Diet fuelling inflammatory bowel diseases: preclinical and clinical concepts

Timon E Adolph, Jingwan Zhang

ABSTRACT
The diet and gut microbiota have been extensively interrogated as a fuel for gut inflammation in inflammatory bowel diseases (IBDs) in the last few years. Here, we review how specific nutrients, typically enriched in a Western diet, instigate or deteriorate experimental gut inflammation in a genetically susceptible host and we discuss microbiota-dependent and independent mechanisms. We depict the study landscape of nutritional trials in paediatric and adult IBD and delineate common grounds for dietary advice. Conclusively, the diet reflects a critical rheostat of microbial dysbiosis and gut inflammation in IBD. Dietary restriction by exclusive enteral nutrition, with or without a specific exclusion diet, is effectively treating paediatric Crohn’s disease, while adult IBD trials are less conclusive. Insights into molecular mechanisms of nutritional therapy will change the perception of IBD and will allow us to enter the era of precision nutrition. To achieve this, we discuss the need for carefully designed nutritional trials with scientific rigour comparable to medical trials, which also requires action from stake holders. Establishing evidence-based dietary therapy for IBD does not only hold promise to avoid long-term immunosuppression, but to provide a widely accessible therapy at low cost. Identification of dietary culprits disturbing gut health also bears the potential to prevent IBD and allows informed decision making in food politics.

INTRODUCTION
Inflammatory bowel diseases (IBDs) encompass a spectrum of chronic inflammatory disorders in and beyond the gut, typically referred to as Crohn’s disease (CD) or ulcerative colitis (UC). Today, these diseases emerged across the globe, which was paralleled by Westernisation of lifestyle and particularly the diet, while a specific environmental factor that would trigger or affect the course of IBD in a genetically susceptible individual remains obscure. The prevalence of IBD is expected to rise to 1% in developed and newly industrialised countries, indicating the need for a better understanding of these relapsing diseases. In the last decade, clinical studies established the efficacy and safety of immunosuppressive therapy (with biologicals and small molecules), while at the same time, the mechanistic basis of experimental diet-induced gut inflammation was increasingly delineated. A vast body of recent evidence indicates that Western dietary constituents and excess of macronutrients fuel experimental gut inflammation, by directly impacting gut mucosal immune responses or by alterations of the gut microbiota. Consequently, compositional and functional alterations of the gut microbiota, collectively termed dysbiosis, have been identified as a fuel for gut inflammation in experimental models and possibly IBD. It is notable that these disease concepts have been similarly described for obesity and related disorders. In line with this, prospective epidemiological studies indicated that obesity emerges as an independent risk factor for CD. Preclinical and translational studies indicated that energy metabolism controls gut immune responses and that excessive intake of carbohydrates and long-chain fatty acids deteriorate or instigate gut inflammation in several mouse models. In human IBD, early surgical studies from the 1990s indicated that luminal factors (potentially nutrients, microbes or related metabolites) are sufficient to evoke gut inflammation, which led to the nowadays established therapeutic concept of ileostomy. At the same time, early nutritional trials indicated that dietary therapy with exclusive enteral nutrition (EEN) (ie, enteral feeding with formula diets) effectively induces remission in paediatric and possibly adult patients with CD. Collectively, these studies led to the appreciation of the metabolic nature of IBD. In comparison to rapidly evolving medical therapies during the last two decades, nutritional trials failed to establish unequivocal evidence for dietary advice (beyond EEN) that would ameliorate the course of IBD in adults. However, evidence from recent experimental, epidemiological and nutritional trials

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The diet and host immune responses determine gut microbial composition and function.
⇒ Excessive intake of specific macronutrients enriched in a Western diet promotes experimental gut inflammation by perturbation of host–microbe commensalism.
⇒ Dysbiosis in inflammatory bowel diseases (IBDs) is fuelling experimental gut inflammation.
⇒ Clinical trials indicate that the diet affects gut inflammation in patients with IBD.

WHAT THIS STUDY ADDS
⇒ This review summarises recent experimental and clinical advances on the role of the diet in IBD

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Patient-tailored dietary advice will be a cornerstone to prevent and treat IBD in the future.
Box 1 Nutrients fuelling gut inflammation

A Western diet is enriched with simple carbohydrates (eg, fructose, sucrose) and fat (eg, long-chain fatty acids such as arachidonic acid), while being largely devoid of fibre. Moreover, a Western diet is enriched with emulsifiers and food colourants contained in processed food. Experimental evidence indicates that diets enriched with carbohydrates or fat deteriorate gut inflammation, similar to emulsifiers and food colourants. These dietary constituents either directly trigger mucosal immune responses, for example, in susceptible epithelial cells, or indirectly modulate mucosal immune responses during gut inflammation by affecting the microbiota. For example, dietary polyunsaturated fatty acids are oxidised at the endoplasmic reticulum in small intestinal epithelial cells, which triggers toll-like receptor 2 activation and an acute inflammatory response in the gut, which is restricted by cellular hubs known to be compromised in CD. Likewise, polyunsaturated fatty acids directly trigger the expression of cytokines in susceptible Crohn’s epithelium and fibroblasts. In turn, dietary restriction with an elemental diet (which may reduce an excess of Western dietary constituents) induces remission in paediatric (and possibly also adult) patients with CD. These experimental and clinical studies indicate that the diet serves as a critical fuel for gut inflammation in IBD.

EXCESSIVE INTAKE OF SPECIFIC NUTRIENTS OR ADDITIVES IN A WESTERN DIET DRIVES GUT INFLAMMATION IN PRECLINICAL MODELS

Western dietary habits are characterised by increased intake of fat and simple carbohydrates, and reduced intake of plant-derived complex carbohydrates (ie, fibre). Recent experimental evidence indicated that specific macronutrients in a Western diet deteriorate experimental gut inflammation that is induced by genetic or chemical means (box 1). Prime evidence for the concept of diet-induced immune perturbation in a genetically susceptible host was provided by Devkota and colleagues, demonstrating that milk fat exposure deteriorates colitis in mice that lack the anti-inflammatory cytokine interleukin 10 (IL10−/−), by the bloom of the gut pathobiont Bilophila wadsworthia. Subsequent studies indicated that a Western style diet impairs epithelial barrier function in mice and susceptibility to chemically induced (toxic) colitis. In line with this concept, a glucose-enriched diet deteriorated colitis in IL10−/− mice and toxic colitis, which was similarly noted for fructose and sucrose enrichment. Not only macronutrients, but also food additives typically enriched in a Western diet (and a related lifestyle) promote susceptibility to colitis. For example, supplementation of food colourants Red 40 (E129) and Yellow 6 (E110) drive colitis in mouse models in which IL-23 expression mediated gut inflammation. These colourants are contained in soft drinks, candy, sauces and dairy products. A second example for a critical role of food additives are emulsifiers which are used to stabilise food in a single phase (eg, in oil-in-water solutions such as mayonnaise or margarine). Chassaing and colleagues demonstrated that carboxymethylcellulose (E466) and polysorbate-80 (E433) promote susceptibility to colitis in IL10−/− mice. Moreover, the additive maltodextrin (E1400, a thickener used in instant pudding, gelatins, sauces and dressings) deteriorates experimental colitis in mice. Notably, in some of these experimental approaches, the gut microbiota (or its metabolites) mediated the inflammatory effects of the diet (beyond association). as also demonstrated for fungi in a mouse model of gut injury. Indeed, gut microbial dysbiosis of bacteria, fungi and viruses (bacteriophages) is a hallmark of IBD (seem the next section), which exerts pro-inflammatory functions when transplanted into genetically susceptible IL10−/− mice. In turn, an EEN formula enriched with specific prebiotics ameliorates experimental (adoptive T-cell transfer) colitis, which could be partly explained by restoration of bacterial communities.

Western dietary constituents also directly impact gut mucosal immune responses. For example, we recently demonstrated that long-chain polyunsaturated fatty acids (PUFAs), contained in red and white meat, eggs and cooking oils, trigger an inflammatory response from gut epithelial cells, which is restricted by Glutathione peroxidase 4 (GPX4). GPX4 is an evolutionary conserved antioxidative enzyme with activity towards PUFAs that protects against lipid peroxidation and related sequelae. Mice that display reduced intestinal epithelial GPX4 activity, which models the epithelium from patients with CD, develop enteritis resembling aspects of human CD when exposed to PUFAs in a Western diet. Enteritis is mediated by toll-like receptor 2 sensing of lipid peroxides (induced by ω-3 and ω-6 PUFAs), which instigates endoplasmic reticulum stress and expression of the IL-8 homologue CXCL1 in this model. Importantly, PUFA exposure evoked an inflammatory response from CD epithelium with impaired GPX4 activity and estimated PUFA intake correlated with a poor course of CD.

