Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases

Arie Levine, Rotem Sigall Boneh, Eytan Wine

ABSTRACT
Recent advances in basic and clinical science over the last 3 years have dramatically altered our appreciation of the role of diet in inflammatory bowel diseases (IBD). The marked increase in incidence of these diseases along with the important role of non-genetic susceptibility among patients with IBD has highlighted that these diseases have a strong environmental component. Progress in the field of microbiome and IBD has demonstrated that microbiome appears to play an important role in pathogenesis, and that diet may in turn impact the composition and functionality of the microbiome. Uncontrolled clinical studies have demonstrated that various dietary therapies such as exclusive enteral nutrition and newly developed exclusion diets might be potent tools for induction of remission at disease onset, for patients failing biologic therapy, as a treatment for disease complications and in reducing the need for surgery. We review these advances from bench to bedside, along with the need for better clinical trials to support these interventions.

INTRODUCTION
The basic understanding of how and why IBD develop has been the focus of research of many disciplines over the last few decades, especially given the complex, multifactorial nature of these conditions. The discovery of NOD2 as the first, and most important, susceptibility gene was then followed by identification of over 200 other loci, but these genetic contributions together likely only explain 19%-26% of the hereditary variance of IBD. Genetic studies have identified defects in innate immunity in Crohn disease (CD) and altered barrier function in Ulcerative Colitis (UC) as some of the key players in disease susceptibility.

The intestinal barrier comprises the mucous layer, epithelial cells and the tight junctions between cells, rendering the mucosa relatively impermeable to bacteria. Some of the early changes in the sequence of events, leading to IBD are seen in the epithelial and mucus layers, which is particularly evident in patients with UC. The mucous layer is a critical barrier separating commensal and pathogenic bacteria from the epithelium, thereby decreasing immune activation. Both CD and UC are characterised by high penetration of the mucous layer by bacteria and increased barrier permeability. Increased barrier dysfunction during remission has been associated with clinical relapse of the disease.

CD and UC are characterised by the presence of mucosal bacteria that differs from healthy human hosts, in which bacteria for the most part do not reside adjacent to the mucosal epithelium. In fact, increased epithelial cell shedding, high vascular flow, depletion of the small bowel mucus layer and presence of mucosa-associated bacteria have been demonstrated in non-inflamed duodenum and ilium of children with UC. Both CD and UC appear to involve translocation of bacteria through the epithelium. Thus, impaired barrier function, defects in innate immunity, changes in microbial composition and the presence of mucosa-associated and translocating bacteria have all been described in IBD. However, differences do exist between CD and UC.

Dysbiosis is more prominent in CD. The predominance of Proteobacteria, specifically individual Escherichia coli strains, especially in CD, has been known for many years; however, whether or not this reflects a true role in driving disease...
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or just a change in the gut setting (eg, due to higher oxygen tension, related to inflammation) remains controversial; it is safe to say that both processes are likely and that the diversity of disease presentation and course likely represent different levels of microbial involvement in different individuals. The presence or decline in specific mucosal genera have been identified in children and adults with IBD. Several researchers have demonstrated that patients with UC appear to have diminished ability to produce short chain fatty acids (SCFA), even with an abundant supply of substrates, suggesting that microbial metabolic dysfunction may play an important role in UC.

Background: diet and IBD

Diet is one of the key players in the normal gut microenvironment, impacting microbial composition, function, the gut barrier and host immunity. Alterations in single food groups have far ranging implications. For example, depriving colonic microbes from fibre in rodent models will favour taxa that can use alternative carbon sources found within the colonic mucus; this then leads to depletion of the mucus layer, disruption of the barrier, immune activation and tissue damage. Changing from a plant-based to an animal-based diet radically changes bacterial taxa and metabolism, leading to alterations in bile acids and sulfide metabolism, both of which may play a role in IBD. Recent data suggest that the most important factors regulating compositional changes are access to calorie, carbohydrate and protein intake. Since diet has such an important role in gut homeostasis, and interacts with the microbiome, host barrier and immunity, we will explore the possible and plausible role of dietary factors in the pathogenesis of IBD.

Clues from epidemiology

Numerous epidemiological studies with inconsistent methodological quality have demonstrated associations between the intake of specific dietary components or dietary patterns and the risk of developing IBD. One of the earliest epidemiological associations with IBD is the strong protective role of breast feeding. Although recall bias needs to be considered, almost all studies from various regions support this dose-dependent association, which is also demonstrated for other immune-mediated conditions. The results from other epidemiological studies should be considered with caution due to a recall bias and possible dietary modification before the diagnosis of IBD. A statistical association between specific dietary factors and disease does not necessarily imply causation. In any complex disease with dietary triggers, it may be difficult to unravel the role of individual dietary risk factors since dietary patterns often involve exposures to clusters of foods. In addition, certain dietary ingredients are likely to cluster together due to industrial processing of food. For example, fat exposure

Figure 1 Western diet and pathogenesis of IBD. (A) Proposed pathogenesis of Crohn disease and effects of western diet. (B) Proposed pathogenesis of UC and effects of western diet observations that can be associated with western diet appear in the marked boxes. Tregs, regulatory T cells.
will likely be associated with emulsifier exposure, processed meats with preservatives, dairy products with thickening agents and emulsifiers, etc. In addition, food frequency questionnaires may be insufficient to address longitudinal exposures.

