genetics alone [1]. Evidence now proposes that while human genetics are important, they explain only a small fraction of the risk of developing the disease, with microbial determinants and other environmental exposures thought to be more important than genetic susceptibility [2]. Among environmental factors, dietary influences have attracted the most interest, and are likely to significantly contribute to the rapid rise in disease epidemiology [3]. There are several lines of evidence to suggest that diet is a key player in the onset, perpetuation and management of the disease: Epidemiological evidence associates certain dietary nutrients and components to increased risk of IBD, exclusive enteral nutrition (EEN) is the primary induction treatment of active paediatric CD and there is emerging evidence that exclusion diets could treat or prevent subsequent disease flare. As malnutrition is a frequent presenting symptom of IBD that fluctuates erratically during the course of the disease, assessment of malnutrition and supportive nutritional therapy are important aspects of the multidisciplinary management of patients with IBD [4].

In contrast to the efforts thus far to understand the genetic and microbial origins of IBD or the development of effective and side-effect free pharmacological treatments in IBD, there is currently very little research on the role of nutrition or diet in these areas. As the current doctrine of IBD pathogenesis proposes a complex interplay between dietary influences, genetics and environment in the aetiology of IBD, there is now a pressing need to review past and current research and identify gaps for future research. The aim of this topical review was to extensively review the literature on the role of diet and nutrition in the aetiology and management of IBD and set the agenda for future research.

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Methodology

A contributors' group was assembled involving all members of the D-ECCO Working Group (https://www.ecco-ibd.eu/index.php/about-ecco/ecco-operational-board/d-ecco-wg.htmland) and competitive application for membership of a Topical Review Group launched by ECCO. Selection of contributors was based on their curriculum vitae, a personal supporting statement and ensuring equal representation of professions and countries, as dictated by ECCO instructions for topical reviews and advised by its Governing Board. Three main thematic areas were selected *a priori* and working groups and thematic leaders were assigned for each.

A thorough literature search was conducted using Medline and a combination of appropriate keywords and Boolean operators. Search was limited to articles published in English and focus was given to recent evidence published over the past 15 years and until January 2016. Draft reports produced by each contributor were reviewed by the thematic leaders and project coordinators. The main research gaps were identified and agreed by consensus in a face-to-face meeting involving all contributing authors in Amsterdam in March 2016. Consensus was defined as agreement of >80% following blind electronic voting and discussion between contributors where required. The final manuscript for publication was reviewed by all members of the Topical Review Group and approved by the Governing Board of ECCO.

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1. Role of diet as an environmental factor in IBD aetiology

1.1 Diet, Microbiota and Pathogenesis of IBD

Diet can contribute to gastrointestinal health, either via direct effects on gut homeostasis and barrier function or indirectly via the intestinal microbiome (Supplementary Figure 1). This densely populated microbial community is shaped by host genetics and environmental factors, and comprises a limited number of phyla, dominated by Bacteroidetes and Firmicutes [5]. It involves complex microbe-microbe and host-microbe interactions that vary along the gastrointestinal tract, with indispensable effects on host functions with regard to the immune system, epithelial and barrier function and its large metabolic capacity [6]. Segregation into three robust clusters (i.e. 'enterotypes') driven by Bacteroides, Prevotella and Ruminococcus [7], is associated with long-term dietary preferences, (*i.e.* high protein and fat consumption with the Bacteroides and carbohydrate-rich diets with the Prevotella enterotype) [8]. Others reported on a bimodal distribution in microbial gene richness, in which a lower richness was associated with impaired metabolic factors and inflammation [9] and being less responsive to dietary interventions [10].

The global increasing incidence in IBD seems to be associated with western lifestyle [11,12]. Diet can shape the microbiota composition and activity and impact host-microbe interactions. Dietary intake of a high protein diet and/or red meat can result in increased production of bacterial metabolites, such as ammonia, indoles, phenols and sulphide, that may be harmful to the gut [13]. On the other hand, bacterial fermentation of non-digestible carbohydrates, results in short-chain fatty acids (SCFAs), which are an energy source for host epithelial cells and act as signaling molecules with anti-inflammatory, immunomodulatory, anti-oxidative and improved mucosal barrier effects [14]. Fat can have effects on the microbiome by release and conversion of bile salts [15] and altering the microbiota composition [16].

However, it is critical to appreciate the limitations of this rapidly expanding research area [17]. Common to all microbiome studies is the inherent variability (intra- and inter-individual) and the fact that even minor variations in research and laboratory methodology dramatically impact findings; this includes sampling, storage, DNA extraction, amplification, sequencing protocols, and data analysis [18,19]. Disease factors (location, activity, medication, and faecal consistency) also impact the microbiome [20,21] and are often not taken into account. Most importantly, even

clear associations between microbes and IBD do not establish cause and effect [20,22]. Therefore, interpretation of findings requires caution and findings may not always be reproducible. Nevertheless, there are several emerging specificities regarding the microbiome in IBD:

Diversity: The single most reproducible finding of studies on microbes in IBD is a reduction in α-diversity. Diversity is generally thought to represent community health; reduced diversity results in less flexibility and adaptation and is likely to impact negatively on the microbial functional capacity. Reduced diversity can be the result of taxa elimination and/or bloom of taxa that displace others. Both are likely to occur in IBD [23]. Reduced diversity as a marker of IBD could indicate pathogenic mechanisms; however, it also has prognostic value since reduced richness (representing number of species) predicts failure to respond to corticosteroids in children with severe UC [24]. Recently, a reduction in the diversity of mucosa-associated bacteria was found in paediatric UC at non-inflamed sites, suggesting that the microbial changes may be an inherent defect in IBD and not just the result of inflammation [25].