Collectively, these studies demonstrated that excessive intake of specific nutrients and additives in a Western diet, such as PUFAs, simple carbohydrates and food colourants, trigger or deteriorate experimental gut inflammation, by exploiting the gut microbiota, or by engaging innate immune receptors and related cellular stress signalling (figure 1). As such, a strength of these approaches is to pin down a specific dietary factor that controls gut inflammation, and to gain mechanistic insights how the diet affects gut health in a genetically susceptible host. A weakness is that the relevance of an experimental approach for human disease often remains unresolved, highlighting the need to go beyond associations, which requires nutritional trials. That this can be rewarding has been demonstrated by recent dietary intervention studies in paediatric and adult CD, which indeed provide evidence for nutritional therapy. For example, EEN with or without a specific exclusion diet (which seeks to correct Western dietary habits) potently induces disease remission in mild-to-moderate CD as outlined below. These studies thus support the concept that the diet is a central rheostat of gut inflammation in IBD. Future studies will expand the growing list of detrimental food constituents that may trigger or deteriorate gut inflammation in preclinical models, and translational efforts should be made to demonstrate a direct role for nutrients during gut inflammation in patients with IBD.

THE DIET IS A CRITICAL DETERMINANT OF GUT MICROBIAL COMPOSITION AND FUNCTION IN MICE AND HUMANS

In IBD, altered microbial signatures (of bacteria, viruses and fungi) have been consistently reported and there is little...
Recent advances in basic science

Figure 1 The Western diet impairs epithelial immune responses and promotes dysbiosis and inflammation. A Western diet is enriched with simple carbohydrates, fat (e.g., saturated and polyunsaturated fatty acids and cholesterol) and food additives (e.g., emulsifiers, food colourants, processed carbohydrates). These compounds may directly induce compositional and functional alterations of the gut microbiota, which partly impairs epithelial functions in the gut, that is, perturbs Paneth cells and the gut barrier. Consequently, a dysbiotic microbiota promotes susceptibility to gut inflammation by perturbation of host–microbe interactions. Polyunsaturated fatty acids in a Western diet trigger acute enteritis in mice without evidence for gut microbial dysbiosis, which is rather controlled by epithelial endoplasmic reticulum homeostasis (maintained by X-box-binding protein 1 and Glutathione peroxidase 4). Cholesterol exposure induces an acute inflammatory response involving neutrophils in the gut of mice, possibly by inflammasome sensing. GPX4, Glutathione peroxidase 4; IL, interleukin; XBP1, X-box-binding protein 1.

Carbohydrates

Carbohydrates are generally classified as digestible and non-digestible and are contained in a wide range of food items. Digestible carbohydrates can be enzymatically degraded into simple sugars that are largely absorbed in the small intestine and passed into the bloodstream through the portal vein. Non-digestible carbohydrates, for example, fibre and resistant starch, are not absorbed in the small intestine but undergo fermentation...
in the large intestine by resident microorganisms, which provide
the host with an energy and carbon source.64 65 Experimental
approaches demonstrated that excessive intake of simple carbo-
hydrates promoted dysbiosis and gut inflammation (see above).
However, the role of excessive simple carbohydrates in the
development or course of IBD is poorly explored. In contrast,
complex carbohydrates (typically derived from vegetables), and
their bacterial metabolites, rather exert a protective effect. For
example, bacterial short chain fatty acid (SCFA) generation such
as butyrate (through fermentation of complex carbohydrates)
allows to maintain gut homeostasis86 by protecting intestinal
barrier integrity and host immune responses. For example,
SCFAs stabilise HIF-1,67 a transcription factor coordinating
barrier protection68 and supplementation of butyrate-producing
bacteria, especially Butyrococcus pullicaecorum, improved
epithelial barrier integrity in CD based on simulations.69 More-
over, butyrate also exerts anti-inflammatory effects in the gut
mucosa by inhibition of histone deacetylases and activation
of G protein-coupled receptors present in gut epithelium and
mucosal immune cells.70 71 Low fibre intake has been associ-
bated with increased IBD risk,72–74 and patients with IBD show
a decrease in butyrate producing bacterial species, as well as a
decreased expression of butyrate transporters.75–77 A reduction
of butyrate-producing bacteria and the dietary substrate for
SCFA generation in patients with IBD may lead to loss of an anti-
inflammatory ‘break’ in the gut. In turn, it appears plausible that
butyrate supplementation ameliorates the course of IBD, which
is currently probed by several clinical trials with butyrate in IBD.

Food additives
Food additives preserve a food product (in terms of safety, fresh-
ness, texture or appearance) or enhance the taste of processed
food. Emerging evidence indicates that the consumption of
food additives perturbs microbial composition and promotes
experimental gut inflammation (also see the above section).
For example, artificial sweeteners such as saccharin promote
dysbiosis in mice (with increased Bacteroides and reduced Lacto-
 bacillus spp),92 which was similarly notable in humans.93 The
sweetener Splenda deteriorated experimental gut inflammation
in SAMP1/YitFcs (SAMP) mice, which was accompanied by over-
growth of Proteobacteria and Escherichia coli.94 Likewise, emul-
sifiers perturb gut microbial community structure and promote
susceptibility to gut inflammation, with increased abundance of
Porphyromonadaceae spp in faeces of P80 fed mice.95 Emulsi-
fier also evoked alterations of the gut microbiota in humans.96
Moreover, titanium dioxide, usually used as a white powder
of different particle sizes (E171) in candies, sweets, pastries
and sugar-coated chewing gums, impairs gut permeability and
potentially promotes gut inflammation as excellently reviewed
recently.97 Finally, food colourants Red40 (E129) and Yellow
6 (E110) drive colitis in mouse models with IL-23 expression,
as well as mediated by metabolism of these colourants in
commensals (Bacteroides ovatus and Enterococcus faecalis).98
The role of food additives on the development or course of
human IBD is poorly explored. However, it is conceivable that
additives contribute to dysbiosis in human IBD which may act as
a fuel for gut inflammation.

Collectively, excessive intake of specific food constituents in a
Western diet may be a potent trigger of gut dysbiosis in humans
(e.g., by increased intake of calories derived from fat, digestible
carbohydrates, animal protein and food additives), and IBD-
associated dysbiosis exerts inflammatory functions in genetically
susceptible mice. However, several aspects are poorly resolved in
this context. For example, what is the specific impact of blooming
pathobionts or loss of symbionts in human IBD and can this be
therapeutically exploited? Critical mechanistic insights are prob-
bly best exemplified by studies on adherent invasive E. coli.99
Moreover, current human studies rarely delineate, which genetic
susceptibility is required to elicit diet-induced gut inflammation,
with or without dysbiosis, in patients at risk for IBD.100 And
finally, other environmental influences (possibly also in early
life) impact gut microbial functions,97 such that the diet emerges
as one, but not sole rhostate of dysbiosis in IBD. Despite these
unresolved issues it was conceived that a specific dietary pattern
could be used to reverse microbial perturbation and to amelio-
rate gut inflammation in IBD, which has been explored by recent
dietary intervention trials.

Fat
Human studies indicated that a high-fat diet increases anaer-
obic abundance of, for example, Bacteroides.78 79 Fifteen clin-
ic studies (including six randomised controlled interventional
studies and nine observational studies) have shown that total
fat or saturated fat suppressed richness and diversity of the gut
microbiota.80 As such, it is conceived that a high-fat Western
diet is a key driver of gut dysbiosis,81 82 which may promote gut
inflammation as evidenced by studies in humanised mice.82 The
impact of specific bacterial strains (blooming during Western
dietary habits) on gut inflammation in IBD requires further
studies.

Protein
Dietary proteins are derived from plants and animals. Several
culture-based studies demonstrated that consumption of whey
and pea protein extracts facilitates growth of Bifidobacterium
and Lactobacillus, while whey impairs abundance of Bacteroides
fragilis and Clostridium perfringens in humans.83–85 The essential
amino acid tryptophan (in dietary protein), which is catabolised
by the colonic gut microbiota, controls bacterial communities
and the gut immune system (through aryl hydrocarbon receptor
signalling).86 In contrast to plant-based protein, the abundance
of bile-tolerant anaerobes such as Bacteroides, Alistipes and
Bilophila increased following consumption of animal-based
protein.87–89 Animal-based protein enhanced the sensitivity to
experimental gut inflammation possibly by expansion of rather
inflammatory strains such as Escherichia, Streptococcus and
Enterococcus.90 In line with this notion, replacement of animal
protein with plant protein in a Western diet protected against
experimental gut inflammation characterised by an increased
Lactobacillaceae and Leuconostaceae abundance.91 In IBD,
the role of dietary protein (and related microbial alterations)
appears unresolved.