D’Souza et al conducted a case-control study to assess the dietary patterns of Canadian children and the risk of developing CD. They evaluated multiple dietary patterns including western diet and a prudent diet. A dietary pattern characterised by meats, fatty foods and desserts (western diet) increased the risk for CD in females (OR 4.7, 95% CI 1.6 to 14.2), whereas the consumption of vegetables, fruits, olive oil, fish, grains and nuts (prudent diet) was associated with a decreased risk for developing CD in both males and females (females: OR 0.3, 95% CI 0.1 to 0.9; males: OR 0.2, 95% CI 0.1 to 0.5). A recent Australian population-based study of environmental risk factors demonstrated an increased risk for CD with frequent consumption of fast food (western diet) before diagnosis. 42

Several studies have associated protein with increased risk for IBD. 32–33–36 As part of the E3N prospective study, which included 67 581 French women, high animal protein was associated with a significantly increased risk of IBD (OR 3.03, 95% CI 1.45 to 6.34), particularly with UC (OR 3.29, 95% CI 1.34 to 8.04). Vegetable protein intake was not associated with either disease. However, other smaller studies have not confirmed this. 37 In a separate study evaluating dietary intake and relapse of UC, red meat was found to have the strongest association (OR 5.19, 95% CI 2.09 to 12.9) with relapse. 38

Data regarding the associations between increased intakes of carbohydrates and the risk for IBD are inconsistent. The E3N study did not identify carbohydrate intake as a risk factor for IBD, CD or UC. 38 Racine et al, evaluated 366 351 participants with IBD from the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohort and found no correlation between dietary intake patterns and CD. 34 They did find an association between high-sugar and low-fibre intake and UC (OR 1.68, 95% CI 1.00 to 2.82).

More recent data from the EPIC study found no association between alcohol consumption and the risk for CD. 40 This contrasted with the study by Jowett et al, who tried to find dietary products associated with the relapse of UC. High alcohol consumption was associated with an increased risk of relapse (OR 2.71, 95% CI 1.1 to 6.67).

Dietary fats are associated with an increase or decrease risk for IBD, depending on the type of fat. Among 170 805 women followed over 26 years, a high intake of dietary long-chain n-3 polyunsaturated fatty acids was associated with a reduced risk of UC. 41 In contrast, high intake of transunsaturated fats was associated with an increased risk of UC. 42

Perhaps the dietary component with the greatest agreement in epidemiological studies is dietary fibre, which is also represented in SCFAs. SCFAs are a vital substrate for the production of butyrate and other SCFAs. Butyrate plays an important role in downregulating inflammation by suppressing transcription of cytokines and increasing differentiation and the population of lamina propria Tregs. 47 Butyrate can also enhance innate immunity by upregulating defensins and cathelicidins in animal models. 48 Low dietary fibre may cause catabolism of the mucous layer, leading to increased permeability of the mucous layer, and allowing increased contact between luminal bacteria and the epithelium. 49

HF or HF/HS diets may act synergistically to a low fibre diet as they may exert many of the same effects described above for low fibre exposure. An HF/HS diet in a CEACAM 10 rodent model has been shown to decrease MUC2 expression and goblet cell mucins while increasing intestinal permeability. 50 These diets have been demonstrated to decrease both butyrate production and expression of the butyrate GPR43 receptor, which is underexpressed in CD. 49 Finally, HF diets (without HS) have been shown to increase tumour necrosis factor (TNF)-α and interferon-γ expression and decrease levels of colonic Tregs. 50

Exposure to gluten may promote an inflammatory state, impair innate immunity or increase intestinal permeability. Dietary gluten significantly decreased intestinal Tregs in non-obese diabetic mice fed gluten compared with standard chow. 51 Dietary gluten was also shown to induce ileitis in TNFαARE/WT mice via an increase in intestinal permeability, 52 which has been identified as a factor associated with relapse in CD. 14

Alpha-amylase/trypsin inhibitors, found in wheat, may have a pro-inflammatory role. They are activators of dendritic cells and macrophages, driving intestinal inflammation in rodents. 53,54 Multiple food additives, commonly present in western diet, may affect host barrier function or immunity. Chassaing et al, demonstrated that IL-10−/− mice exposed to two common emulsifiers, carboxymethylcellulose and polysorbate-80, developed increased intestinal permeability and significant thinning of the mucous layer, leading to increased proximity of the microbiota to the intestinal epithelium. 55 Maltodextrins, used as thickeners and sweeteners, have demonstrated the ability to affect mucosal proximity (by a presumed effect on mucosal layer thickness) and to impair clearance of intracellular Salmonella. 56,57 Carrageenans, used for texture and as thickening agents in the dairy and sauce industry, may induce intestinal permeability. 58,59 Other factors, which may promote intestinal permeability are listed in table 1 and are beyond the scope of this paper.