Compositional changes: For the reasons stated above, it is difficult to commit to specific reproducible alterations in microbiota in IBD. Frequent phylum-level observations include reduction in Firmicutes and Bacteroidetes and an increase in Proteobacteria [26]. Enterobacteriaceae are frequently increased in IBD, and are especially relevant since they include *Escherichia coli* (such as adherent-invasive strains) [27]. Rodent models of colitis have demonstrated that colonisation with adherent-invasive *E. coli* (AIEC) may be affected by diet [28]. Other taxonomic groups are depleted in IBD, such as Clostridia, Ruminococcaceae, and Bifidobacteria, and at species level, many have reported losses of *Faecalibacterium prausnitzii*, which may also have functional roles [22,29]. Beyond the identity of bacteria, one must also consider their spatial organization, which is altered in IBD [30]. Some of the observed changes are mediated by access to nutrients and oxygen gradients [31].

Functional changes: Current focus is shifting towards the functional capacity of the microbiome, as ‘what are they doing’ might be more important than ‘who is there’. The European MetaHIT Project identified a functional microbial dysbiosis in patients with IBD [32], supported also by others [33]. Metabolomic analyses of breath or faeces revealed differences in IBD *versus* controls, (e.g. reduced butyrate, acetate, and (tri)methylamine and elevated amino acid levels) [34-36]. Interestingly, individuals with UC appear to have defective or deficient production of SCFA [37,38].

Furthermore, analysis of microbiota-derived small molecules, considered important mediators in microbe-microbe and microbe-host interactions, reveal a variety of biological actions, including antibiosis and immune modulation [39]. Further studies integrating the metagenome with proteome and/or metabolome data in IBD, and taking into account disease phenotypes, activity and medication use, are needed.

The observed microbial perturbations can result from the disease itself, but may also contribute to inflammation as shown by transfer of microbiota from colitis models to wildtype donors [40,41] and improvement of disease activity after decontamination of the gut lumen [42,43]. So far, microbial modulation of disease activity by administration of probiotics or prebiotics showed limited efficacy [44]. However, findings, mainly resulting from metabolic and animal studies, clearly demonstrate that diet can impact gut homeostasis and immune function via the microbiome.

Research gaps:

- ***Establishing causality between diet, microbiome and IBD is an important research gap. Priority should be given to a systems biology approach.***
- ***Longitudinal studies investigating early life exposure including diet, microbiome, and other environmental factors on IBD onset are needed.***
- ***Stratification of patients by disease phenotype, specific microbial perturbations and dietary intake will be necessary to develop successful therapeutic and/or preventive strategies.***
- ***Studies evaluating the ability to modify the microbiota by dietary interventions, and the effect on disease in affected individuals should be a priority.***

1.2 Effect of Diet on Rodent Models and Cell Lines

Multiple dietary components have been shown to cause or aggravate inflammation in animal models of IBD [20,28,45-47]. Due to the concise nature of this review, we will confine ourselves to landmark studies that demonstrate an association between dietary components and inflammation in IBD models, or those studies that best highlight research gaps.

Key dietary components thought to be possibly associated with CD in animal models and cell lines include high fat (HF), high animal or milk fat, or high fat/high sugar (HF/HS) diets [20,28,45,46], as well as gluten [47], maltodextrin [48], emulsifiers [49-51] titanium dioxide nanoparticles [52], luminal iron [53] and aluminum a food chain contaminant [54].

All of these are common components of diets in economically-developed countries, so-called 'Western diets'. Martinez-Medina et al [28] used a transgenic CEABAC10 mouse that uniquely expresses CEACAM6, the ligand for CD-associated bacteria AIEC, to compare the effect of standard chow to HF/HS 'Western diet' and AIEC infection. Both wild type and transgenic mice fed a HF/HS diet were more likely to develop dysbiosis, increased intestinal permeability, decreased expression of mucins and mucus thickening. In addition, CEABAC10 mice fed HF/HS were rapidly colonized by AIEC and presented higher degree of crypt abscesses when compared to the standard chow group. Another study highlighting the role of specific fats, namely isocaloric low fat (LF), polyunsaturated fatty acids (PUFA) and milk-derived fat (MF), in IL-10$^{-/-}$ mice was conducted by Devkota and colleagues [20]. They reported an increase in colitis severity in the MF group compared to PUFA- and LF-fed IL-10$^{-/-}$ mice. Colitis was also associated with the bloom of colitogenic *Bilophila wadsworthia* in the MF group, and was dependent of exposure to MF-induced taurine conjugated bile acids. Sodium caprate in MF has been shown to increase intestinal permeability independent of the taurine dependent mechanism previously described [20]. High fat was also shown to accelerate ileitis in a TNF$^{\Delta ARE/WT}$ mouse model [45]. The same group subsequently demonstrated that gluten induced ileitis in these mice through the gluten-dependent increased intestinal permeability [47].

