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REVIEW

Exclusive Enteral Nutrition in Adult Crohn's Disease: an Overview of Clinical Practice and Perceived Barriers

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Abstract: Recently, the role of nutrition in the management of Crohn's disease (CD) is of increasing interest and the exploration of novel nutritional interventions to improve long-term management of the disease is challenging. So far, the majority of the studies on the role of exclusive enteral nutrition (EEN) in CD are conducted in the pediatric population and have highlighted the efficacy of EEN for achieving mucosal healing. This implicates that a similar approach would be beneficial in adult patients. However, the evidence for EEN in adults is heterogeneous, with meta-analyses reporting it as inferior to steroids while growing data demonstrate improvement in complicated CD. Currently, EEN is less used in adult patients with IBD. Indeed, the lack of palatability of enteral formula leads to difficulties in acceptance and compliance. The search for more tolerable and still effective diets has become an intense area of research aiming to explore the potential role of diet to control inflammation in patients with CD. Thus, this narrative review provides the state-of-the-art on the use of EEN treatment in CD and highlights the perceived barriers to its implementation in adult CD patients.

Keywords: Crohn's disease, exclusive enteral nutrition, barriers, diet, nutritional interventions

Introduction

Crohn's disease (CD) is a chronic, idiopathic, and disabling inflammatory bowel disease (IBD), of unknown etiology that affects any segment of the gastrointestinal tract.[1,2] Recently, CD has evolved into a global burden, given its high incidence in developed countries and at the same time the substantial increase in incidence in developing countries.[3] Multiple factors, such as genetic background, environmental and luminal factors, and mucosal immune dysregulation, have been suggested to contribute to CD pathogenesis.[4] The leading hypothesis involves an inflammatory damage to the intestine due to an aberrant immune response against the gut microbiota (GM), in genetically predisposed individuals.[5–9] Importantly, an improved understanding of the mechanisms underlying CD has led to the development of new treatments.

New therapeutic strategies include *treat to target* algorithm and *tight control* in order to modify the natural course of disease, avoid disease complications and prevent disability.[1,10–14] However, in the last years, diet has become the focus of intense research aiming to improve nutritional interventions with particular interest in the modulation of GM.

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In this context, exclusive enteral nutrition (EEN), containing macro- and micro-nutrients in powder or liquid form, represents a low-risk and minimally invasive first-line therapy for pediatric patients affected by CD. Several studies showed that EEN induces mucosal healing in about 80% of patients and provides likewise an appropriate nutritional feed and growth.[15–19] Meanwhile, there is emerging but limited evidence on the role of EEN in adults and on its efficacy in inducing remission in CD.[20–23] Indeed, the routine use of EEN in adult CD patients in Western countries is still controversial. Thus, this narrative review provides an up-to-date analysis on the use of EEN in CD and highlights the perceived barriers to its implementation in adult with CD.

Literature Search

An electronic database search using PubMed and Medline was done by RdS and OMN from inception to October 2021 using the search terms "Crohn's disease" OR "CD", OR "inflammatory bowel disease", OR "IBD", AND "exclusive enteral nutrition", OR "EEN", OR "enteral nutrition", OR "EN", AND "clinical remission", AND "endoscopic remission", OR "mucosal healing", AND "adults", AND "adherence", AND "barriers".

A supplementary search was done on the basis of the references of the selected papers. Only articles published in English were included. We screened the articles for suitability for the scope of this narrative review, then reviewed the full text of articles and excluded those that did not fit the aim of our paper.

Mechanism of Action of Exclusive Enteral Nutrition

The role of EEN in the obtaining of remission in CD is still unclear and not fully understood. However, it might be explained by its anti-inflammatory properties, modulating systemic and bowel inflammation, intestinal permeability, and GM, all considered as principal key players in the pathogenesis of CD.[24]

It is documented that the use of EEN in CD is able to modulate the inflammatory status that characterizes active CD, normalizing inflammatory biomarkers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin (FC), and decreasing levels of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF)-α.[25–28] Further, in CD patients who achieved remission after EEN, a trend is seen for normalizing of the inflamed mucosal microRNA expression profile, becoming similar to healthy controls' profile.[29] Considering in vitro studies, it has been demonstrated that EEN plays a direct effect on enterocytes in the downregulation of IL-6 and IL-8 response, modulating the nuclear factor (NF)-κB and p38 mitogen protein kinase pathways, implicated in the development of gut inflammation.[30–32]

The increase of intestinal permeability is widely considered as an indicator of intestinal barrier dysfunction implicated not only in IBD, but also in other gastrointestinal and extraintestinal disorders.[33] Several studies documented that the epithelial barrier function is impaired in CD patients with consequent translocation of bacterial endotoxins, such as lipopolysaccharide, into systemic circulation, leading to the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-related stimulation of dendritic cells and macrophages to produce pro-inflammatory cytokines and mediators, such as cyclooxygenase-2 (COX-2), TNF-α, inducible nitric oxide synthase (iNOS), and IL-6.[34–37] Furthermore, it has been demonstrated that EEN has anti-inflammatory properties on the intestinal epithelial cells in CD patients, by restoring the physiological intestinal permeability after 6 weeks of treatment.[38] With regards to barrier functions, Nahidi et al. analyzed the impact of EEN on tight junctions in presence of TNF-α. Interestingly, EEN enhances the integrity of the gut barrier by reducing myosin II regulatory light-chain kinase (MLCK) protein expression in in vitro models of Caco-2 epithelial monolayers.[39] Similar animal studies documented the role of EEN treatment in restoring gut barrier function, by maintaining tight junction integrity and likewise reversing inflammatory status.[40]