Diet and altered host immunity

Host factors that may play an important role in pathogenesis or active inflammation include defects in barrier function, depletion of the intact mucus layer, decreased regulatory T cells (Tregs) and impaired bacterial clearance mechanisms (figure 1A, B). A major limitation to date is that most of the evidence comes from animal models and human cell lines, which makes extrapolation difficult. Dietary factors that may affect host immunity are presented in table 1 and figure 2. Western diet is characterised by alterations in the amount of exposure to natural dietary ingredients such as high fat (HF), high sugar (HS), high wheat and high dairy exposure, accompanied by low fibre exposure, and by high exposure to multiple food additives. 45,46 We will focus our discussion on the dietary products with the most evidence from animal models, which include fibre, animal fat, wheat and food additives.

Low dietary fibre, identified through epidemiological studies as a possible risk factor, 33–35 could affect host immunity via multiple pathways. Fibres and starches found in fruits and vegetables are a vital substrate for the production of butyrate and other SCFAs. Butyrate plays an important role in downregulating inflammation by suppressing transcription of cytokines and increasing differentiation and the population of lamina propria Tregs. 47 Butyrate can also enhance innate immunity by upregulating defensins and cathelicidins in animal models. 48 Low dietary fibre may cause catabolism of the mucous layer, leading to increased permeability of the mucous layer, and allowing increased contact between luminal bacteria and the epithelium. 49

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Diet and microbiota

Dietary components linked to changes in the microbiome that have been associated with IBD appear in table 2 and figure 3. For example, adherent invasive E. coli (AIEC) strains cannot induce inflammation under normal conditions. Pathogenicity may arise
### Table 1  Dietary factors potentially affecting host barrier and immunity

<table>
<thead>
<tr>
<th>Dietary component</th>
<th>Reference</th>
<th>Model</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High fat+high sugar diet</td>
<td>Martinez-Medina, Gut, 2014</td>
<td>CEABAC 10 mice</td>
<td>▶ Decreased MUC2 expression</td>
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<tr>
<td>Wheat (ATIs)</td>
<td>Zevallos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat (ATIs)</td>
<td>Zevallos. Gastroenterology, 2017</td>
<td>TLR4-responsive mouse and human cell lines</td>
<td>▶ Activation of dendritic cells in mesenteric lymph nodes</td>
</tr>
<tr>
<td>Wheat (ATIs)</td>
<td>Bassaganya-Riera. J Nutr, 2011</td>
<td>C57BL6/Wt mice IL-10−/− mice</td>
<td>▶ Decreased ileal and colonic inflammatory lesions</td>
</tr>
<tr>
<td>Soluble fibres and resistant starch</td>
<td>Hung. J Nutr, 2016</td>
<td>BALB/c mice aged 7 weeks</td>
<td>▶ Increased expression of claudin and claudin-3, claudin-4 and claudin-7 (reduced permeability)</td>
</tr>
<tr>
<td>Dietary pectin</td>
<td>Ye. J Agric Food Chem, 2010</td>
<td>IL-10−/− mice</td>
<td>▶ Reduced expression of TNF-R and GATA-3</td>
</tr>
<tr>
<td>Fermentable fibre (guar gum, partially hydrolysed GG)</td>
<td>Hung. J Nutr, 2016</td>
<td>IL-10−/− mice</td>
<td>▶ Higher total faecal SCFA concentrations</td>
</tr>
<tr>
<td>Multifibre mix diet</td>
<td>Wang. J. Exp Med, 2016</td>
<td>IL-10−/− mice</td>
<td>▶ Reduced disease activity index score</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Forsyth. Alcohol Clin Exp Res, 2017</td>
<td>Mice</td>
<td>▶ Colonic (but not small intestinal) hyperpermeability</td>
</tr>
<tr>
<td>Dietary salt</td>
<td>Tubbs. J Immunol, 2017</td>
<td>IL-10−/− murine model of colitis</td>
<td>▶ Exacerbation of inflammatory pathology</td>
</tr>
</tbody>
</table>

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Table 1  Continued

<table>
<thead>
<tr>
<th>Dietary component</th>
<th>Reference</th>
<th>Model</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxymethylcellulose (E466) and polysorbate-80 (E433)</td>
<td>Chassaing, <em>Nature</em>, 2015</td>
<td>IL-10−/− mice</td>
<td>▶ Increased intestinal permeability</td>
</tr>
<tr>
<td>Carboxymethylcellulose (E466)</td>
<td>Swidzinski, <em>Inflamm Bowel Dis</em>, 2009</td>
<td>IL-10−/− mice</td>
<td>▶ Distension of spaces between villi, with bacteria filling these spaces</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>Miyazato, <em>Biosci Microbiota Food Health</em>, 2016</td>
<td>BALB/c mice</td>
<td>▶ Increased total IgA levels in the intestinal tract</td>
</tr>
<tr>
<td>Carrageenan (E407)</td>
<td>Choi, <em>Toxicol Lett</em>, 2012</td>
<td>HCT-8, HT-29 and Caco-2 cells</td>
<td>▶ Lowered transepithelial resistance</td>
</tr>
<tr>
<td>Titanium dioxide (TiO₂)</td>
<td>Ruiz, <em>Gut</em>, 2017</td>
<td>WT and NLRP3−/− mice with DSS</td>
<td>▶ Oral administration of TiO₂ worsened acute colitis through a mechanism involving the NLRP3 inflammasome</td>
</tr>
</tbody>
</table>