Adherence of AIEC via CEACAM6 appears to be critical for the pathogenic effect of this strain in human CD. Maltodextrin, a key polysaccharide used in sweeteners (Sucralose) and as a thickening agent was shown to enable AIEC adherence and biofilm formation independently of the presence of CEACAM6. In a viewpoint article, Roberts and colleagues hypothesised that the increased incidence of CD could be attributed to a higher consumption of emulsifiers in processed foods [55]. In support of this hypothesis, Chassaing and colleagues [48] showed that TLR5$^{-/-}$ and IL-10$^{-/-}$ mice exposed to two common emulsifiers, carboxymethylcellulose and polysorbate-80, develop obesity/metabolic syndrome in TLR5$^{-/-}$ and severe colitis in IL-10$^{-/-}$. Both mice strains fed the emulsifiers showed increased gut permeability, reduced mucus thickness, higher penetration of intestinal bacteria and dysbiosis. These changes resulted in an accelerated metabolic syndrome in TLR5$^{-/-}$ mice and in an increased incidence and extent of colitis and enrichment in *Bilophila* spp. in IL-10$^{-/-}$ mice with both CMC and polysorbate-80. In line with these results, translocation of *E. coli* across M-cells was increased in the presence of polysorbate-80 [50].

The studies outlined above accentuate the aggravating effect of HF diets in models of CD, however, the results to date on the effect of HF on disease in animal models of UC are inconclusive [56-59]. The reason being differences in diet composition (e.g. fat/sugar ratio, n-3/n-6 ratio), duration of diet consumption and type of model used. For example, HF or n-6 PUFA feeding to mice exposed to Dextran Sodium Sulphate (DSS)-induced colitis resulted in either worsening or amelioration of disease [56,57,59]. In contrast, HF feeding to Mdr1$^{-/-}$, a spontaneous model of UC, led to worsening of colitis, although no colitis was observed in WT mice [58].

An exciting new concept involves "humanised mice" which may contain human genes or microbiome. Studies involving diet with such models could shed more light on the interaction between diet, microbiome and IBD in humans. An important research gap is the development of a model in which different food ingredients could be tested with relevance to the human condition.

In conclusion, the collected data points towards diet-induced effects on microbiota composition, epithelial responses and inflammation primarily in genetic susceptible animals but less in wild type animals. The translational relevance of these findings to the human conditions is yet to be addressed.

Research gaps:

- ***Studies should evaluate if improvement of intestinal inflammation can be achieved with dietary interventions in animal models***
- ***Development of experimental models as a platform for testing multiple dietary ingredients potential to cause or inhibit inflammation should be a priority.***

1.3 Epidemiology Linking Diet with risk of IBD

Epidemiological evidence shows that individuals migrating from regions of low IBD prevalence to higher-prevalent regions are at increased risk of developing IBD [60]. Numerous studies have evaluated the association between pre-illness intake of specific nutrients such as fats, carbohydrates and protein and food groups such as fruits, vegetables and meats for UC. All were case–control studies and analysed dietary intake retrospectively. The most frequently reported food components associated with IBD were cereals, fibre-containing food, bread, sugar and

sugar-containing foods, fruits and vegetables, fat, sucrose, starch or total carbohydrate and protein intake or energy drinks [14,61-64].

Despite methodological limitations, several prospective studies have consistently identified animal protein to be associated with increased risk of UC [61,64,65]. In the study by Jantchou *et al*, the highest tertile for consumption of animal protein had a hazard ratio of 3.29 for developing UC (p=0.005). Jowett *et al*. studied 191 UC patients, and they demonstrated a significant association between high meat intake and risk of relapse of UC [65].

Although several studies suggested significant associations of particular dietary habits in UC [14], an equal or even higher number of studies could not confirm these findings. Since many of the current methodologies are based on historical food frequency questionnaires (FFQ) the current evidence is not sufficient to draw firm conclusions on the role of specific nutrients in the aetiology of UC. Dietary ingredients in western diet are not limited to the "natural components" listed above. There is an increased consumption of food additives, such as sweeteners, emulsifiers, thickeners, preservatives and food colorings. These products, some of which have been linked to IBD [49,62,66], should be further investigated in large well-designed epidemiological studies that provide data regarding exposure to these products.

The Nurses' Health Study examined the association between fibre intake and incident IBD. Subjects consuming large amounts of fibre, particularly fruits, were less likely to be subsequently diagnosed with CD, although no association was observed for UC [67]. There is evidence for a gene–diet interaction, in which variants in genes for fatty acid metabolism affect the relationship between IBD risk and PUFA consumption [68]. Together, these findings support the hypothesis that consumption of fruits and possibly vegetables, rather than meats and fats, can lower the risk of IBD. The study using the European Prospective Investigation into Cancer and Nutrition (EPIC) database prospectively investigated the impact of nutrition on IBD development [69]. The EPIC-IBD study is a sub-cohort involving a total of 401,326 initially healthy men between 1991-1998. In this large multicenter prospective study using dietary data from a validated FFQ, they did not find any associations between total dietary carbohydrate, sugars (monosaccharides and disaccharides), or starch intakes and the odds of developing CD and UC. D'Souza *et al* assessed Canadian children for dietary patterns, and idenified a diet rich in fruit and vegetables (prudent diet) as protective for CD while a partial 'Western diet' increased risk for CD [70].

