

Review Article

Mechanisms underlying clinical efficacy of enteral nutrition in inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD) is a chronic life-long disease of unknown etiology, affecting the entire digestive tract in addition to a host of extraintestinal manifestations. Two major manifestations include ulcerative colitis (UC) and Crohn's disease (CD). Pharmacotherapy is often effective, but associated with substantial side effects. Fortunately, however, enteral nutrition (EN) is often effective for inducing and maintaining disease remission, with few side effects. Despite the widespread use of EN in the clinical management of IBD, its mechanisms of action are not clearly understood. In this review, we attempt to elucidate the mechanisms by investigating the current body of biomedical literature vis-à-vis the pathophysiology of IBD.

Keywords: Digestive tract, dietary composition, enteral nutrition, IBD, mechanism

Introduction

Inflammatory bowel disease (IBD) is an aberrant chronic intestinal inflammation attributed to an abnormal immune response to the intestinal microflora [1]. The disease typically manifests itself at puberty and is both life-long and incurable. Palliative treatment is expensive, and inflicts substantial costs to society [2]. Two major manifestations of IBD differing in clinical presentation and to a certain extent in clinical management include ulcerative colitis (UC) and Crohn's disease (CD). Although the etiology of both CD and UC remains largely obscure, the pathogenesis of IBD depends on the interaction of genetic, environmental and immunological factors as well as psychological factors including stress [3, 4]. Mechanistically, the disease involves an unbalanced response of the intestinal immune system against the enteric microflora, which often appears symbiotic in IBD patients [5]. In apparent agreement, nutritional therapy aimed at improving gut flora or increasing mucosal tolerance is partly successful in the management of IBD, although it can hardly be considered a panacea [6]. Nevertheless, nutritional therapies are attractive in light of the costs and side-effects associated

with pharmacological treatment. Indeed, despite the availability of 5-aminosalicylates, corticosteroids, immunosuppressive, biological agents and antibiotics for the treatment of IBD, in addition to endoscopic and surgical options, many physicians opt for nutritional therapy for the disease, either as a stand-alone strategy or in conjunction with other options [7]. Nutrition has proven to be indispensable in the clinical care of patients with IBD. Initial reports of enteral nutrition (EN) in the treatment of CD appeared in the late 1960s, and primarily focused on the improvement of nutritional status in this often malnourished patient group [8]. Nutritional support aims to correct malnutrition and macro- or micro-nutrient deficiencies and reversal of their metabolic consequences remains an important clinical goal for EN [9]. However, it has also emerged that EN is effective in inducing and maintaining clinical remission of IBD, and, at least for pediatric CD, it is the initial and most preferred treatment modality [10-12]. In pediatric CD, EN is associated with equivalent or better remission rates than those achieved with some of the other drugs currently in use. Remarkably, even mucosal healing following EN has been reported [13]. Its clinical success sometimes obviates the need

for steroids. It is fair to say that EN is now firmly established as an important treatment option in IBD. Surprisingly, however, the mechanisms of action underlying EN effects in IBD remains poorly understood, prompting further analysis. In this review, we mine the body of contemporary biomedical literature for potential mechanisms and try to relate these to current insights into the pathophysiology of IBD.

The role of diet in IBD

Western diets are associated with IBD, even if the IBD-promoting elements remain unclear [14]. Although clear-cut evidence is largely absent, there are plausible theories suggesting that intake of abundant sucrose, refined carbohydrates, omega-6 fatty acids as well as reduced consumption of fruit and vegetables may be linked to IBD. In addition, substantial microparticle load derived from dust and food additives may be antigenic and thus elicit mucosal immune response. Relatively novel dietary patterns, including fast food, appear to relate to an increased risk for contracting IBD and may explain the global increase in IBD incidence in the last decades. A few studies have suggested a protective effect of n-3 polyunsaturated fatty acids (PUFAs) on IBD [15], whereas monounsaturated and polyunsaturated fats are both associated with a higher risk for developing UC [16]. Butyrate-derived and propionate-derived short chain fatty acids (SCFAs) are produced in the process of the chronic fermentation of dietary fiber and other unabsorbable carbohydrates, and a relation to the pathophysiology of UC has been made [17, 18]. Diet predisposes or protects against IBD development via modulation of the intestinal microflora, promoting or counteracting dysbiosis. Further studies involving prospective cohorts of juveniles, however, are being conducted. For example, the large Rotterdam generation cohort comprises 10000 children who are now 14 years of age, the age at which onset of IBD increases. Until other etiologies are established, direct interaction of dietary components with the mucosal immune systems cannot be excluded.