Dietary interventions in IBD
Experimental, translational and clinical evidence suggest
that IBD arises from unresolved perturbation of mucosal immune
responses that is determined by genetic variation and the
exposome (including the diet and gut microbiota). This
concept implies that a variety of cues, rather than a single inci-
dent, promotes the development of chronic unresolved gut
inflammation, which may explain heterogenous results of key
dietary intervention trials (and medical trials alike), which are
summarised in table 1.100 As such, recent guidelines explicitly
state that there is no ‘IBD diet’ that can be generally recom-
mended to induce or maintain remission in patients with IBD.101
However, affected individuals suspect a critical role of the diet
for their disease.102 In line with this, a specific Western dietary

Adolph TE, Zhang J. Gut 2022;71:2574–2586. doi:10.1136/gutjnl-2021-326575
2577
## Table 1  Characteristics of key nutritional trials in IBD

| Inclusion of disease entity | Number of patients | Dietary intervention | Groups | Duration | Results of the main end-point(s) | References |
|-----------------------------|--------------------|----------------------|--------|----------|---------------------------------|------------|
| **Exclusive enteral nutrition (EEN)** | | | | | | |
| Paediatric CD cases (age 3–17 years) with weighted Paediatric CD Activity Index score (wPCDAI) >40 | 100 paediatric CD | Group1: FL-IFX; Five infusions of 5mg/kg IFX. Group2: Conventional: EEN or Oral prednisolone (1mg/kg, maximum 40mg) | Group1: 50 Group2: 50 | 52 weeks | FL-IFX was superior to conventional treatment in achieving short-term clinical and endoscopic remission, and had greater likelihood of maintaining clinical remission | Jongsma et al\(^{13}\) |
| Children with new diagnosis CD | 26 paediatric CD | EEN | – | 6 weeks | EEN is effective for inducing early clinical, biochemical, mucosal and transmural remission. Early endoscopic remission improves outcomes at 1 year. | Grover et al\(^{14}\) |
| **New-onset active CD (aged 6–17 years) with Harvey-Bradshaw Index (HBI) >5** | 19 paediatric CD | Group1: CS Group2: EEN | Group1: 6 Group2: 13 | 8 weeks | Both steroid and EEN induced clinical remission. Patients with EEN-induced remission showed a higher rate of mucosal healing and this was associated with a different gut microbiota compositional shift in these children. | Pigneur et al\(^{15}\) |
| Paediatric CD cases with a paediatric Crohn’s Disease Activity Index (PCDAI) >20 | 50 paediatric CD | Group1: 50% PEN with unrestricted diet. Group2: 100% TEN | Group1: 26 Group2: 24 | 6 weeks | TEN suppresses inflammation in active Crohn’s disease but PEN does not. | Johnson et al\(^{17}\) |
| **The Crohn’s disease and ulcerative colitis exclusion diet (CDED/UCED)** | | | | | | |
| Paediatric CD cases with active disease (Paediatric Crohn’s Disease Activity Index >7.5 or Harvey-Bradshaw Index >5) | 37 paediatric CD | CDED | – | 6 weeks | Dietary therapy involving PEN with an exclusion diet lead to high remission rates in early mild-to-moderate luminal Crohn’s disease in children and young adults. | Sigali-Boneh et al\(^{28}\) |
| Children with mild to moderate CD | 72 paediatric CD | Group1: CDED plus 50% of calories from formula for 6 weeks followed by CDED with 25% PEN for another 6 weeks. Group2: EEN for 6 weeks followed by a free diet with 25% PEN for another 6 weeks | Group1: 40 Group2: 38 | 12 weeks | CDED plus PEN was better tolerated than EEN in children with mild-to moderate CD. The combination CDED plus PEN induced sustained remission in a significantly higher proportion of patients than EEN, and produced changes in the faecal microbiome associated with remission. | Levine et al\(^{41}\) |
| Adult patients with CD (aged 18–55 years) with mild-to moderate CD (defined by a Harvey-Bradshaw Index score of 5–15 points) | 44 adult CD | Group1: CDED plus PEN Group2: CDED alone | Group1: 20 Group2: 24 | 24 weeks | 68% of patients treated with CDED plus partial enteral nutrition achieved clinical remission, which was also achieved in 57% of patients with CDED alone. | Yanai et al\(^{16}\) |
| Adult patients with active UC (Simple Clinical Crohn’s Disease Activity Index (SCCAI) of ≥5 and ≤11 and endoscopic Mayo score 2–3) | 51 adult UC | Group1: Free diet plus FT. Group2: FT with dietary pre-conditioning of the donor for 14 days and a UCED. Group3: UCED alone | Group1: 17 Group2: 19 Group3: 15 | 8 weeks | UCED alone appeared to achieve higher clinical remission and mucosal healing than single donor FT with or without diet. | Sarbagli Shabat et al\(^{41}\) |
| Children diagnosed with CD | 61 paediatric CD | Group1: CDED plus PEN (80% with prior 1–2 weeks of EEN) Group2: EEN | Group1: 20 Group2: 41 | 6–8 weeks | Treatment with CDED w PEN (with prior 1–2 weeks of EEN) has comparable efficacy to EEN therapy alone in inducing remission in children with CD, and it leads to better weight gain. | Niseteo et al\(^{33}\) |
| Patients with CD with loss of response (LoR) to biologics | 21 CD (11 adults and 10 children) | Partial enteral nutrition (PEN)+CDED (severe paediatric patients received prior 14 days of EEN) | – | 12 weeks | Dietary treatment combining PEN w CDED may be a useful salvage regimen for patients failing biological therapy despite dose escalation. | Sigall Boneh et al\(^{17}\) |
| **The specific carbohydrate diet (SCD)** | | | | | | |
| Paediatric patients (aged 10–17 years) with mild to moderate IBD defined by Paediatric Crohn’s Disease Activity Index (PCDAI 10–45) or Paediatric Ulcerative Colitis Activity Index (PUCAI 10–65) | 12 paediatric IBD | SCD | – | 12 weeks | SCD therapy in IBD is associated with clinical and laboratory improvements as well as concomitant changes in the faecal microbiome. | Suskind et al\(^{36}\) |

*Continued*
Recent advances in basic science

Table 1  Continued

| Inclusion of disease entity | Number of patients | Dietary intervention | Groups | Duration | Results of the main end-point(s) | References |
|----------------------------|--------------------|----------------------|--------|----------|-----------------------------------|------------|
| Patients with IBD in remission | 58 CD and 84 UC | MD | – | 6 months | A reduction of malnutrition-related parameters and liver steatosis in patients with IBD after MD, which associated with a spontaneous improvement of disease activity and inflammatory markers. | Chicco et al 138 |
| Adult patients with CD with mild-to-moderate symptoms | 197 adult CD | Group1: SCD Group2: MD | Group1: 101 Group2: 96 | 12 weeks | The SCD was not superior to the MD to achieve symptomatic remission, FC response, and CRP response. Given these results, the greater ease of following the MD and other health benefits associated with the MD, the MD may be preferred to the SCD for most patients with CD with mild to moderate symptoms. | Lewis et al 142 |

The low FODMAP diet (LFD)

| Number of patients | Dietary intervention | Groups | Duration | Results of the main end-point(s) | References |
|--------------------|----------------------|--------|----------|-----------------------------------|------------|
| IBD in remission or with mild-to-moderate disease and coexisting IBS-like symptoms (Rome III) | 28 CD and 61 UC | Group1: LFD Group2: ND | Group1: 44 Group2: 45 | 6 weeks | A low-FODMAP diet reduced IBS-like symptoms and increased quality of life in patients with IBD in remission. | Pedersen et al 143 |
| IBD in remission or with mild disease activity | 35 CD and 20 UC | Group1: LFD Group2: SD | Group1: 26 Group2: 29 | 6 weeks | LFD is safe for patients with IBD, and is associated with an amelioration of faecal inflammatory markers and quality of life | Bodini et al 144 |

The gluten-free diet (GFD)

| Number of patients | Dietary intervention | Groups | Duration | Results of the main end-point(s) | References |
|--------------------|----------------------|--------|----------|-----------------------------------|------------|
| Patients with IBD | 106 patients with IBD | Group1: GFD Group2: VD | Group1: 54 Group2: 52 | – | No relevant impact of a specific diet on the course of the disease, but a significant association with lower psychological well-being in patients with VD and GFD. | Schreiner et al 145 |