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Research gaps:

- ***Risk associated with consumption of commercially processed food, including, but not limited to nutrients, additives and processing should be assessed in longitudinal studies***
- ***Future studies should address dietary patterns rather than individual dietary components***

2. Diet as induction and maintenance therapy in IBD

2.1 Exclusive Enteral Nutrition in Management of IBD

Exclusive enteral nutrition is the most extensively researched dietary intervention for induction of remission in mild to moderate CD both in children and adults. Case series and clinical trials have demonstrated the ability of EEN to induce clinical remission in approximately 80% of patients. Treatment response rates varied depending upon type of study design (retrospective or prospective), type of analysis (per protocol or intention to treat) [71-73], but seem to be independent of type of formula and its constituent nutrients.

In paediatrics, a meta-analysis of studies comparing EEN to standard treatment has demonstrated an overall combined remission rate for EEN of 73% [74,] whereas two large, single-center studies have confirmed a treatment efficacy of approximately 80% [71,73]. Similar remission rates were reported in studies conducted in adults, particularly one randomised controlled study demonstrated that 21/30 adults refractory to steroids entered remission with EEN [75,76]. However, the most recent meta-analysis demonstrated that steroids were more effective than EEN [77]. Studies on EN in adults are sparse, of poor quality and therefore it is difficult to draw clear conclusions. Interestingly, and in contrast to steroids effect, EEN also has the potential to induce mucosal healing. In a prospective Australian study, 58% of patients had early endoscopic response, and one third had complete transmural healing on small bowel imaging [78].

Disease severity and luminal disease seem to be the only significant predictors of response to EEN [69,70]. According to the ECCO/ESPGHAN consensus, EEN should be the first line therapy to induce remission in children with active mild-to-moderate luminal CD [79]. There are no data supporting the use of EEN for extra-intestinal manifestations or penetrating disease.

It has traditionally been speculated that use of EEN should be limited to patients with small bowel involvement, however results from further meta-analyses have shown no difference in the efficacy of EEN when considering disease location [73,74,80]. Likewise, there are no confirmatory data on the effectiveness of such treatment in severe isolated Crohn's pancolitis, and no data for isolated oral or perianal disease.

The efficacy of EEN has been attributed to different mechanisms including bowel rest, anti-inflammatory effects, restoration of the epithelial barrier and favorable changes in the intestinal microbiota [81]. As both polymeric and elemental formulas show similar efficiency [76,82],

gut rest is unlikely to be the primary mechanism. More recently, the effect of EEN has also been related to the exclusion of specific components from the diet [83].

A few studies have demonstrated a decrease in pro-inflammatory [84] and an increase in anti-inflammatory molecules (TGF-β) [85] in response to EEN. Incubation of CD-biopsies with elemental formula led to an increased ratio of IL-1Ra to IL-1 β compared to control samples [86]. Other authors confirmed the direct effect of a polymeric formula on colonic epithelial cell chemokine responses to the pro-inflammatory cytokine TNF-α [87]. At the mesenteric fat level, EEN treatment decreased pro-inflammatory adipokines (TNF-α and leptin) and increased adiponectin levels [88].

The effects of EEN on the intestinal barrier have mostly been clarified by *in vitro* or animal studies. In human colonic epithelial cells, EEN has been found to prevent epithelial barrier dysfunction in the presence of TNF-α [89]. In IL-10$^{-/-}$ mouse model of colitis, EEN treatment maintained normal gut barrier function and integrity and reversed inflammatory changes [90].

Profound changes in the composition of mucosal microbiome induced by EEN have been suggested by pioneer investigations [91] and recently confirmed by several studies. Reduced diversity of the microbiota, occurring after a few days or weeks of EEN, has been frequently reported [92-95]. The microbiome effect induced by EEN differs from the one induced by anti-TNF medications and most importantly from partial EN (PEN) [96]. In contrast, one study demonstrated an increase in species diversity after elemental diet [97]. Species specific effects induced by EEN were reported by different authors, particularly a significant decrease in Bacteroides [92-94,98]. A reduction of *F. prausnitzii* was observed both in adults [99] and children [92], challenging the previous paradigm of a protective role in CD. Reports describing changes in the intestinal metabolic profile are unequivocal [92,100]. A single study reported the metagenomic changes induced by EEN, particularly an increase in relative abundance of genes involved in cell growth and renewal and possibly in tissue healing [95].

The efficacy of EEN related to the exclusion of some dietary components is indirectly supported by studies indicating that PEN associated with a normal diet did not induce remission [72], while 70% of children and 69% of adults on a PEN combined with a specific CD exclusion diet achieved remission [83]. Furthermore, specific dietary restriction seems to be therapeutic in CD [101,102].

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There are not enough studies to determine the optimal duration of EEN; the reported duration of an induction therapy varied from 2 to 12 weeks in studies, however it is most frequently used for 6 to 8 weeks. If the clinical response is not achieved within 3 weeks an alternative treatment should be considered. There is a paucity of evidence to guide the reintroduction of normal food after the end of EEN. There are few studies that have evaluated reintroduction of foods. Faiman *et al* demonstrated that rapid food reintroduction (3 days) after EEN is as equally effective as delayed food reintroduction (5 weeks) after follow up of 1 year [103].