Malnutrition and IBD

Malnutrition and avitaminosis is common in patients with IBD, especially in those with active disease. Approximately 65% to 75% of

CD patients are undernourished [19]. Malnutrition in IBD at large is an astounding 85% [20]. Nutritional disturbances in patients with IBD include macro- and micro-nutrient deficiencies such as hypoproteinemia and hypoalbuminemia, electrolyte (calcium, magnesium, potassium) and trace element (zinc, copper, and selenium) disturbances, vitamin (B12, A, complex B, C, D, and E) deficiencies, anemia (due to iron, B12, and folic acid deficiency), and loss of weight [21, 22]. Especially in growing children, but in principle for the entire population of IBD patients, nutrition status needs to be vigilantly monitored.

Nutrition and mucosal antigenicity

A probate action in especially malnourished IBD patients is the introduction of EN. EN can be divided into elemental formula, semi-elemental formula, and polymeric formula [23]. The elemental formula contains only amino acids, fatty acids, and the nutrients which do not need digestion. The semi-elemental formula contains small peptides, oligosaccharides, and medium-chain fatty acids. The polymeric formula contains proteins, carbohydrates, medium- and long-chain fatty acids, vitamins, and trace elements. Nutritional therapy supports uptake of essential nutrients, improves poor nutritional status, corrects a negative nitrogen balance, and supports growth of IBD patients. A prospective, open-label study [24] in pediatric patients with CD analyzed the effect of short-term and supportive EN for 4 weeks, followed by 1 year of treatment, and indicated that it may be effective in pediatric CD patients for improving nutritional status while simultaneously moderating disease severity. Berni Canani et al. [25] showed that the nutritional therapy was more effective than steroids in restoring linear growth in pediatric CD patients. Royal et al. [26] assessed the nutrition of 30 adult patients with newly diagnosed CD who received enteral therapy for 3 weeks. The results indicated that the total body protein and fat increased, and all patients gained weight. Further studies on the effect of EN in IBD [27] showed that serum concentrations of n-3 fatty acids were reduced significantly in CD patients compared with the control group, and the disease was characterized by an increased ratio of n-6 versus n-3 fatty acids. Importantly, the n-6: n-3 ratio was related significantly to the Crohn's Disease Activity Index. A double-blind,

randomized multicenter European trial [28] demonstrated that levels of total fat or n-6 polyunsaturated fatty acids were decreased in patients with CD following EN for four weeks. EN may promote nutritional rehabilitation and iron storage in the body, and improve hematological profile. Werkstetter et al. [29] investigated the short-term impact of nutritional therapy on bone mineral density, geometry, and muscle mass in pediatric CD. The results showed that the poor bone remodeling and severe loss of muscle mass in this patient group was improved within 3 months after starting exclusive EN. In addition, EN increases protein synthesis and suppresses catabolism [30]. The decrease of total fat or protein intake might lower the antigenicity in the intestinal lumen, and the production of eicosanoid precursors (prostaglandins and leukotrienes), thereby reducing inflammation [31-34]. Elemental formulas slow down the emptying of the stomach, but concomitantly reduce acid secretion and the release of pancreatic enzymes [35], as the volume of ingested food by itself activates mechanoreceptor responses, which in turn activate neuronal negative feedback loops [36]. When the formula is sipped or infused at a slow rate, the mechanoreceptor responses may be decreased. EN provides obvious caloric nutritional support and is trophic (either directly or through neuronal loops) for the intestinal epithelial compartment, an effect likely to be beneficial, especially for UC [37]. Furthermore, the antigenic load, low levels of n-6 PUFAs, relatively high levels of n-3 PUFAs, and jejunum-dominant absorption are expected to be beneficial [38, 39]. Further, improved nutritional intake and status may limit luminal antigen exposure [40]. In brief, alteration of dietary composition associated with EN reduces antigenic load through various mechanisms while concomitantly improving barrier function and may be an important contributing factor in the beneficial effects of EN in IBD [41, 42]. Studies on the role of EN in nutrition and mucosal antigenicity are summarized in **Table 1**.