ATI, α-amylase/trypsin inhibitors; CD, Crohn disease; IFN, interferon; IL, interleukin; SCFA, short chain fatty acids; Th, T helper; TNF, tumour necrosis factor; Tregs, T regulatory cells; WT, wild-type; ZO, zonula occludens. IEL (intrepithelial lymphocytes), DSS (dextran sulfate sodium).

If the ligand CEACAM 6 is presented by intestinal epithelial and M cells. Under these conditions, AIEC may form small intestinal biofilms, adhere and translocate via M cells, and then invade the associated epithelium. An HF/H5 diet may promote colonisation with IBD-associated pathobionts. CEABAC 10 mice, expressing CEACAM 6, fed HF/H5 but not standard chow were rapidly colonised by mucosa-associated AIEC and presented higher degrees of crypt abscesses when compared with the standard chow group. Transplantation of faeces from HF/H5-treated mice to germ free mice increased susceptibility to AIEC. A study that compared HF with HS diet in a mouse model demonstrated that HF but not HS induced dysbiosis, characterised by an increase in Proteobacteria and a decrease in Firmicutes, similar to that seen in CD. HF diets result in accumulation of secondary bile acids, such as deoxycholic acid, which in turn can inhibit the growth of members of the Bacteroidetes and Firmicutes phyla, characteristic of the dysbiosis found in CD.

Maltodextrins have been shown to promote AIEC biofilm formation independent of the presence of the ligand CEACAM 6, while AIEC growth in medium was enhanced particularly with polysaccharides used as thickening agents, such as maltodextrin and xanthan gum, but not by glucose or sucrose. The source of dietary fat may play an important role in promoting colitogenic bacteria. Devkota *et al* reported an

Figure 2  Possible effects of dietary factors on host barrier and immunity leading to IBD (based on cell lines and animal models). Tregs, regulatory T cells.
Table 2  Dietary factors potentially affecting the microbiota in IBD

<table>
<thead>
<tr>
<th>Dietary component</th>
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<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Natural components</td>
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</tbody>
</table>
| High fat+high sugar diet | Martinez-Medina. Gut, 2014<sup>52</sup> | CEABAC 10 mice | ▶ AIEC Colonisation  
▶ Low diversity  
▶ Dysbiosis  
▶ Higher degree of crypt abscesses |
| High fat+high sugar diet | Agus. Sci Rep, 2016<sup>60</sup> | CEABAC 10 mice | ▶ Intestinal mucosa dysbiosis  
▶ Decreased butyrate production  
▶ Reduced expression of the butyrate GPR43 receptor  
▶ Overgrowth of Escherichia coli  
▶ Significantly decreased SCFA concentrations |
| High fat vs high sugar | Lai. Environ Pollut, 2016<sup>61</sup> | CD1 mice | ▶ High fat but not high sugar induced dysbiosis characterised by an increase in Proteobacteria and a decrease in Firmicutes and Clostridia  
▶ Growth induction of the family Helicobacteraceae |
▶ Induced pro-inflammatory Th1 immune response  
▶ Increased incidence of colitis  
▶ Low diversity  
▶ Dysbiosis |
| High fibre diet | Silveira. Eur J Nutr, 2017<sup>115</sup> | BALB/c female mice | ▶ High fibre diet protected from acute colitis |
| Fibre | James. GUT, 2015<sup>52</sup> | Patients with UC and controls | ▶ High fibre diet did not increased SCFA production in patients with UC |
| Animal vs plant diet | David. Nature, 2014<sup>56</sup> | Healthy volunteers | ▶ Animal-based diet increased the abundance of bile-tolerant microorganisms and decreased the levels of Firmicutes |
| Alcohol | Forsyth. Alcohol Clin Exp Res, 2017<sup>10</sup> | Mice | ▶ Decreased butyrate/total SCFA ratio in stool |
| Food additives |           |       |        |
| Carboxymethylcellulose (E466) and polysorbate-80 (E433) | Chassaing. Nature, 2015<sup>15</sup> | IL-10−/− mice Human intestinal microbial ecosystem (M-SHIME) | ▶ Increased mucosal-associated bacteria  
▶ Increased Flagellin expression  
▶ P-80 altered species composition |
| Carboxymethylcellulose (E466) | Szwiderski. Inflamm Bowel Dis, 2009<sup>12</sup> | IL-10−/− mice | ▶ Bacterial overgrowth  
▶ Distension of spaces between villi, with bacteria filling these spaces  
▶ Adherence of bacteria to the mucosa  
▶ Migration of bacteria to the bottom of the crypts of Lieberkühn |
| Polysorbate-80 (E433) | Roberts. Gut, 2010<sup>65</sup> | M cells Caco-2 cells Human Peyers patches | ▶ Increased translocation of E. coli across M cells  
▶ Reduction in translocation of E. coli across M cells |
| Plantain and broccoli fibre | Nickerson. PLoS One, 2012<sup>11</sup> | Human intestinal epithelial cell monolayers | ▶ Biofilm formation AIEC  
▶ Enhanced E. coli adhesion independent of the cellular receptor CEACAM 6 |
| Carrageenan (E407) | Munyaka. Front Microbiol, 2016<sup>14</sup> | Piglet model of IBD | ▶ Decreased bacterial species richness  
▶ Shifted community composition  
▶ Bacterial dysbiosis |