Research gaps

- ***Mechanisms of action of EEN need to be explored, including the interaction of epigenetic, immunological and microbiological changes.***
- ***Studies evaluating the reintroduction of specific foods following EEN need to be performed***
- ***EEN should be evaluated in a variety of conditions, including adults with CD, in UC, complicated CD, and pre- and post-operative setting.***

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2.2 Partial Enteral Nutrition in Management of IBD

Partial enteral nutrition (PEN) is the use of liquid enteral formula in addition to consuming food for maintenance of remission or treatment of active CD; using <100% of total energy requirements from liquid nutrition. There is increasing interest in the use of PEN (Supplementary Table 1). In part, as a result of the limitations of EEN, with food abstinence and the monotony of drinking enteral formula being common reasons for poor compliance to and subsequent success of EEN [104]. The mechanisms via which PEN might impact on CD activity, if at all, are poorly understood. Unlike EEN, the complete removal of dietary antigen as a hypothetical mechanism is no longer the case, therefore if studies indicate that PEN is at least as effective as EEN then this might also exclude this as a mechanism for the effectiveness of EEN.

Type of supplementation varies widely between studies and clinical practice [72,83,105-110]. The volume investigated has ranged from 35-90% of total energy requirements and the food consumed can either be a free diet or a defined restrictive diet. A small number of studies have investigated PEN compared to normal diet for maintenance of remission [105,106,109-112]. One RCT evaluated PEN with normal diet for the maintenance of adults with recently-induced remission of CD [106]. The study was halted early due to an interim analysis showing improved outcome in those following PEN. The relapse rates in the PEN arm (35%) were lower compared with normal diet (64%), with a multivariate adjusted hazard ratio for relapse of 0.40 [106].

Another RCT compared PEN (≥900 kcal/day) with 6-mercaptopurine (6-MP) and to no drug therapy (normal diet, no placebo) [105]. At 2 years, PEN resulted in 56% relapse, 6-MP in 43% (no difference) but both were lower than control normal diet (79%).

Several non-randomised trials have investigated the effect of PEN on maintenance of remission; a selection of key studies is presented here (Supplementary Table 1). In another study, patients in medically-induced remission were selected to continue to have PEN plus low fat diet (if they had previously been compliant to EEN) or to follow normal diet (if they had previously been non-compliant to EEN) [109]. At 12-months, PEN resulted in lower relapse rates, lower disease activity and lower endoscopic inflammation compared with normal diet. In an identical study published by the same group but in those with surgically-induced remission, PEN was confirmed to lower relapse rates and endoscopic recurrence compared with normal diet at 12 months [110], whereas in those with infliximab-induced remission it was not shown to impact relapse rates [113]. Finally a retrospective, non-randomised trial in children with EEN-induced

remission, compared relapse rates in those who chose to continue nocturnal PEN compared with those who did not [112]. PEN reduced relapse rate at both 6 months and 12 months.

There is only one RCT of PEN in the treatment of active CD in comparison with normal diet. This was a randomised, cross-over trial in adults with on average very mildly active CD and malnutrition [114]. Although some nutritional markers were improved, PEN did not impact on disease activity (Harvey Bradshaw Index) [114]. One RCT has compared elemental PEN and EEN for induction of remission in children with moderate to severely active disease over a six-week period. However, PEN resulted in fewer patients entering remission and a smaller reduction in PCDAI compared with EEN [72].

A recent, non-randomised trial compared PEN with EEN or anti-TNF treatment for the treatment of active CD in children/adolescents, with patients allocated to the intervention based upon the unit in which they were recruited [115]. Following 8-weeks, fewer patients receiving PEN had a clinical response compared with either EEN or with anti-TNF treatment and fewer were in clinical remission. However, the limitation of non-randomised treatment allocation and clinically important differences in baseline characteristics makes interpretation of these findings difficult [115]. One uncontrolled trial has investigated PEN in conjunction with a CD exclusion diet in children/young adults, reporting a clinical response in 78.7% and with 70.2% entering full disease remission [83].

Research gaps

- ***Investigation of the effectiveness of PEN as a monotherapy or in combination with medical therapy for preventing relapse in IBD is a research gap***
- ***The optimal regimen of PEN for maintenance of CD, including the dose, composition, duration, method of delivery of feeding, and nature of the accompanying oral diet should be identified.***

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2.3 Elimination Diets in Management of IBD

EEN is an effective therapy for induction of remission in CD [74]; however there are drawbacks. EEN is difficult to adhere to, particularly in adults [104], and there is limited evidence for post-EEN strategy. Understanding the mechanism of response could lead to diets that are easier to comply and follow that could be implemented for longer duration.

Several elimination diets have been developed and evaluated for induction of remission, maintenance of remission or improvement of functional symptoms (Supplementary Table 2). This field still lacks adequately powered high quality studies. Most of the published data have severe methodological limitations or did not report standardised clinical outcomes such as remission, decline in inflammation or mucosal healing.

Diets reviewed included the Specific Carbohydrate Diet (SCD) [116], the Crohn's Disease Exclusion Diet (CDED) [83], the Anti-inflammatory diet (IBD-AID) [117], Allergen elimination diet (IgG) [118], the Semi-vegetarian diet (SVD) [119], the low Fermentable Oligo-saccharides, Di-saccharides, Mono-saccharides And Polyols diet (FODMAP) [120,121], and the Mediterranean Diet [122]. Only one study for UC met requirements for outcomes [123]. A summary of these diets is presented in Supplementary Table 2. However, only two diets (SCD and CDED) reported significant improvement in clinical remission and data demonstrating a significant reduction in inflammation and therefore are discussed here.