Altered gut microbiota and dysbiosis

Imbalance of beneficial bacteria and harmful bacteria, called “dysbiosis” contributes to the development of IBD, but has yet to be related to EN [43]. IBD relates to a decrease in intestinal microbiota diversity [43-47]. The relative pro-

portion of Firmicutes is decreased, whereas the fraction of Proteobacteria and Actinobacteria is increased in IBD [35]. Importantly, EN has low residue and contains important prebiotic properties [48], which modify the gut microflora. Thus, it is plausible that EN affects gut microbiota composition by changing fecal metabolic activity [49]. In apparent agreement, various studies [50] indicated that EN also reduces intestinal permeability via modulation of tight junctions and downregulates the production of inflammatory cytokines by modulating the intestinal microbiome. Unfortunately, until now, only few studies have investigated the effect of EN on the gut microbiota of CD patients. However, Kaakoush et al. [51], using 16S rRNA gene and whole-genome high throughput sequencing determined changes in the fecal microbiota of five CD children, before, during, and after EN therapy, and showed that the microbial diversity observed in CD patients tended to be lower than in controls, consistent with the dysbiosis hypothesis, but also specific EN-dependent microbiome effects of EN. Also Lionnetti et al. [52], using the slightly less advanced temperature gradient gel electrophoresis (TGGE) arrived at almost similar conclusions. Leach et al. [53] using denaturing gradient gel electrophoresis (DGGE), examined the fecal microbiota in 6 pediatric CD and also found that intestinal bacterial composition was significantly affected by EN, reporting that the Bacteroides-Prevotella group was associated with disease activity. Tjellstrom et al. [54] did not study microbiome composition *per se* but used the short chain fatty acid (SCFA) pattern as a surrogate marker. Investigation of the intestinal microflora function in fecal samples from 18 children with active CD, revealed that the success of EN in children with active small bowel/colonic CD was associated with an anti-inflammatory SCFA pattern, further suggesting the importance of EN-dependent microbiome changes. Thus, the evidence that EN-dependent microbiological changes in the intestine are clinically significant despite the lack of large-scale systematic studies seems compelling [55]. Studies on the role of EN in gut microbial and dysbiosis are listed in **Table 2**.

EN alters immune responses

Cytokines play a key role in the regulation of the intestinal immune system, and thus are criti-

Clinical efficacy of EN

Table 1. Studies on the role of EN in nutrition and mucosal antigenicity

First author, year	Methods	Results
Kang et al. [24], 2015	A prospective, open-label study: 78 patients in all, with 17 severe CD undergoing short-term partial EN (SPEN) for 4 weeks; followed all patients for 1 year and nutritional parameters and PCDAI analyzed.	Nutritional status improved after 1 year of treatment in the severe CD group. Nutritional status in SPEN group improved significantly compared to non-SPEN group.
Berni Canani et al. [25], 2005	Retrospective study: 37 pediatric active CD patients with Elemental, Semi-elemental, and Polymeric (Modulen IBD), 10 patients with corticosteroids, assessed the efficacy in inducing remission and mucosal healing and growth recovery.	Clinical remission similar. The mucosal inflammation improved significantly in EN group (64.8%), and seven subjects achieved complete mucosal healing.
Royal et al. [26], 1995	Prospective study: 30 active CD patients with 21 days of EN, 30 healthy controls. Body composition (total body protein, fat, water and potassium) were analyzed.	Body weight increased 1.9 ± 0.3 kg ($P < 0.005$), accompanied by an increase in body protein, fat and water.
Gassull [28], 2002	Multicenter, randomized, double blind trials: Two polymeric enteric diets not more than 4 weeks versus prednisone. One diet (PEN1) was rich in n9 MUFA, and the other diet (PEN2) rich in n6 PUFA; clinical activity, biological and nutritional parameters were assessed.	The remission rates were lowest in PEN1, whenever adjusted for confounding variables.
Werkstetter et al. [29], 2013	Prospective study: Ten newly diagnosed CD patients with 8 weeks EN, trabecular and cortical bone mineral density, total bone, and muscle cross-sectional area (CSA) were assessed before and after 12 and 52 weeks.	Eight achieved remission at week 12; low trabecular density improved ($P = 0.006$), and cortical density normalized ($P = 0.027$).