AIEC, adherent invasive E. coli; SCFA, short chain fatty acids; Th, T helper.

increase in colitis severity after exposure to milk fat diet but not to isocaloric polyunsaturated fatty acid diet or a low fat diet in IL-10−/− mice. Colitis was associated with the bloom of colitogenic *Bilophila wadsworthia* in the milk fat group, which was dependent on milk fat, and induced taurine conjugated bile acids.

Interestingly, emulsifiers may affect the microbiome as well as the host. The emulsifier polysorbate-80 was associated with increased translocation of AIEC through M cells and the follicular associated epithelium; this effect was suppressed by certain dietary fibres. Emulsifiers appear to affect compositional changes associated with inflammation. Polysorbate-80 induced inflammation and flagellin expression variation of microbial dysbiosis, whereas the emulsifier carboxymethylcellulose rapidly induced flagellin and alterations in gene expression for flagellin in a model for gut dysbiosis. Exclusion of western diet by exclusive enteral nutrition (EEN) or an exclusion diet in children with CD were shown to cause a marked reduction in Proteobacteria and in taxa associated previously with CD including *Escherichia, Haemophilus, Veillonella* and Fusobacteria (Van Limbergen and Dunn, unpublished data).

The metabolic activity of the microbiota may be as important, or even more important than compositional changes, especially in UC. Both CD and UC are characterised by a decrease in SCFA-producing genera, which are stimulated by the presence of dietary fibre. However, UC seems to be characterised by deficient production of SCFA, even when substrates such as resistant starch are provided. Sulfide-reducing bacteria and increased sulfide production have been reported in UC. Animal protein-based diets favour production of SCFA, even when substrates such as resistant starch are provided. However, UC seems to be characterised by deficient production of SCFA-producers. 

### Diet as a therapeutic intervention

Recent studies have expanded our understanding of the possible roles for dietary therapy, primarily in CD. Dietary therapies, such as EEN, were traditionally and primarily used to induce remission in early or new-onset CD or as supportive therapy in children and adults with malnutrition or in the preoperative setting.
EEN involves the exclusive use of a liquid nutrition in the form of medical formulas, without exposure to other foods, usually for 6–8 weeks (table 3). This effect does not depend on the protein source (type of formula), but is very dependent on exclusion of ordinary table food.68 69 Newer open-label studies have demonstrated that existing and new dietary strategies may have a wider role and can be employed to maintain remission, induce remission in patients failing biologics and for patients with complicated disease (figure 4). As data from randomised controlled trials (RCTs) are absent or pending, we will confine ourselves to more recent studies that have expanded our understanding beyond the use of EEN at diagnosis for induction of remission, which is reviewed elsewhere.67

Induction of remission
Several recent paediatric studies have demonstrated and confirmed that EEN may induce remission in 60%–86% of children accompanied by a significant decrease in inflammatory markers such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and faecal calprotectin.69–73 This recent body of literature has evaluated long-term benefits associated with use of EEN in mild-to-moderate paediatric CD. In comparison to use of steroids and corrected for disease severity, EEN was associated with higher remission rates, better growth and longer steroid-free periods,71 72 but did not differ with regard to other outcomes such as relapse. Cohen-Dolev et al demonstrated that EEN was superior to corticosteroids for induction of remission and linear growth in a multicentre prospective inception cohort of mild-to-moderate CD at diagnosis. EEN was not superior with respect to other outcomes such as time to relapse or complications over 2 years.72 Grover et al performed a prospective trial to assess mucosal healing by performing colonscopy before and after 8 weeks of EEN with azathioprine. At the end of 8 weeks, complete mucosal healing was observed in 33%, near complete in another 19% of patients.73 Patients who achieved complete mucosal healing had better sustained remission over 3 years of follow-up.