This table summarises key aspects of recent nutritional trials in IBD. CD, Crohn’s disease; CS, corticosteroid; FC, faecal calprotectin; FL, first-line treatment; FT, faecal transplantation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IFX, infliximab; ND, normal diet; PEN, partial enteral nutrition; SD, standard diet; TEN, total enteral nutrition; UC, ulcerative colitis; VD, vegetarian.

pattern (characterised by consumption of grain products, oils, potatoes, processed meat, condiments and sauces, and sugar, cakes and confectionery) was associated with the risk for developing a UC flare during an observational period of 2 years in 427 patients that were in remission at study inclusion.103 In turn, EEN (which replaces solid food with a liquid elemental diet) is effective in paediatric (and possibly adult) CD, which is however difficult to adhere (see below). In contrast to the notion that the diet may act as a fuel for gut inflammation in IBD, unequivocal evidence indicates that malnutrition (usually alluding to energy and/or nutrient deficiency consequent to gut inflammation) commonly affects patients with IBD and comes along with increased mortality,104 and thus should be treated.101 In this chapter, we critically review which and how nutritional approaches could ameliorate the course of IBD. Notably, diverse nutritional approaches make studies difficult to compare, and nutritional trials suffer from inadequate power with risk for bias, as summarised in a 2019 Cochrane review.105 Therefore, interpretation of many dietary intervention studies (and comparisons between them) must be made with caution, as discussed below.

Exclusive enteral nutrition

EEN takes advantage of an elemental (liquid) diet that meets all nutritional demands of macronutrients and micronutrients and thus allows replacing (solid) dietary habits. There are plenty of formulas available, which greatly vary in their composition of macronutrients and micronutrients.106 These formulas usually provide protein derived from whey and casein, simple carbohydrates from sucrose, maltodextrin or glucose syrup and fat from sunflower, soybean or fish oil, and they contain a range of food additives. In contrast, all formulas lack lactose and gluten and most of them lack fibre (complex carbohydrates). These formulas most significantly reduce energy intake derived from long-chain (saturated) fatty acids (when compared with dietary habits in the UK),106 which likely confers some of its efficacy.107 In this context, it appears notable that formulas contain a variable degree of monounsaturated fatty acid and PUFA enrichment.106

EEN is the recommended first-line therapy in children and adolescents with active (luminal) mild-to-moderate CD that is usually used for 6–8 weeks,108–110 with arguably comparable efficacy compared with corticosteroids.111 112 Efficacy between formula diets in mild-to-moderate CD appears comparable,106 while head-to-head trials are lacking. In contrast, there appears to be little therapeutic value in paediatric patients with severe CD.111 Notably, EEN can induce mucosal healing in mild-to-moderate CD (probably in ~50% of responders),114 which reflects a primary goal in medical trials.115 Monotherapy with maintenance enteral nutrition (ie, at least 50% of daily energy is derived from the formula diet) can prolong remission in paediatric CD.109 Indeed, mild small intestinal disease has the strongest predictive value of therapeutic response.116 EEN comprehensively impairs gut microbial diversity but increased its functional capacity,117 which appeared reversible after a switch to a standard diet.118 Notably, the microbiome and metabolome of responders to EEN differs from that of non-responders,
Recent advances in basic science

Recent advances in basic science suggest the existence of a bacterial metabolic signature in some patients with CD. As such, the mode of action of EEN could involve anti-inflammatory functions of the gut microbiota, a mere reduction of (dietary or microbial) antigen load or a reduction of nutrient-induced immune responses. In contrast to a plethora of paediatric CD studies, little is known about the therapeutic efficacy of EEN in patients with UC. In adult patients with mild-to-moderate active CD, only few small studies suggest efficacy of EEN, which may nevertheless be recommended as an alternative to corticosteroids. For example, a randomised enteral nutrition trial in 55 adult patients with CD from Germany (published in 1991), demonstrated that an oligopeptide diet via nasogastric tube effectively induced clinical remission in 55% of patients in more and less severe disease (stratification by Crohn’s Disease Activity Index >300) after 6 weeks. This was however, less effective than corticosteroid and sulfasalazine therapy which induced clinical remission in 78% of patients with CD. Reduced efficacy of formula feed in adult IBD could generally be explained by impaired compliance (study discontinuation: ~40%) due to poor palatability or a distinct disease biology when compared with paediatric patients. Generally, EEN may induce mucosal healing and a clinical response in adult CD, which however could be confounded by co-medication, compliance issues and the lack of a placebo control (or study blinding). As such, these studies suggest that EEN improves gut inflammation in some adults with CD, the quality of evidence arguing for EEN is poor and prone to bias, which is why the routine use in adults is debated. This is also reflected by the fact that EEN in adult IBD is poorly depicted in current international consensus guidelines.

The Crohn’s disease and ulcerative colitis exclusion diet (CDED/UCED)

A study in paediatric CD published in 2006 indicated that unrestricted partial enteral nutrition in combination with an elemental formula was less effective in inducing remission than EEN. Thus, it was conceived that a specific exclusion diet, which reduces or eliminates potentially detrimental food items (based on experimental evidence), would allow partial enteral nutrition that increases compliance with long-term dietary advice. Indeed, this concept is superior in Israeli and Canadian children with CD when compared with EEN. In this prospective study with 78 mild-to-moderate paediatric patients with CD, an elemental formula provided 50% of calories, while dietary advice with restriction of Western food items (to reduce an excess of animal fat, deep fried and processed food, dairy, emulsifiers, artificial sweeteners, soft drinks and wheat) provided the rest of calories in the first 6 weeks. This CDED then served as dietary maintenance therapy (with 25% of calories from an elemental formula) for another 6 weeks. CDED with partial enteral nutrition (with an elemental formula) was better tolerated and more effective after 12 weeks when compared with EEN for 6 weeks (followed by a free diet with

Figure 2 The diet and gut microbiota perturb immune responses in IBD. Dietary constituents such as macronutrients and food additives have been shown to affect the gut microbiota in humans. Diet-induced alterations of the gut microbiota may exert diverse effects on gut mucosal immune responses and IBD-associated dysbiosis promotes gut inflammation in preclinical models, partly by loss of production of beneficial microbial metabolites, such as SCFAs and indole derivatives. In addition, the bloom of certain pathobionts may impair the epithelial barrier and stimulate a proinflammatory environment. AhR, arylhydrocarbon receptor; BA, bile acid; ER, endoplasmic reticulum; H2S, hydrogen sulfide; IBD, inflammatory bowel diseases; IL, interleukin; SCFAs, short chain fatty acid.

suggesting the existence of a bacterial metabolic signature in some patients with CD. As such, the mode of action of EEN could involve anti-inflammatory functions of the gut microbiota, a mere reduction of (dietary or microbial) antigen load or a reduction of nutrient-induced immune responses. In contrast to a plethora of paediatric CD studies, little is known about the therapeutic efficacy of EEN in patients with UC. In adult patients with mild-to-moderate active CD, only few small studies suggest efficacy of EEN, which may nevertheless be recommended as an alternative to corticosteroids. For example, a randomised enteral nutrition trial in 55 adult patients with CD from Germany (published in 1991), demonstrated that an oligopeptide diet via nasogastric tube effectively induced clinical remission in 55% of patients in more and less severe disease (stratification by Crohn’s Disease Activity Index >300) after 6 weeks. This was however, less effective than corticosteroid and sulfasalazine therapy which induced clinical remission in 78% of patients with CD. Reduced efficacy of formula feed in adult IBD could generally be explained by impaired compliance (study discontinuation: ~40%) due to poor palatability or a distinct disease biology when compared with paediatric patients. Generally, EEN may induce mucosal healing and a clinical response in adult CD, which however could be confounded by co-medication, compliance issues and the lack of a placebo control (or study blinding). As such, these studies suggest that EEN improves gut inflammation in some adults with CD, the quality of evidence arguing for EEN is poor and prone to bias, which is why the routine use in adults is debated. This is also reflected by the fact that EEN in adult IBD is poorly depicted in current international consensus guidelines.