Table 2. Studies on the role of EN in gut microbial and dysbiosis

First author, year	Methods	Results
Gerasimidis et al. [49], 2014	Prospective study: Five fecal samples from CD children: 4 during EN (start, 15, 30, end EEN 60 days) and the fifth on habitual diet; two samples collected from healthy control; measured bacterial metabolites, global microbial diversity abundance, and composition stability, etc.	Global bacterial diversity abundance decreased in CD patients ($P < 0.05$). After EN treatment, the magnitude of the observed changes was greater and the concentration of Bacteroides/Prevotella group decreased ($P < 0.05$).
Kaakoush et al. [51], 2015	Prospective study: Fecal samples from five CD patients and five healthy controls collected before, during and after EN therapy at baseline and at 1, 2, 4, 6, 8, 12, 16 and 26 weeks, assessed changes in the fecal microbiota using 16S rRNA gene and whole-genome high throughout sequencing.	Microbial diversity in CD group lower than in controls ($P = 0.11$), and dysbiosis observed in CD patients. Six families within the Firmicutes were correlated with disease activity during and following EN therapy.
Lionnetti et al. [52], 2005	Prospective study: Nine children and adults with active CD and five healthy children, 8 weeks EN with PF (Modulen IBD), fecal microflora assessed with 16S rRNA gene and temperature gradient gel electrophoresis (TGGE).	Eight of nine patients achieved clinical remission with EN. The fecal microflora were modified in all CD patients with EN.
Leach et al. [53], 2008	Prospective study: Fecal samples from 6 CD patients and 7 healthy controls collected before, during and after EN treatment at baseline and at 1, 2, 4, 6, 8, 16, 26 weeks, assessed the diversity of bacteria using denaturing gradient gel electrophoresis (DGGE).	Bacterial composition changed significantly with EN, and remained altered for four months.
Tjellstrom et al. [54], 2012	Retrospective study: Fecal samples from 18 children with active CD, analyzed gut microflora before and after EN treatment using SCFA pattern.	With EN, 11 (79%) showed decreased level of pro-inflammatory acetic acid and increased concentration of anti-inflammatory butyric acids and valeric acids.

cally involved in mucosal inflammation. Pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor (TNF)- α , and anti-inflammatory mediators like IL-1 receptor antagonist (IL-1ra) are increased in IBD [56-59]. Anti-TNF therapies successfully targeted this cytokine in the pathogenesis of IBD [63]. Interestingly, anti-TNF therapies show highly varying effects in IBD: infliximab and humira are very effective, but etanercept was worse than placebo [60]. EN is synergistic with infliximab but not etanercept in the treatment of CD, suggesting common effector mechanisms [61]. Although the reduction of antigen load through EN therapy is an obvious mechanism, recent studies suggest that EN-dependent effects on the production of mucosal proinflammatory cytokines may be more important [62]. It is reported that EN with TGF- β_2 -enriched formula may induce remission and mucosal healing [63]. The mechanistic basis of these proposed effects remains unclear although a few hypotheses have been postulated. Wedrychowicz et al. [64] assessed the influence of EN on serum vascular endothelial growth factor (VEGF) and transforming growth factor-beta 1 (TGF- β_1) levels in children and adolescents with IBD, and showed that the concentrations of serum VEGF and TGF- β_1 are increased in the CD group with 2 to 4 weeks following treatment of EN, which might explain the higher effectiveness of EN in CD group. Fell et al. [65] investigated IL-1 β , IL-8, interferon- γ and TGF- β_1 mRNA in the terminal ileum with 8 weeks of EN in pediatric CD patients, and reported that the level of the immune-modulatory cytokine TGF- β_1 mRNA was significantly increased, whereas concomitantly the level of IL-1 β , IL-8, and interferon- γ was reduced. Yamamoto [66] assessed mucosal cytokine concentrations (IL-1 β , IL-1ra, IL-6, IL-8, and TNF- α) in the terminal ileum and large bowel in active CD patients who were treated with an elemental diet (Elental) for 4 weeks. This study showed that Elental reduced production of mucosal cytokine production and apparently corrected an imbalance between proinflammatory and anti-inflammatory cytokines in these patients. Simultaneous endoscopic and histologic healing of mucosal inflammation was associated with a decline in mucosal inflammatory cytokines. Yamamoto [66] also investigated the impact of long-term EN (1 year) on disease activity and mucosal levels of tissue cytokines in patients with quiescent CD and pro-

vided evidence that whereas mucosal tissue IL-1 β , IL-6, and TNF- α levels significantly increased over time in the non-EN group, in the EN group these cytokines were significantly suppressed. In apparent agreement, Breese et al. [67] found that EN reduce the level of lymphokine-secreting cells in the gut mucosa of pediatric CD patients. Furthermore, in a pre-clinical *in vitro* model, de Jong et al. [68] found that the polymeric formulas act directly on the intestinal epithelial cells and downregulate the level of the proinflammatory factor IL-8. Overall, EN might change the proportion of eicosanoids (leukotriene B₄, thromboxane A₂, prostaglandin E₂) and increase the number of anti-inflammatory cytokine producing cells [34, 69], reduce the number of cytokine producing cells and byproducts [65, 67, 70-74], leading to suppression of the immune response and decreased inflammation. Hence, EN appears to exert remarkably strong immune system attenuating effects. Studies on the role of EN in immune responses are listed in **Table 3**.