The theoretical assumption underlying the SCD is that CD is caused by malabsorption of disaccharides and complex carbohydrates resulting in bacterial overgrowth and intestinal injury [124]. Cohen et al [116] conducted a prospective pediatric study in 9 children with active CD using the SCD. Patients were evaluated using the PCDAI, Harvey-Bradshaw Index (HBI), and Lewis score at baseline, week 12 and week 52. At week 12, 6/10 entered remission (PCDAI<10) and 8/10 showed significant mucosal improvement (P=0.012) compared with baseline. The Lewis score declined significantly from 2153±732 to 960±433 (P=0.012). Three patients had scores consistent with mucosal healing. Seven patients continued the diet up to 52 weeks, by which

point the HBI (0.1 ± 0.4) and PCDAI (5.4 ±_5.5) remained low (P = 0.016 and 0.027 compared to baseline), with 2 patients showed sustained mucosal healing. Obih et al [101] conducted a retrospective study with the SCD in 26 patients (20 CD, 6 UC). They demonstrated an improvement in the abbreviated PCDAI during 12 months, however several patients received additional induction medication while others started the diet while being in remission. Walters et al [125] evaluated the composition and complexity of the gut microbiota and resolution of IBD symptoms between the SCD and a Low Residue Diet. They demonstrated a general increase in the microbial diversity of faecal samples under the SCD and decrease in diversity among the Low Residue Diet.

The Crohn's Disease Exclusion Diet (CDED) is based on exclusion of dietary components that in rodent models have been demonstrated to impair innate immunity, increase intestinal permeability, cause microbial dysbiosis or allow bacteria to adhere and translocate through the intestine epithelium. The diet is rich in fibre and natural sources of resistant starch. Sigall Boneh et al [83] conducted a retrospective study to demonstrate their experience in 47 children and young adults with active CD treated for 12 weeks. Patients were reviewed at baseline, week 6 and week 12 and were evaluated with PCDAI, HBI, CRP, ESR, and albumin at each point. The diet was coupled with Partial Enteral Nutrition up to 50% of the energy requirements in most cases. After 6 weeks, clinical remission was achieved in 33/47 patients (70%). Six out of seven (85.7%) patients who used the diet without supplemental formula, entered remission. Normalization of CRP was obtained in 21/30 (70%) patients with previously elevated CRP. At last follow-up, 11/15 patients evaluated had complete mucosal healing. This diet is currently being evaluated in two prospective randomised controlled trials.

Chiba et al conducted a prospective two year trial to evaluate the effect of a semi-vegetarian diet in maintenance of remission in 22 adult patients in medical remission, with the control group comprising only 6 patients on regular diet. After 2 years of follow up, 16/22 patients continued the semi-vegetarian diet and 15/16 maintained remission compared to 2/6 in the control group (p=0.0003) [119].

The original rationale for the low FODMAP diet in IBD was that several dietary FODMAPs may undergo fermentation that may cause tissue injury as a result of increased intestinal permeability [126]. The use of FODMAP diet to manage functional symptoms in patients with IBD will be discussed later in this topical review.

In conclusion, dietary manipulation offers promise for IBD, however there is an urgent need for RCTs to evaluate the efficacy of those diets together with their effect on the microbiota.

Research gaps

- ***Clinical trials to develop and evaluate efficacy of elimination diets for induction and maintenance of remission in IBD are required***
- ***Dietary ingredients added or eliminated that are responsible for the clinical effects, and definition of mechanisms underlying response need to be identified.***

3. Assessment of nutritional status and supportive nutritional therapy in IBD

Malnutrition is an extra-intestinal manifestation of IBD comprising undernutrition and overnutrition. It presents with different forms via a range of mechanisms and its severity varies during the natural course of IBD (Supplementary Figure 2). The origin and manifestations of undernutrition in IBD are multifactorial including suboptimal nutritional intake, alterations in energy/nutrient requirements and metabolism, malabsorption, excessive gastrointestinal losses and medication [4]. While literature is still inconclusive, a higher basal metabolic rate:FFM ratio has regularly been reported in IBD patients compared with healthy controls [127-129] and children with CD fail to adapt their resting energy expenditure (REE) per kg lean mass to the same extent that patients with anorexia do [127]. In adult CD patients, malabsorption is a major contributor to being underweight when in remission [130] and impaired gastric acid and pancreatic enzyme secretion were observed in undernourished patients [131]. The effect of proinflammatory cytokines on energy/nutrient requirements, bone and development can also interact independently in the

aetiology of undernutrition [132]. Physical activity as contributor of total energy expenditure has barely been studied [133]. Hence, assessment of nutritional status, prevention and correction of deficits is imperative and the cornerstone to multidisciplinary management of IBD patients.

3.1 Assessment of Nutritional Status

Involuntary weight loss and being underweight are common features of the newly diagnosed IBD patient and frequently accompany episodes of disease relapse. Whilst more common in CD than UC, presenting in approximately 60% and 35% of new cases respectively [4], recent evidence suggests that fewer patients currently present underweight, reflecting either the obesity epidemic or earlier disease recognition [134,135]. There are limited data on the progression of undernutrition following diagnosis and whether this is predictive of disease outcomes. In a paediatric study, a similar proportion of children with CD had short stature two years post-diagnosis but being underweight decreased dramatically from 35% to 2% [134].

IBD-specific alterations in body composition, with depletion of lean mass and normal or increased fat mass have been consistently reported [136]. Hence, a high degree of adiposity and less lean mass should be expected for a given BMI. Interestingly, normalisation of BMI at two years follow-up has not been associated with an increment in fat-free mass (FFM) in CD [137], which suggests that BMI changes may not be good proxies for body composition changes in IBD. Such features of sarcopenia might be clinically relevant as people with IBD may have an increased risk of cardiovascular events [138] and recently intra-abdominal body composition has been associated with adverse clinical outcomes but both of these findings need to be replicated in prospective studies [139,140].