The Crohn’s disease and ulcerative colitis exclusion diet (CDED/UCED)

A study in paediatric CD published in 2006 indicated that unrestricted partial enteral nutrition in combination with an elemental formula was less effective in inducing remission than EEN. Thus, it was conceived that a specific exclusion diet, which reduces or eliminates potentially detrimental food items (based on experimental evidence), would allow partial enteral nutrition that increases compliance with long-term dietary advice. Indeed, this concept is superior in Israeli and Canadian children with CD when compared with EEN. In this prospective study with 78 mild-to-moderate paediatric patients with CD, an elemental formula provided 50% of calories, while dietary advice with restriction of Western food items (to reduce an excess of animal fat, deep fried and processed food, dairy, emulsifiers, artificial sweeteners, soft drinks and wheat) provided the rest of calories in the first 6 weeks. This CDED then served as dietary maintenance therapy (with 25% of calories from an elemental formula) for another 6 weeks. CDED with partial enteral nutrition (with an elemental formula) was better tolerated and more effective after 12 weeks when compared with EEN for 6 weeks (followed by a free diet with
were allocated to receive either CDED plus an elemental
time.130 These studies indicate that CDED may be recommended
35% of patients with CD achieved endoscopic remission at that
was maintained up to 24 weeks in 80% of the ‘responders’, and
57% of patients with CDED alone. Notably, clinical remission
formula achieved clinical remission, which was also achieved in
weeks that 68% of patients treated with CDED and an elemental
dietary counselling that recommended enrichment of fruits and
biota transplantation could be effective. The UCED required
tigated whether an exclusion diet with or without faecal micro-
and possibly malnutrition, complications that may be over-
line the importance of dietary guidance by specialised dietitians
long-term efficacy. This is notable because such restrictive diets
considered to promote poor or disordered eating behaviour and
possibly malnutrition, complications that may be over-
looked in the reported short-term studies. These caveats under-
the importance of dietary guidance by specialised dietitians
to avoid harm.121 Notably, it is also unclear whether these diets
are helpful for maintenance of remission.
In active mild-to-moderate UC patients that were refractory
to therapy (ie, aminosalicylates, corticosteroids, azathioprine or
anti-tumour necrosis factor antibodies), a blinded, randomised,
controlled trial with 62 participants from Israel and Italy inves-
tigated whether an exclusion diet with or without faecal micro-
bacteria transplantation could be effective. The UCED required
dietary counselling that recommended enrichment of fruits and
vegetables and disallowed Western dietary habits (eg, intake of
processed or ready-made food and twice a weak chicken breast
or fish). The study was terminated early because the primary
hypothesis that such a dietary approach would be beneficial in
combination with faecal microbiota transplantation was rejected.
However, the restriction diet alone induced clinical remission in
40% and endoscopic remission in 26% of patients at week 8
in this therapy refractory cohort,41 providing a basis for future
nutritional studies in UC.

Collectively, these early clinical trials provide evidence that
the diet impacts gut inflammation in mild-to-moderate CD and
UC, and real-world experience suggested that dietary approaches
are efficacious beyond clinical trials.131 The strengths of dietary
therapy would be the easy access across the world, the low cost
(probably 10%–30% compared with biologics in the first year)
and, most importantly, avoidance of immunosuppression. Nutri-
tional trials are also informative as they potentially allow to
identify culprits of gut inflammation in IBD, as exemplified by
reintroduction of meat and cereals which was associated with
increased faecal calprotectin concentration after EEN in paedi-
atriac CD.132 Moreover, dietary approaches bear the potential to
treat patients in whom biological therapies fail.133 Despite these
observations, conclusive large clinical trials that would corrobo-
rate these concepts to establish evidence for an efficacious IBD
diet are lacking. This approach is of utmost importance because
published clinical trials are statistically underpowered (due to
small cohort sizes), and they often lack a relevant comparator
(eg, dietary counselling according to national guidelines). More-
over, current studies can neither depict nor delineate the hetero-
geneous response towards a restrictive diet in patients with IBD.
As such early nutritional trials did not identify or resolve indi-
vidual differences or disease phenotypes, which is required to
approach the era of personalised nutrition. This may be partly
explained by the lack of resources that are needed to execute
studies that can compare with sponsored medical trials. Current
studies also did not address whether more severe or complicat-
disease phenotypes would benefit from nutritional therapy
 beyound correction of malnutrition), and whether a combination
with medical therapy is beneficial. Finally, adherence to nutri-
tional counselling must be evaluated to control for the bias of
non-compliance, which can be frequently observed in daily prac-
tice and clinical trials alike.134 Overcoming these limitations will
lead to evidence-based targeted nutritional therapies in IBD.

The specific carbohydrate diet (SCD)
SCD is a restrictive grain-free diet which claims to maintain
remission in patients with IBD. The diet allows digestible mono-
saccharide carbohydrates, which are made of a single molecule

| Table 2 | Proposed common ground for dietary therapy in CD and UC |
|---------|--------------------------------------------------------|
| **Rationale** | **Recommendation** |
| **Disallow** | | |
| Artificial sweetener (saccharine, splenda) | Experimentally promoting gut inflammation,17–20 altering human gut microbiota,10 restriction in nutritional trials19–44 | Stop ultra-processed, ready-made or canned food, sweets, soft drinks |
| Emulsifiers (P80, CMC) | Experimentally promoting gut inflammation,21–25 altering human gut microbiota,26 restriction in nutritional trials19–44 | Stop ultra-processed, ready-made or canned food, sweets, soft drinks |
| Food colourants (Red 40/E129, Yellow 6/E110) | Experimentally promoting gut inflammation,17–20 restriction in nutritional trials19–44 | Stop ultra-processed, ready-made or canned food, sweets, soft drinks |
| Ultra-processed food | Experimentally promoting gut inflammation (see additives above), restriction in nutritional trials19–44 | Stop ultra-processed, ready-made or canned food, sweets, soft drinks |
| **Restrict** | | |
| Saturated and polyunsaturated fatty acids | Experimentally promoting gut inflammation,17–20 restriction in nutritional trials19–44 | Restrict animal fat (regardless of source), deep fried and ultra-processed food |
| Sucrose, Glucose, Fructose | Experimentally promoting gut inflammation,17–20 restriction in nutritional trials19–44 | Restrict soft drinks, sweets, ready-made food |
| **Enrich** | | |
| Plant-based food items (fibre source) | Enrichment in nutritional trials19–44 | Encourage plant-based diet |

Note that the efficacy and safety of the proposed dietary alterations requires corroboration by controlled nutritional trials in patients with IBD. CD, Crohn’s disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.
and easily to be broken down without enzyme participation, for instance contained in fruits, nuts, eggs, most (non-starchy) vegetables, non-process meat and fish, while complex carbohydrates derived from grains, corn, milk and cream and artificial sweeteners are restricted. In a survey of 50 quiescent IBD subjects who employed an SCD for 10 months, complete symptom resolution by self-report appeared to be 66%. A study conducted with 12 paediatric patients with mild to moderate CD or UC subjected to an SCD diet demonstrated clinical improvement after 12 weeks, while two patients were unresponsive and two discontinued due to poor diet adherence. A distinctive dysbiosis for each individual in most pre-diet microbiomes ending in significant changes in microbiota composition after dietary switch. However, changes were not consistent in all patients. Besides these inconclusive studies, it was also hypothesised that an SCD could be efficacious from an observational point of view, since no evidence today, an SCD should not be recommended for patients with IBD.

### Table 3 Potential inflammatory nutrients in elemental diets

| Remove or reduce | Rationale |
|------------------|-----------|
| Milk fat         | Experimentally promoting gut inflammation |27 |
| Fish oil         | Experimentally promoting gut inflammation |36 |
| Soybean oil      | Experimentally promoting gut inflammation |36 |
| High omega-3 or omega-6 PUFA oil | Experimentally promoting gut inflammation |36 |
| Maltodextrin     | Experimentally promoting gut inflammation |34 |

### Enrich

- **Fibre (eg, inulin and fructoooligosaccharides)**: Experimental and clinical evidence |87 |
- **Plant-based protein**: Experimental evidence, human gut microbiota modulation |67 |
- **Olive oil**: Experimental evidence |133 154 |

Elemental diets (formula feed) contain potentially inflammatory nutrients indicated by experimental studies. These studies suggest to restrict or enrich specific food constituents to improve efficacy. Note that an elemental diet should be used in conjunction with counselling by nutritionists and that the efficacy and safety of the proposed regimens require corroboration by controlled nutritional trials in patients with IBD. IBD: inflammatory bowel disease; PUFA, polyunsaturated fatty acid.