Effects on mesenteric adipose tissue

Mesenteric adipose tissue (MAT) plays an important role in the pathogenesis of Crohn's disease (CD). In 1932, Burill B. Crohn [75] described mesenteric fat hypertrophy, fat wrapping and highly typical aspect of creeping fat in patients with CD. Feng Y et al. [76] evaluated the effects of EN on CD patients, focusing upon MAT alterations, such as adipocyte size and adipokine production, and showed that EN ameliorated mesenteric fat alteration in IBD, apparently by restoring adipocyte morphology and diminishing the inflammatory environment of the mesenteric fat. Li Y et al. [77] calculated the mesenteric fat index (MFI), as defined by the ratio of visceral fat area (VFA) to subcutaneous fat area (SFA), and found that EN induction therapy was associated with a significant decrease in VFA in patients with CD, whereas the MFI was significantly correlated with the CD activity index and also with C-reactive protein levels in active CD. Although effects on the adipose compartment appear to correlate with beneficial effects of EN in IBD, the issue whether this is an epiphenomenon or a causal effect has yet to be established.

Conclusion

In conclusion, the pathogenesis of IBD involves multiple aspects, which are potentially targeted

Clinical efficacy of EN

Table 3. Studies on the role of EN in immune responses

First author, year	Methods	Results
Hartman [63], 2008	Retrospective study: 28 CD patients received Modulen IBD, which is rich in TGF- β_2 , 18 with polymeric formula, (lactose-free polymeric diet) and 18 without nutrition, and investigated the clinical manifestations, growth and PCDAI.	In the Modulen IBD group, significant improvements in body mass index ($P = 0.01$) and erythrocyte sedimentation rate ($P = 0.03$) were indicated.
Wedrychowicz [64], 2011	Prospective study: 39 patients with newly diagnosed (24 CD and 15 UC), assessed VEGF and TGF- β_1 at the baseline and after 2 and 4 weeks of EN.	During EN, serum VEGF decreased in the UC and CD groups ($P < 0.05$), the TGF- β_1 only increased in the CD group ($P < 0.05$), and the CD group achieved disease remission faster than the UC group.
Fell [65], 2000	Prospective study: 29 consecutive pediatric CD cases treated with oral polymeric diet (CT3211) for 8 weeks, IL-1 β , IFN- γ , TGF- β_1 and IL-8 mRNA measured in mucosal biopsies before and after treatment by qRT-PCR.	Complete clinical remission in 79%; macroscopic and histological healing associated with a decline IL-1 β ($P = 0.006$). TGF- β_1 mRNA increased in the ileum ($P = 0.04$), the IL-8 mRNA decreased ($P < 0.05$).
Yamamoto [66], 2005	Prospective, single center, pilot trial: 28 consecutive patients with active CD with an elemental diet (Elental) for 4 weeks, and assessed mucosal concentrations of IL-1 β , IL-1ra, IL-6, IL-8, and TNF- α .	The clinical remission was 71%. After treatment, cytokine concentrations decreased to the levels of control. Endoscopic and histologic healing of the mucosal inflammation was associated with a decline of the mucosal cytokines and an increase of the IL-1ra/IL-1 β ratio.
Yamamoto [74], 2007	Prospective, single center study: 40 CD patients achieved clinical remission (20 with EN and 20 with non-EN), followed for 1 year, IL-1 β , IL-6 and TNF- α of mucosal biopsies were assessed.	On an intention-to-treat basis, 5 patients (25%) in the EN and 13 (65%) in non-EN group relapsed ($P = 0.03$), and EI scores higher in the non-EN group ($P = 0.04$). Cytokine levels increased in the non-EN group in 12 months ($P < 0.05$).
De Jong [68], 2007	In an in vitro model of epithelial cell inflammation, investigated the anti-inflammatory effects of exclusive enteral nutrition using polymeric formula (PF).	PF did not affect cell viability over a range of dilutions. PF addition to the culture medium significantly reduced the IL-8 response to proinflammatory stimuli.

by EN, in particular by supporting nutritional status of patients, by improving intestinal epithelial barrier function and reducing antigenic load, while counteracting dysbiosis. In addition, EN directly affects mucosal immunity and the intestinal adipose compartment. Thus the effects of EN are truly kaleidoscopic but generally beneficial. Increased insight into the mechanisms of EN in IBD will certainly aid in the design of improved formulas.

Disclosure of conflict of interest

None.

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