Osteopenia and osteoporosis are often seen in CD. Adult patients have a 60–70% higher risk for vertebral and hip fracture incidence compared with healthy controls [59,141]. In children, data are not suggestive of increased fracture risk during childhood but it might be that a higher risk of fracture occurs early in adulthood. Up to 25% of CD patients will present with growth deficits, and a proportion will not attain their height predicted by genetic potential [142].

While clinical presentation of frank micronutrient deficiencies in IBD is rare and largely limited to case reports, low circulating levels are reported for most of micronutrients [4,143]. However, caution should be paid in the interpretation of plasma micronutrient measurements in

the presence of systemic inflammatory response (e.g. high CRP). Plasma concentrations of various micronutrients (e.g. iron, zinc, selenium, copper, vitamins A, C and E) are substantially affected by nutrient carrier protein concentration changes [144-146] so are unlikely to reflect total body reserves and inappropriate clinical interpretation may trigger unnecessary interventions [147]. Development of novel biomarkers of micronutrient body stores are required and dietary intake assessment should complement biochemical indices.

In contrast to the wealth of data on clinical diagnostics and pharmacological management of IBD, limited data have explored the frequency of routine nutritional assessment and management of IBD, particularly in elderly patients where data are scarce. Data from a United Kingdom survey identified adult service resource gaps/shortages and absence of uniform practice standards on nutritional assessment and management [104]. Assessment of nutritional status requires at least measurement and interpretation of anthropometry and dietary intake, making dietitians integral members of the multi-disciplinary team caring for patients with IBD [148]. Assessment of body composition using sophisticated techniques is appealing, but the implications of this for clinical practice improvement and patient benefit need to be explored and justify the resources used.

Research gaps

- ***There are limited data on the evolution of malnutrition following diagnosis and whether this is predictive of disease outcomes.***
- ***New biomarkers of micronutrient status are needed to overcome limitations of plasma measurements in the presence of systemic inflammatory response.***
- ***More research is needed on nutritional status and management of IBD patients, particularly in pregnancy, the elderly and pre-operative state.***

3.2 Supportive therapy in Short Bowel Syndrome in IBD

Short bowel syndrome (SBS) is a rare but devastating complication of IBD characterised by malabsorption, typically following extensive or repeated intestinal resection. It is a form of (temporary) intestinal failure or intestinal insufficiency compromising fluid, electrolyte, and nutrient malabsorption leading to dependency of intravenous supplementation required for

growth and health maintenance (e.g. in high-output (ileal) stoma or enterocutaneous fistula) [149-151]. Retrospective case-control studies report that early onset, family history of IBD, stricturing disease, younger age at first surgery, surgical complications and delay in diagnosis predispose towards SBS and intestinal failure in IBD [152-156].

Since SBS is accompanied by reduced intestinal surface, a biomarker is needed to diagnose clinically significant reduced intestinal mass/ intestinal function and monitor adaptation and mucosal healing. Potential biomarkers are serum citrulline (generation test) and intestinal fatty acid binding protein (I-FABP) [157-159]. Studies on biomarkers that can predict or diagnose the presence of intestinal failure/intestinal insufficiency are required.

Glucagon-like peptide-2 (GLP-2; Teduglutide) enhances structural adaptation of the small intestinal mucosa in patients with SBS [160-162]. Studies are lacking on the reparative (adaptation, mucosal healing) and immunomodulatory effects of GLP-2 in IBD patients with SBS.

Intestinal transplantation may be considered in intestinal failure as a high-risk, last option treatment. A prospective study in 20 CD patients with chronic intestinal failure who were dependent on parenteral nutrition (PN) suggested that a scoring system enables the physician to identify which patients may benefit from intestinal transplantation before PN-associated secondary organ failure develops [163]. Further work assessing which CD patients with intestinal failure receiving PN will benefit from intestinal transplantation are necessary to improve clinical and patient outcomes.

Enterocutaneous fistula can often be a serious complication of CD. Aggressive nutritional support to treat sepsis and reverse catabolic state can improve outcome [164]. Enteral nutrition for three months is an effective therapeutic strategy [165] and can prevent enterocutaneous fistula post-operatively in CD [166]. PN can also have a supportive role where enteral nutrition is compromised, but evidence is lacking on the efficacy to heal enterocutaneous fistula and other complicated fistulas in CD patients [167]. Whether EN or PN is a more effective nutritional strategy in patients with fistulizing CD needs to be further elucidated.

High-output stomas in CD are common within three weeks of ileostomy and resolve spontaneously in almost half of patients, while the remaining need ongoing treatment due to a short small-intestinal remnant. Successful treatments include hypotonic fluid restriction, oral rehydration solution, salt rich diets, exclusive enteral nutrition and/or short-term parenteral electrolytes [168-171]. Prospective research on optimal nutritional strategies to manage high-output stomas in IBD preventing dehydration and avoiding acute hospital admission (e.g. hypotonic fluid restrictions, and/or oral rehydration solutions, iv-glucose-sodium) should be compared with 'free diet'. Patient reported outcomes (e.g. quality of life) should also be considered.

Multiple factors relating to clinical, social, and economic issues contribute to lower quality of life (QOL) in patients dependent upon home PN[172]. Living with CD and intestinal failure reduces QOL and hugely impacts day-to-day living and inhibits autonomy [173], however there is limited research on QOL in CD patients with SBS.