## The Mediterranean diet

The MD is rich in arguably healthy foods including vegetables, fruits, legumes, cereals, fish and unsaturated fats. Results from clinical and translational research on the MD point towards a use in managing IBD. In a prospective Italian study comprising 84 patients with UC and 58 patients with CD in remission, all participants were counselled to adhere to an MD and disease was evaluated after 6 months by clinical and biochemical means. Quality of life improved for patients with CD and UC after 6 months, and patients appeared to have a reduced risk for a disease flare (concomitant to conventional medical therapy). In the DINE-CD study, 40% of patients with mild-to-moderate adult CD demonstrated clinical remission after 6 and 12 weeks (with little impact on biochemical inflammatory parameters), suggesting that an MD could be effective in some patients. Close adherence to an MD is associated with high level of beneficial **Prevotella** and fibre-degrading **Firmicutes**. The MD may be recommended for patients with IBD in remission, partly because of lack of evidence-based alternatives and a well-documented effect on cardiovascular disease, non-alcoholic fatty liver disease and depression. More clinical evidence should corroborate efficacy, safety and adherence in comparison to more stringent exclusion diets during active disease and remission to express this dietary recommendation with confidence.

### The low FODMAP diet (LFD)

Fermentable oligosaccharides, disaccharides, monosaccharides and polys (FODMAPs) are short-chain carbohydrates contained in wheat, onion, cabbage, legumes and stone fruits that are poorly absorbed in the small intestine. A diet low in these fermentable carbohydrates is called an LFD. In 89 adult patients with IBD (28 CD, 61 UC) in remission or with mild-to-moderate disease, a randomised low FODMAP trial (vs a standard diet) for 6 weeks resulted in significant improvement in terms of quality of life and reduction of symptoms of concomitant irritable bowel syndrome. A similar prospective study with 55 IBD subjects (35 CD, 20 UC) demonstrated that an LFD reduced clinical disease activity in patients with mild disease (or in remission) when compared with a standard diet after 6 weeks. In a study with 9 patients with CD in remission, an LFD affected gastrointestinal symptoms and increased relative abundance of butyrate-producing **Clostridium** cluster XIVa and mucus-associated **Akkermansia muciniphila**. An LFD is currently recommended for patients with irritable bowel syndrome, but not for active IBD. Further clinical trials are needed to establish a clinical efficacy of an LFD to control gut inflammation in IBD.

### The gluten-free diet (GFD)

A GFD excludes all food items containing gluten, which is contained in wheat (and derivatives), barley, rye, triticale and brewer’s yeast, so that pasta, baked goods and beer (with other nuances) must be excluded from the diet. A cross-sectional questionnaire study with 1647 patients with IBD (with 0.6% concomitant coeliac disease or gluten-sensitivity) indicated that 20% have tried a GFD and that 66% of patients reported clinical improvement and 38% reported less flares. In contrast, a large prospective study involving 1254 patients with IBD in Switzerland reported no significant differences between patients who followed a GFD and those who did not, with regards to disease activity, complications, hospitalisation and surgery rates. A GFD is not recommended for patients with IBD.
CONCLUSION AND FUTURE DIRECTIONS

Preclinical and clinical studies from the last years demonstrated that the diet is a rheostat of microbial composition and function and may evoke dysbiosis, as exemplified by a human Western diet.\textsuperscript{34} Prime examples demonstrated that a specific dietary constituent triggers or deteriorates experimental gut inflammation in the context of genetic susceptibility, which is partly explained by gut microbial dysbiosis.\textsuperscript{23, 30, 31, 38} Likewise, a dysbiotic microbiota from patients with IBD is fuelling an inflammatory response in the gut of mice.\textsuperscript{34} These studies collectively indicate that the diet and IBD-associated gut dysbiosis are tightly interrelated and control mucosal homeostasis by complex and context-specific immunomodulation through specific dietary constituents, microbial antigens or metabolites. In such a context, heterogeneity of human IBD is not only related to genetic variation but also to a variable exposome (eg, the diet and gut microbiota) (figure 2). Nutritional trials in mild-to-moderate paediatric CD indicate that the diet is fuelling gut inflammation, because EEN with or without an exclusion diet (restricting Western dietary habits) effectively induces remission and allows mucosal healing in a substantial proportion of paediatric patients with CD, which arguably exhibits a comparable efficacy as immunosuppressive therapy. However, carefully designed nutritional studies of reasonable size, comparable to medical trials, are needed to disentangle disease heterogeneity and efficacy of nutritional therapy in adults with IBD, to overcome the limitations of dietary intervention studies of today. We propose a concept how to improve EEN formulas and the exclusion diet in CD and UC, which is largely based on preclinical evidence (tables 2 and 3). For example, elemental diets contain a range of food additives and they are largely deprived from fibre, both of which is known to compromise the gut microbiota and gut health.\textsuperscript{106, 146} Moreover, elemental diets provide simple carbohydrates from sucrose and fat from fish oil, which demonstrated detrimental effects in mouse models of gut inflammation.\textsuperscript{25, 36, 38, 106} These observations indicate the potential of basic research as a guide for novel nutritional concepts, which should be considered in the design of EEN formulas and future nutritional trials. While animal models imperfectly depict the complexity of our diet for gut health, they allow to study host–microbe interactions and related immune responses. Although difficult to translate, this approach will be rewarding, as only mechanistic insights in mammals allows to disentangle complex host–microbe interactions (shaped by the diet) that deserve to be exploited in controlled nutritional trials. Understanding the intricate interplay between the host and its commensals, and delineating the impact of specific dietary factors on this interplay, will also set the ground for our phenotypic understanding of heterogeneous IBDS and at the same time bears the potential to prevent IBD as it would allow informed decision making in food politics. And refinement and corroboration of existing dietary therapy in IBD harbours the potential to avoid immunosuppressive treatment (with related side effects and costs). When compared with coeliac disease, it appears unlikely that one diet suits most patients, which is another reason to perform large scale nutritional trials to specifically define disease phenotypes (or traits) that are responsive to nutritional therapy. Thus, future nutritional trials should not only evaluate long-term efficacy, safety and dietary adherence to overcome limitations of EEN (eg, poor palatability), but also establish quantitative and reproducible tools beyond dietary questionnaires to allow monitoring of food intake that are not prone to recall bias, such as blood and stool metabolomics. Advances in this field will change the perception of IBD, and will allow identification of nutritional phenotypes, which may enable us to enter the era of personalised nutrition. To achieve this, scientists and practitioners should not only revisit their perception of the diet in IBD, but stake holders should take action. This step appears critical because nutritional trials should scientifically hold up with medical trials in IBD, which requires dedication from nutritional sponsors and support from policy makers. That this may be rewarding for individuals, and socio-economically, has been recognised by other fields and will change nutritional practice, as for example in oncology.\textsuperscript{147} The concept of precision nutrition is expected to change the way we understand and treat IBD.

Contributors TEA and JZ wrote the manuscript and designed the figures.

Funding TA is grateful for the support from the Austrian Science Fund (FWF P33070), the European Research Council (ERC STG #101039320) and the European Crohn’s and Colitis Organisation (ECCO). WZ is grateful for the support from the National Nature Science Foundation of China (82100573) and Hong Kong Research Grants Council (14121322).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.
Recent advances in basic science

16 Chan SSM, Chen Y, Casey K, et al. Obesity is associated with increased risk of Crohn's disease, but not ulcerative colitis: a pooled analysis of five prospective cohort studies. Clin Gastroenterol Hepatol 2022;20:1048–58.

17 Rutgeerts P, Goboes K, Peeters M, et al. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. Lancet 1991;338:771–4.

18 De Vlaers GR, Goboes K, Peeters M, et al. Early lesions of recurrent Crohn’s disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology 1998;114:262–7.

19 Aldous MC, Meister D, Ghosh S. Modification of enteral diets in inflammatory bowel disease. Proc Nutr Soc 2001;60:457–61.

20 Piovan D, Danese S, Peyrin-Biroulet L, et al. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. Gastroenterology 2019;157:647–59.

21 Devkota S, Wang Y, Much MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiomark expansion and colitis in IL10-/- mice. Nature 2012;487:104–8.

22 Martinez-Medina D, Denizot J, Dreux N, et al. Western diet induces dysbiosis with increased E. coli in CEBACAC10 mice, alters host barrier function favoring AIEC colonization. Gut 2014;63:116–24.

23 Amore D, Valleri M, Hergalan S, et al. Long-Term Overconsumption of fat and sugar causes a partially reversible Pre-inflammatory bowel disease state. Front Nutr 2021;8:78518.

24 Agus A, Denizot J, Thévenot J, et al. Western diet induces a shift in microbe composition enhancing susceptibility to adherent-invasive E. coli infection and intestinal inflammation. Sci Rep 2016;6:19032.