Use of EEN poses challenges to physicians and patients alike, as patients have to deal with monotony of food and taste fatigue. Furthermore, up to 50% of patients may require nasogastric tubes and many might refuse to start therapy due to these issues.74 75 This limits access and availability of the therapy. Therefore, it is no surprise that the last 3 years have seen several attempts to achieve the effect of EEN while allowing access to whole foods. Investigators from three centres in the USA and Canada compared outcomes from three cohorts treated with either: 1) high volume partial enteral nutrition (PEN) using a mean of 77% of estimated energy requirements from PEN with free access to food; 2) EEN and 3) infliximab. Clinical remission rates were similar between infliximab and EEN (73%–76%) and lower (50%) in the PEN group. Faecal calprotectin <250 g/dL as an inflammatory end point was found only in 14% of patients treated with PEN and ad libitum diet, compared with 45% with EEN and 62% treated with infliximab at week 8. This suggests that high-volume PEN with access to free diet is ineffective at improving inflammation compared with EEN or infliximab, reaffirming the principle of exclusivity.67 68

Other research groups have employed a different strategy based on the combination of PEN with a specific exclusion diet that allows access to whole foods. This review will be confined only to studies that evaluated clinical remission and objective markers of inflammation or mucosa healing. The Crohn’s disease exclusion diet was developed based on the principles outlined in figures 1–3, by excluding foods that have been associated with altered host barrier or bacterial clearance, dysbiosis and virulence factors that may allow bacteria to become mucosa-associated and enable translocation, based on the bacterial penetration cycle hypothesis for CD first proposed by the authors.76 The premise behind this theory is that CD is caused by mucosal translocating bacteria. This diet was evaluated initially in 47 children and adults with mild-to-moderate disease. Clinical remission was achieved in
Table 3  Key studies and recent advances with EEN in children and adults