Multidisciplinary team working is crucial for optimising the management of SBS/intestinal failure in IBD [174]. The value of the dietitian is important where available, however when not available, it is unknown whether there are failings in clinical and patient outcomes.

Research gaps

- ***New biomarkers that can predict, diagnose, monitor intestinal failure or intestinal insufficiency are needed in IBD***
- ***Nutritional treatment strategies for the management of high output stoma and intestinal failure/insufficiency in IBD need to be developed***

3.3 Supportive nutritonal therapy for functional bowel symptoms in IBD

Functional bowel symptoms include abdominal pain, bloating, increased flatulence, diarrhoea and/or constipation and affect 35% of patients with inactive IBD [175]; however, these symptoms can be mistaken for active IBD. Patients with IBD and coexisting functional bowel symptoms

also exhibit increased anxiety/depression and reduced QOL compared with patients without [176]. Clinical (symptoms) and objective (histological and inflammatory markers (e.g. faecal calprotectin, CRP)) assessment helps to distinguish between functional bowel symptoms and active IBD, although often the diagnostic validity is poor [177,178]. Identification of functional bowel symptoms in inactive IBD is of utmost importance to ensure unnecessary and potentially harmful treatment strategies are avoided, conversely presence of active IBD lesions should be excluded before determining that symptoms are functional in nature.

Similar treatment strategies as those used in irritable bowel syndrome (IBS) such as antispasmodics, antidiarrhoeals and low dose antidepressants can be used for functional bowel symptoms in IBD, however there is limited research on their safety and effectiveness in IBD. From a dietary perspective, identification of dietary triggers can be helpful [179] but is difficult to determine the culprits due to the complexity of the diet and delay of symptom generation following consumption of the food or ingredient. In IBS, alteration of dietary fibre intake can be beneficial [180,181]; however, there is limited research for functional bowel symptoms in IBD. A low (FODMAP) diet is recognized as a successful management strategy for functional bowel disorders like IBS [180,182]. FODMAPs are poorly absorbed carbohydrates that can increase small intestinal luminal water and colonic fermentation by the gastrointestinal microbiota [183-185] which, in susceptible individuals, induces functional bowel symptoms [182]. Some FODMAPs are prebiotic (e.g. fructo-oligosaccharides and galacto-oligosaccharides presumably having a beneficial effect on the gastrointestinal microbiota. In IBS, short-term FODMAP reduction correlates with reduced luminal Bifidobacterium spp. and *F. prausnitzii* [186,187] which may negatively impact the gastrointestinal microbiome. For this reason, the low FODMAP diet incorporates short-term FODMAP restriction (4-8 weeks) to induce symptom control, followed by FODMAP reintroduction using food challenges to personal tolerance. Thus, in the long-term, only high FODMAP foods that trigger symptoms are avoided maintaining long-term nutritionally adequacy [188]. Whether the gastrointestinal microbial changes seen following FODMAP restriction return to normal in the long term is unknown.

In active Crohn's disease, a RCT of FOS supplementation significantly increased the incidence and severity of abdominal symptoms compared to placebo, although it was not known if any of these patients had concomitant IBS [189]. A double-blind crossover, re-challenge RCT in

patients with inactive IBD and functional bowel symptoms who had responded to a low FODMAP diet showed that FOS, but not GOS or the polyol sorbitol, induced symptoms [190].

In a retrospective case-note review of 72 IBD patients (CD=52) who had previously received low FODMAP dietary advice, 56% reported overall symptom improvement [121]. A prospective study of the low FODMAP diet in 88 IBD patients (CD=39) showed significantly more patients reported satisfactory relief from their functional bowel symptoms at follow-up (78%) compared to baseline (16%; $p<0.001$) [191]. Abdominal pain, bloating, flatulence, belching, incomplete evacuation, nausea and heartburn also improved. Similar findings were reported when Crohn's and ulcerative colitis were sub-analysed. In a non-blinded RCT in patients with inactive IBD and functional bowel symptoms greater symptom ($p=0.02$) and QOL ($p<0.001$) improvements were reported for the low FODMAP diet (n=44) versus habitual diet (n=45) [192].

Research gaps

- ***Mechanisms of food-related functional symptoms in IBD need to be identified***
- ***Functional symptoms should be assessed after excluding inflammation, food intolerance, coeliac disease etc.***
- ***Studies are needed to demonstrate whether dietary interventions are effective and safe for the management of functional symptoms in patients with inactive IBD.***

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Conclusions

Hereby, we provide a summary of our current knowledge and emerging evidence on the broad role of diet and nutrition in the aetiology and management of IBD. The subject is topical and findings of current and future multidisciplinary research are expected to have major impact on understanding the dietary influences of CD onset and improving dietary therapies in all aspects of IBD management. We propose a list of research gaps that we anticipate to set the future research agenda in the topic of nutrition and diet in IBD.

DISCLAIMER TEXT

The ECCO Topical Review Projects are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Topical Reviews. The European Crohn's and Colitis Organisation and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in an ECCO Topical Review.

CONFLICT OF INTEREST

ECCO has diligently maintained a disclosure policy of potential conflicts of interests (CoI). The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors (ICMJE). The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but also open to public scrutiny on the ECCO website (https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html) providing a comprehensive overview of potential conflicts of interest of authors.

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