25 Khan S, Walluillat S, Godfrey V, et al. Dietary simple sugars alter microbial ecology in the gut and promote colitis in mice. Sci Transl Med 2020;12:101126.2. [Epub ahead of print: 28 10 2020].

26 Montrose DC, Nishiguchi R, Basu S, et al. Dietary fructose alters the composition, localization, and metabolism of gut microbiota in association with worsening colitis. Cell Mol Gastroenterol Hepatol 2021;11:525–50.

27 Kawabata K, Karamouzina S, Morinaga Y, et al. A high-fructose diet induces epithelial barrier dysfunction and exacerbates the severity of dextran sodium sulfate-induced colitis. Int J Mol Med 2019;43:1487–96.

28 Fajtova A, Galanova N, Coufal S, et al. Diet rich in simple sugars promotes pro-inflammatory response via gut microbiota alteration and TLR4 signaling. Cells 2020;9:1039. doi:10.3390/cells9122701. [Epub ahead of print: 16 12 2020].

29 Laffin M, Fedorak RN, Zalasky A, et al. A high-sugar diet rapidly enhances susceptibility to colitis via depletion of luminal short-chain fatty acids in mice. Sci Rep 2019;9:12294.

30 He Z, Chen L, Catalan-Díebe J, et al. Food colorants metabolized by commensal bacteria promote inflammation in mice with dysregulated expression of interleukin-23. Cell Metab 2021;33:1358–71.

31 Chassaing B, Koren O, Goodrich JK, et al. The food additive maltodextrin promotes inflammation. Cell 2014;163:116–24.

32 Rodriguez-Ramos C, Manel-Said J, Fouque D, et al. Diet induces intestinal inflammation, and tumorigenesis. Cell Host Microbe 2020;22:289–300.

33 Lavelle A, Sokol H. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. Cell Host Microbe 2021;20:327–39.

34 Sartor RB, Wu GD., Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology 2017;152:327–39.

35 Pilchta DR, Graham DB, Subramanian S, et al. Therapeutic opportunities in inflammatory bowel disease: mechanistic dissection of host-microbiome relationships. Cell 2019;178:1041–56.

36 Sultans E, El-Mowafy M, Elgamaa A, et al. Metabolic influences of gut microbiota dysbiosis on inflammatory bowel disease. Front Physiol 2021;12:715506.

37 Metwally A, Reitemeier S, Haller D. Microbiome risk profiles as biomarkers for inflammatory and metabolic disorders. Nat Rev Gastroenterol Hepatol 2019;16:393–87.

38 Cał, S, Li, Gonzalez. LJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. Cell Host Microbe 2020;22:289–300.

39 Paik D, Yao L, Zhang Y, et al. Human gut bacteria produce T_{3G}-modulating bile acid metabolites. Nature 2022;603:907–12.

40 Uli W, Pilchta D, Hogston J. Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. Cell Host Microbe 2021;22:1294–304.

41 Wang C, Huang Z, Yu K. High-Salt diet has a certain impact on protein digestion and gut microbiota: a sequencing and proteome combined study. Front Microbiol 2018;9:178.

42 Zhang Y, Bhose A, Bae S, et al. Discovery of bioactive microbial gene products in inflammatory bowel disease. Nature 2022;606:754–60.

43 Mahdavi A, Szychowski, J, Ngu T, et al. Identification of secreted bacterial proteins by noncanonical amino acid tagging. Proc Natl Acad Sci U S A 2014;111:433–8.

44 Cornelis GR. The type III secretion injection. Nat Rev Microbiol 2006;4:811–25.

45 Rothschild D, Weissbrod O, Barkan E, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature 2016;555:210–25.

46 Salie R. Insulin signaling in the control of glucose and lipid homeostasis. Handb Exp Pharmacol 2016;231:53–71.

47 Lozupone CA, Stombaugh J, Gordon JI, et al. Diversity, stability and resilience of the human gut microbiota. Nature 2012;489:220–30.

48 Sonnenburg ED, Sonnenburg JL. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. Cell Metab 2014;20:279;780.

49 Looijer–Van Langen MAC, Dieleman LA. Prebiotics in chronic intestinal inflammation. Inflamm Bowel Dis 2009;15:454–62.

50 Kelly CJ, Zheng L, Campbell EL, et al. CROSSTALK between Microbiota-Derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. Cell Microbe 2015;17:662–71.

51 Farham GT, Turner JR, Taylor CT, et al. Hyposia-Inducible factor 1–Dependent induction of intestinal trefoil factor protects barrier function during hypoxia. J Exp Med 2001;193:1027–34.

52 Geimbert A, Calatayud M, Grootaert C, et al. Butyrate-producing bacteria supplemented in vitro to Crohn's disease patient microbiota increased butyrate production and enhanced intestinal epithelial barrier integrity. Sci Rep 2017;7:11450.

53 Thangaraju M, Cresci GA, Liu K, et al. Gpr109a is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. Cancer Res 2009;69:2826–32.

54 Chang PV, Hao L, Offermann S, et al. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci U S A 2014;111:2472–57.

55 Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol 2013;5:237–47.

56 Sonnenberg A. Geographic and Temporal Variations of Sugar and Margarine Consumption in Relation to Crohn’s Disease. Digestion 1989;41:161–71.

57 Oktoraurou M, Merikas E, Malgarinos G. A prospective study of pre-inflamed diet in newly diagnosed patients with Crohn’s disease. Rev Med Clin Soc Med Nat Iasi 2019;16:840–49.

58 Machels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut 2014;63:1275–83.
Recent advances in basic science

76 Thibault R, Blachier F, Darcy-Vrillon B, et al. Butyrate utilization by the colonic mucosa in inflammatory bowel diseases: a transport deficiency. *Inflamm Bowel Dis* 2010;16:884–95.

77 Di'Narro AF, Houten SM, Kosoy R, et al. Integrative analysis of the inflammatory bowel disease serum metabolome improves our understanding of genetic etiology and points to novel putative therapeutic targets. *Gastroenterology* 2022;162:828–84, e1.

78 Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbiotal enterotypes. *Science* 2011;334:105–8.

79 Fava F, Gitau R, Griffin BA, et al. The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome 'at-risk' population. *Int J Obes* 2013;37:216–22.

80 Wolters M, Ahrens I, Romani-Perez M, et al. Dietary fat, the gut microbiota, and metabolic health - A systematic review conducted within the MyNewGut project. *Clin Nutr* 2019;38:2504–20.

81 Pendyala S, Walker JM, Holt PR. A high-fat diet is associated with endotoxemia that originates from the gut. *Gastroenterology* 2012;142:1100–1.

82 Zindokar MK, Lindseth IA. The Western Diet-Microbiome-Host Interaction in metabolic disorders. *Nutrients* 2018;10: doi: 10.3390/nu10030365. [Epub ahead of print: 17 Mar 2018].

83 Świątecka D, Dominika Świątecka, Narabà D, et al. The study on the impact of glycated peas protein on human intestinal bacteria. *Int J Food Microbiol* 2011;145:267–76.

84 Meddah AT, Yazoumi A, Desmet I, et al. The regulatory effects of whey tetrapeptide from bifidobacteria fermented milk on the microbiota of the simulator of the human intestinal microbial ecosystem (SHIME). *J Appl Microbiol* 2001;91:1110–7.

85 Romond M-B, Asa S, Guillomet F, et al. Cell-Free whey from milk fermented with *Bifidobacterium breve* C50 used to modify the colonic microflora of healthy subjects. *J Dairy Sci* 1996;81:1229–35.

86 Rosager HM, Locht TR. Microbial tryptophan catabolites in cathepsin and disease. *Nat Commun* 2018;9:3924.

87 David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the gut human microbiome. *Nature* 2014;515:599–63.

88 Reddy BS, Weisburger JH, Wynder EL. Effects of high risk and low risk diets for colon carcinogenesis on fecal microflora and steroids in man. *J Nutr* 1975;105:878–84.

89 Cotillard A, Kennedy SP, Kong LC, et al. Dietary intervention impact on gut microbial gene richness. *Nature* 2014;509:585–98.

90 Kostovskakova K, Coufál S, Galanova N, et al. Diet rich in animal protein promotes pro-inflammatory macrophage response and exacerbates colitis in mice. *Front Immunol* 2019;10:919.

91 Rafffner Basson A, Gomez-Nguyen A, LaSalla A, et al. Replacing Animal Protein with Soy-Protein in an “American Diet” Controls Murine Crohn Disease-like Ileitis Regardless of Firmicutes: Bacteroidetes Ratio. *J Nutr* 2021;151:579–90.