<table>
<thead>
<tr>
<th>Study design</th>
<th>Population</th>
<th>Duration of EEN</th>
<th>Comparator</th>
<th>Number of patients</th>
<th>Outcome</th>
<th>Key findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trial</td>
<td>Adults</td>
<td>3–6 Weeks</td>
<td>EEN vs CS and sulfasalazine</td>
<td>EEN: 51 pts Drugs: 44 pts</td>
<td>Improvement in CDAI: EEN: 41% Drugs: 72% p&lt;0.05</td>
<td>Equal effectiveness of EEN compared with drugs per protocol</td>
<td>Malchow. Scand J Gastroenterol, 1990</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>Adults</td>
<td>4–6 Weeks</td>
<td>EEN vs CS and sulfasalazine</td>
<td>EEN: 52 pts Drugs: 55 pts</td>
<td>Remission: EEN: 55% Drugs: 74% p&lt;0.01</td>
<td>Comparison to medications</td>
<td>Lohs, Gastroenterology, 1991</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>Adults</td>
<td>4 Weeks</td>
<td>EEN: n-6 PUFA vs MUFA vs CS with ward diet</td>
<td>MUFA: 20 pts PUFA: 23 pts CS: 19 pts</td>
<td>Remission rates (ITT): MUFA EEN: 20% PUFA EEN: 52% CS: 79% p=0.001</td>
<td>Composition of fat</td>
<td>Gassull, Gut, 2002</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>Paediatric CD</td>
<td>6 Weeks</td>
<td>Elemental formula vs polymeric formula</td>
<td>Elemental formula: 16 pts Polymeric formula: 17 pts</td>
<td>Remission: Elemental: 69% Polymeric: 82% p=0.44</td>
<td>Polymeric equivalent to elemental</td>
<td>Ludwigsson. Acta Paediatr, 2004</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>Paediatric CD</td>
<td>6 Weeks</td>
<td>EEN vs 50% PEN with free diet</td>
<td>EEN:24 pts PEN: 26 pts</td>
<td>Remission: PEN: 15% EEN: 42% p=0.035</td>
<td>Principle of exclusivity</td>
<td>Johnson. GUT, 2006</td>
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<td>Randomised controlled trial</td>
<td>Newly diagnosed paediatric CD</td>
<td>10 Weeks</td>
<td>Polymeric formula vs CS</td>
<td>EEN: 19 pts CS: 18 pts</td>
<td>Remission: polymeric EEN: 79% CS: 67% p=0.4 Mucosal healing EEN: 74% CS: 33% p&lt;0.05</td>
<td>Mucosal healing comparing EEN with CS</td>
<td>Borrelli. Clin Gastroenterol Hepatol, 2006</td>
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<td>Retrospective</td>
<td>Paediatric CD</td>
<td>8 Weeks</td>
<td>Oral vs continues enteral feeding</td>
<td>Oral: 45 pts Enteral: 61 pts</td>
<td>Remission: Oral EEN: 75% Tube EEN: 85% p=0.157</td>
<td>Oral equivalent to enteral feeding</td>
<td>Rubio. Aliment Pharmacol Ther, 2011</td>
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<td>Prospective inception cohort</td>
<td>Newly diagnosed children</td>
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<td>EEN vs CS mild-to-moderate CD</td>
<td>5-ASA: 29 pts CS: 114 pts</td>
<td>CS-free remission week 12: EEN: 71% CS: 46% 5-ASA: 55% p=0.0006 NCR: EEN: 39% CS: 25% 5-ASA: 24%</td>
<td>EEN superior to CS for reduction of inflammation</td>
<td>Levine. IBD, 2014</td>
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<td>Prospective cohort</td>
<td>Paediatric CD</td>
<td>6 Weeks</td>
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<td>EEN: decreased butyrate, decreased diversity, Faecalibacterium prausnitzii concentration decreased</td>
<td>EEN mechanism</td>
<td>Gerasimidis. IBD, 2014</td>
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<td>Prospective cohort</td>
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<td>34 Children</td>
<td>Clinical remission: 84% Early good endoscopic response: 58% Complete transmural healing ileal CD: 21%</td>
<td>Mucosal healing</td>
<td>Grover. J Gastroenterol, 2014</td>
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<td>Prospective cohort</td>
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<td>8 Weeks</td>
<td>EEN vs anti-TNF vs PEN with ad libitum diet</td>
<td>Anti-TNF: 52 pts PEN: 16 pts</td>
<td>Clinical response: PEN: 64% EEN: 88% Anti-TNF: 84% p=0.08 FCP:&lt;250 mg/ml PEN: 14% EEN: 45% Anti-TNF: 62% p=0.001</td>
<td>Comparison with anti-TNF EEN reduced calprotectin</td>
<td>Lee. IBD, 2015</td>
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<td>Retrospective</td>
<td>Newly diagnosed CD</td>
<td>8–16 Weeks</td>
<td>EEN vs CS</td>
<td>EEN:76 pts CS 35 pts</td>
<td>EEN: 86.6% remission vs CS: 58.1% p&lt;0.01</td>
<td>Reduced need for steroids</td>
<td>Connors. JCC, 2017</td>
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<tr>
<td>Prospective inception cohort</td>
<td>Newly diagnosed children</td>
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5-ASA, 5-aminosalicylic acid; CD, Crohn disease; CDAI, Crohn’s Disease Activity Index; CS, corticosteroids; EEN, exclusion enteral nutrition; FCP, faecal calprotectin; ITT, intention to treat; MUFA, monounsaturated fatty acids; NCR, normal C reactive protein remission; PEN, partial enteral nutrition; PUFA, polyunsaturated fatty acids.
70% of patients; this was accompanied by a significant drop in ESR and CRP and was associated with mucosal healing among patients who achieved remission and were evaluated during the maintenance phase of the diet. The diet is low in animal fat, rich in complex carbohydrates, with moderate exposure to soluble fibre. It excludes wheat and dairy, emulsifiers, maltodextrins, carrageenans and sulfites. This diet was subsequently evaluated for induction of remission in children and adults failing biologics. Among 21 patients with active disease after loss of response to biologics despite dose escalation or combination therapy, 61% achieved clinical remission, again with a significant drop in inflammatory markers. While limited by design, these two retrospective studies reported remission with an exclusion diet at both ends of the spectrum of clinical disease, suggesting that diet may be an important tool for controlling active disease even in established disease and among biologic unresponsive patients. These reports should be viewed as preliminary data that need to be validated in prospective controlled trials. Several RCTs using this method are ongoing at the present time (NCT01728870, NCT02843100, NCT02231814). The specific carbohydrate diet restricting carbohydrates and processed foods has been advocated for CD and UC. This was previously evaluated in 10 children with very mild disease and among biologic unresponsive patients. These reports are ongoing at the present time (NCT02213835, NCT01749813). The specific carbohydrate diet restricting carbohydrates and processed foods has been advocated for CD and UC. This was previously evaluated in 10 children with very mild disease and among biologic unresponsive patients. These reports are ongoing at the present time (NCT02213835, NCT01749813). The specific carbohydrate diet restricting carbohydrates and processed foods has been advocated for CD and UC. This was previously evaluated in 10 children with very mild disease and among biologic unresponsive patients. These reports are ongoing at the present time (NCT02213835, NCT01749813).

Maintenance of remission

The idea of maintaining remission with diet is compelling and challenging at the same time. On the one hand, once remission is established, it is certainly possible that diet will be sufficient to maintain homeostasis and prevent the cascade of pro-inflammatory events leading to flare; however, long-term studies are challenging to perform and adherence becomes a serious concern. Nevertheless, several studies have assessed PEN for maintenance of remission, some showing promising results.

One of the first studies to suggest the merit of PEN was published in Gut in 1996. Wilschanski et al followed 28 children who responded to EEN induction therapy for up to 12 months and agreed to receive nightly nasogastric PEN; they were less likely to flare than the 19 patients who chose not to receive PEN. A review, which included 10 published studies, most of which were not randomised, demonstrated some endoscopic improvement with PEN, but the overall quality of these studies was limited, highlighting the need for large, prospective RCTs.

A retrospective, single-centre study from Israel followed 42 children who responded to EEN and then went on PEN (50% liquid formula, 50% free diet) for a median of 40 months. Although a survival analysis was not included, median time for remaining in remission was 6 months; however, the median time in remission without need for additional therapy was 0 months (0–16 months). Eighty-six percent of patients started on PEN as maintenance therapy required additional therapy by 6 months. There is insufficient evidence to recommend PEN as the only maintenance therapy in children based on existing data.

Another approach, mainly based on studies in adults from Japan, has focused on partial elemental diet (ED), providing a minimum of 900 kcal/day combined with a free diet. An RCT comparing this approach to a fully free diet showed lower relapse rates at a mean follow-up of 1 year (34.6% vs 64%). More recent retrospective studies have indicated a potential advantage for partial ED in reducing loss of response to infliximab and adalimumab. PEN has also been shown to be effective in preventing postoperative recurrence of CD. Twenty adults who were compliant to EN were treated with nightly ED and a low fat diet during the day and were followed for 5 years; remarkably, 16 maintained the diet. Only two had disease recurrence (vs 9/20 in a normal-diet control group; p=0.03) and 1 (vs 5) required additional surgery. Japanese researchers randomised adult patients...
Dietary therapy for complicated CD

CD is associated with several complications that eventually can lead to surgery. Treatment of complicated disease, such as strictures, abscesses and fistulae has traditionally been either medical or surgical. Recent studies have demonstrated that dietary therapy with EEN may have the potential to treat complications and have a ‘surgery sparing effect’.

Two studies conducted by a group from China evaluated the efficacy of EEN in complicated CD. Hu et al conducted a prospective, observational study to examine the effects of 12 weeks of EEN on inflammatory bowel strictures. They performed cross-sectional CT before and after therapy. Sixty-five per cent of patients achieved clinical remission, while 54% achieved radiologic remission. This was accompanied by a significant increase in luminal diameter and a significant decrease in bowel wall thickness. Yan et al conducted a prospective study to identify the predictors of response to 12 weeks of EEN in patients with CD who had enterocutaneous fistulae. They demonstrated that 30/48 (62.5%) had a successfully closure of fistula after EEN therapy with average closure time of 32.4±8.85 days. They found that decreased CRP and elevated body mass index levels were associated with response to EN in patients with CD with enterocutaneous fistulae.

EEN has also been demonstrated to reduce the need for surgery in complicated disease. Heerasing et al demonstrated in a retrospective case-control study that EEN for a period of 6 weeks could lead to avoidance of surgery in 13/51 (25%) of patients who were scheduled for an elective surgical resection. They also showed by multivariable logistic regression analysis that patients who went to surgery without EEN had a ninefold increase in the incidence of postoperative abscess and/or anastomotic leak (OR:9.1; 95%CI 1.2 to 71.2, p=0.04). An additional recent retrospective study conducted by a group from China reported that patients with CD with intra-abdominal abscesses who were treated with 4 weeks of EEN and antibiotics were less likely to require surgical intervention compared with those who did not use EEN (26.1% vs 56.3%, p=0.01). Several studies have confirmed that perioperative EEN can improve surgical outcomes, reduce complications and the need for immune suppression. Use of preoperative EEN may have long-lasting effects. Wang et al found that EEN prior to resection was accompanied by a significant reduction of endoscopic recurrence rates after resection for CD after 6 months. In addition, a large retrospective study demonstrated that administration of EEN for approximately 4 weeks led to lower rates of stoma creation (p<0.05), a decrease in urgent operation requirement (p<0.05) and extended preoperative drug-free intervals (p<0.001).

Diet for functional symptoms

Patients with IBD may experience GI symptoms even during remission without undergoing inflammation. Recent studies have demonstrated that restriction of several groups of fermentable carbohydrates (low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet) is effective in the management of functional symptoms. Prince et al found that 78%, p<0.001 with IBD reported satisfactory relief of functional symptoms after 6 weeks of low FODMAP diet. A recent meta-analysis concluded that a low FODMAP diet is beneficial for reducing GI symptoms in patients with quiescent IBD. Halmos et al showed that the low FODMAP diet had no effect on the calprotectin results in patients with CD. Furthermore, altering dietary FODMAP intake was associated with possible detrimental changes in faecal microbiota and therefore is not recommended for extended periods of time.

Summary

In summary, there seems to be a growing body of evidence to suggest that dietary factors may play an important role in the pathogenesis of CD. Use of EEN has expanded from a tool for induction of remission in children at disease onset, to a tool with potential to treat very complicated long duration disease in adults (figure 4). Use of perioperative EEN has the potential to avoid the need for surgery, reduce poor surgical outcomes and delay postoperative recurrence in CD. Perhaps the most exciting development is the potential to induce and maintain remission by use of exclusion diets and PEN, which would enable wider use of dietary therapy across the spectrum. However, the field still has insufficient high-quality evidence due to the small number of well-designed trials performed to date, but the future appears to be bright in CD. RCTs with newer dietary interventions or indications are warranted. Perhaps the largest research gaps at the present are in the field of UC. Although there are emerging clues linking diet to UC as well, researchers have yet to make the jump from bench to bedside in UC, and we still do not know if dietary therapy would be effective in UC.

Contributors

All authors contributed to the writing of the manuscript.

Funding

This study was funded by grants from Nestle and the Aziem Foundation.

Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Commissioned; externally peer reviewed.

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