92 Suez J, Koren T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 2014;514:181–6.

93 Ruiz-Ojeda FJ, Plasencia-Díaz J, Sáez-Lara MA, et al. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. *Adv Nutr* 2019;10:531–48.

94 Rodriguez-Palacios A, Harding A, Menghini P, et al. The artificial sweetener Splenda promotes gut *Bifidobacterium*, *Dysbiosis*, and myeloperoxidase reactivity in Crohn’s disease-like ileitis. *Inflamm Bowel Dis* 2018;24:1005–20.

95 Singh RK, Wheldon N, Ishikawa S. Food additive P-50 impacts mouse gut microbiota promoting intestinal inflammation, obesity and liver dysfunction. *SOI Microbiol Infect* 2016;6:401–10.

96 Nami S, Viennois E, Gewirtz AT, et al. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome* 2014;2:16.

97 Barreau F, Tisseau C, Méard S, et al. Titanium dioxide particles from the diet: promoting intestinal inflammation, and exacerbates colitis in mice *Escherichia coli* in inflammatory bowel disease. *Clin Exp Immunol* 2018;178:49–59.

98 Palmela C, Chevarin C, Xu Z, et al. Adherent-invasive *Escherichia coli* in inflammatory bowel disease. *Gut* 2018;67:574–87.

99 Costea I, Macksoud M, LeBlanc RN, et al. Interactions between the dietary polysaturated fatty acid ratio and genetic factors determine susceptibility to pediatric Crohn's disease. *Gastroenterology* 2014;146:929–31.

100 Weber AT, Shah ND, Sauk J, et al. Popular diet trends for inflammatory bowel diseases: claims and evidence. *Curr Treat Options Gastroenterol* 2019;17:564–76.

101 Bischoff SC, Escher J, Hübtermann X, et al. ESPEN practical guideline: clinical nutrition in inflammatory bowel disease. *Clin Infect Dis* 2020;39:623–53.

102 van Rheezen PF, Aliò M, Assa A, et al. The medical management of paediatric Crohn’s disease: an ECCO-ESPghan guideline update. *J Crohns Colitis* 2020;13: doi:10.1093/cccj/ccaa161. [Epub ahead of print: 07 Oct 2020].

103 Sscarolla L, Lionetti P. Dietary management in pediatric patients with Crohn's disease. *Nutrients* 2021;13: doi: 10.3390/nu13050611. [Epub ahead of print: 11 May 2021].

104 Cohen-Dolov N, Sladek M, Hussey S, et al. Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate Crohn’s disease: results from the growth CD study. *J Crohns Colitis* 2018;12:306–12.

105 Naraula N, Shillion A, Zhang D, et al. Enteral nutritional therapy for induction of remission in Crohn’s disease. *Cochrane Database Syst Rev* 2018;4:CD000542.

106 Logan M, Gikkas K, Svolo V, et al. Analysis of 61 exclusive enteral nutrition formulas used in the management of active Crohn’s disease-new insights into dietary disease triggers. *Aliment Pharmacol Ther* 2020;51:935–47.

107 Middleton SJ, Rucker JT, Kirby GA, et al. Long-Chain triglycerides reduce the efficacy of enteral feeds in patients with active Crohn’s disease. *Clin Nutr* 1995;14:229–36.

108 Riordan AM, Hunter JQ, Cowan RE, et al. Treatment of active Crohn’s disease by exclusion diet: East Anglian multicentre controlled trial. *Lancet* 1993;342:1131–4.

109 van Rheenen PF, Aliò M, Assa A, et al. The medical management of paediatric Crohn’s disease: an ECCO-ESPHan guideline update. *J Crohns Colitis* 2020;13: doi:10.1093/cccj/ccaa161. [Epub ahead of print: 07 Oct 2020].

110 Sscarolla L, Lionetti P. Dietary management in pediatric patients with Crohn’s disease. *Nutrients* 2021;13: doi: 10.3390/nu13050611. [Epub ahead of print: 11 May 2021].

111 Cohen-Dolov N, Sladek M, Hussey S, et al. Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate Crohn’s disease: results from the growth CD study. *J Crohns Colitis* 2018;12:306–12.

112 Naraula N, Shillion A, Zhang D, et al. Enteral nutritional therapy for induction of remission in Crohn’s disease. *Cochrane Database Syst Rev* 2018;4:CD000542.
Recent advances in basic science

132 Glikas K, Logan M, Nichols B, et al. Dietary triggers of gut inflammation following exclusive enteral nutrition in children with Crohn’s disease: a pilot study. *BMC Gastroenterol* 2021;21:454.

133 Sigall Boneh R, Sarbaghi Shabat C, Yanai H, et al. Dietary therapy with the Crohn’s disease exclusion diet is a successful strategy for induction of remission in children and adults failing biological therapy. *J Crohns Colitis* 2017;11:1205–12.

134 Greenley RN, Kunz JH, Walter J, et al. Practical strategies for enhancing adherence to treatment regimen in inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1534–45.

135 Kakodkar S, Farooqui AI, Mikolaitis SL, et al. The specific carbohydrate diet for inflammatory bowel disease: a case series. *J Acad Nutr Diet* 2015;115:1226–32.

136 Suskind DL, Brittnacher MJ, et al. Clinical and fecal microbial changes with diet therapy in active inflammatory bowel disease. *J Clin Gastroenterol* 2018;52:155–63.

137 Britto S, Kellermayer R. Carbohydrate Monotony as protection and treatment for inflammatory bowel disease. *J Crohns Colitis* 2019;13:942–8.

138 Chicco F, Magri S, Cingolani A, et al. Multidimensional impact of Mediterranean diet on IBD patients. *Inflamm Bowel Dis* 2021;27:1–9.

139 De Filippis F, Pellegrini N, Vannini L, et al. High-Level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* 2016;65:1812–21.

140 Pedersen N, Ankersen DV, Felding M, et al. Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease. *World J Gastroenterol* 2017;23:3356–66.

141 Bodini G, Zanella C, Crespi M, et al. A randomized, 6-wk trial of a low FODMAP diet in patients with inflammatory bowel disease. *Nutrition* 2019;67:68:110542.

142 Halmos EP, Christophersen CT, Bird AR, et al. Consistent probiotic effect on gut microbiota with altered FODMAP intake in patients with Crohn’s disease: a randomised, controlled cross-over trial of well-defined diets. *Clin Transl Gastroenterol* 2016;7:e164.

143 Herfarth HH, Martin CE, Sandler RS, et al. Prevalence of a gluten-free diet and improvement of clinical symptoms in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2014;20:1194–7.

144 Schreiner P, Yilmaz B, Rossel J-B, et al. Vegetarian or gluten-free diets in patients with inflammatory bowel disease are associated with lower psychological well-being and a different gut microbiota, but no beneficial effects on the course of the disease. *United European Gastroenterol J* 2019;7:767–81.

145 Wan Y, Wang F, Yuan J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. *Gut* 2019;68:1417–29.

146 Morton H, Pedley KC, Stewart RC, et al. Inflammatory bowel disease: are symptoms and diet linked? *Nutrients* 2020;12. doi:10.3390/nu12102975. [Epub ahead of print: 29 Sep 2020].

147 Spencer CN, McQuade JL, Gopalakrishnan V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science 2021;374:1632–40.*

148 Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005;81:341–54.

149 Alzoghabi MA, Walsh SW, Willey A, et al. Linoleic acid, but not oleic acid, upregulates the production of interleukin-8 by human intestinal smooth muscle cells isolated from patients with Crohn’s disease. *Clin Nutr* 2003;22:529–35.

150 Penagini F, Diillo D, Borisani B, et al. Nutrition in pediatric inflammatory bowel disease: from etiology to treatment. A systematic review. *Nutrients* 2016;8. doi:10.3390/nu8060334. [Epub ahead of print: 01 Jun 2016].

151 Liu T-C, Kern JT, Jain U, et al. Western diet induces Paneth cell defects through microbiome alterations and farnesoid X receptor and type I interferon activation. *Cell Host Microbe* 2021;29:988–1001.

152 Progatzy F, Sangha NJ, Yoshida N, et al. Dietary cholesterol directly induces acute inflammation-dependent intestinal inflammation. *Nat Commun* 2014;5:5864.

153 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, et al. Dietary extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice. *J Nutr Biochem* 2013;24:1401–13.

154 Morvandi M, Jafarzad S, Seyedian SS, et al. The effects of extra virgin olive oil and canola oil on inflammatory markers and gastrointestinal symptoms in patients with ulcerative colitis. *Eur J Clin Nutr* 2020;74:891–9.