It has been hypothesized that EEN plays a role in the modulation of GM, a complex ecosystem consisting of more than 10^{14} bacteria and more than 1000 species as well as fungi, viruses, phages, parasites, and archea, colonizing the entire gastrointestinal tract.[24,41] It is widely recognized that CD is associated with gut dysbiosis, characterized by a generalized decrease in biodiversity and a specific reduction of Firmicutes and Bacteroidetes, Lactobacillus and Eubacterium, leading to a dysregulation of the innate and adaptive immune responses in genetically predisposed subjects, by promoting intestinal inflammation, with other concomitant environmental factors.[42–47] In this context, it has been demonstrated that EEN treatment in CD is associated with particular taxonomic shifts, such as a decrease in the abundance of Firmicutes (e.g., Faecalibacterium),

Bacteroides/Prevotella, and Proteobacteriaceae and an increase in Bacteroidetes.[48]

Enteral Nutrition Formulations and Practical Issues

Enteral nutrition (EN) is classified as either (1) "elemental", amino-acid based, made by mixing free single amino acids; (2) "semi-elemental", oligopeptide-based, made by protein hydrolysis, characterized by a mean peptide chain length of four or five amino acids; (3) "polymeric", whole protein-based, from sources such as milk, meat, egg, or soy.[49] Semi-elemental and elemental formulations are about 450 kcals per 100 g of powder, consisting approximately of 55% carbohydrate, 10% protein, and 35% fat, best suited in cases of severe CD, containing peptides and medium chain triglycerides, and are more absorbable compared with polymeric regimens.[49] Polymeric formulations are about 500 kcals per 100 g of powder, consisting approximately of 45% carbohydrate, 15% protein, and 40% fat, derived from corn syrup, soybean protein, sunflower and corn oil, and suggested as first-line for CD patients without a severe malabsorption or milk protein allergy.[50] Nowadays, more than 90% of IBD centers use polymeric regimens, such as Modulen IBD®, Ensure plus Milkshake style®, and Fortisip®, considering a similar efficacy for the induction of remission in pediatric CD patients, and likewise with more palatability and a lower cost compared with elemental formulations.[51–54]

A recent update of the European Crohn's and Colitis Organization [ECCO] - European Society of Pediatric Gastroenterology, Hepatology and Nutrition [ESPGHAN] guidelines on the medical management of pediatric CD recommends EEN as the first-line therapy for inducing remission of active CD.[55]

The duration of EEN to induce remission in pediatric CD patients, regardless of disease localization and given orally or by nasal or gastrostomy tubes, is 6–8 weeks. A fall of inflammatory biomarkers has been observed after the first two weeks of treatment.[16,56] Notably, once remission is achieved, the recommendation to use EEN ceases; however, EN can be used in case of malnutrition.[18] Regarding food reintroduction after the 6–8 weeks of EEN, prospective controlled studies that recommend a specific nutritional management are still lacking. Thus, a gradual reintroduction of food groups every 2–3 days over a period of 2–3 weeks with a simultaneous decrease of EN is generally adopted in clinical practice.[57]

Exclusive Enteral Nutrition in Adult Crohn's Disease Patients

The routine use of EEN is still debated in adults with CD in particular in Western countries rather than in Japan and progressively in China.[50] However, the poor adherence to therapy remains a significant and insurmountable barrier for its use. In order to assess the impact of EEN on clinical symptoms, nutritional status and inflammatory biomarkers in young adults with active CD, Wall et al. performed a prospective non-randomized pilot study, sequentially recruiting 38 patients treated with a 2-week EEN model of care, followed by either 6 weeks of EEN or partial EN (PEN) with one small meal of usual food.[20] Almost 90% of patients completed the "induction treatment" with a significant clinical improvement, assessed by Harvey Bradshaw Index (from a median value of 5 to 3 mg/L), associated with a significant decrease in CRP (from a median value of 10 to 5 mg/L) and FC (from a median value of 927 to 674 μg/g) and an increase in serum IGF-1, considered as a marker of nutritional status and likewise of disease activity.[20] Clinical remission and improvements in inflammatory biomarkers were sustained over the next 6 weeks with no significant difference between the 2 groups at week 8, proving that EN is an effective treatment in adults with CD for inducing remission.[20] A further prospective, single-center, observational study showed that 85% of adult CD patients (27 patients, aged 45±13 years, 63% female) successfully adhered to 6 weeks of EEN treatment with a weekly specialist dietetic support.[21] After EEN, about 75% achieved clinical remission, assessed by a CDAI score <150, with a trend for improvement of FC and platelets, and no significant differences observed in CRP, white cell count, and albumin.[21]

Similarly, a prospective trial in adult patients by Yamamoto et al. in 28 active CD patients found that after 4 weeks of EEN, 71% of patients achieved clinical remission, with endoscopic healing in 44% in the terminal ileum and 39% in the large bowel. Histologic healing was observed in 19% in the terminal ileum and in 20% in the large bowel.[28]

In a multicenter, randomized, double blind trial Gassull et al. reported that clinical remission in adult CD patients is achieved in about two thirds of cases after 4 weeks of exclusive polymeric enteral diet containing 35 g of lipids per 1000 kcal high in linoleate (45%) and low in oleate (28%), when excluding those patients who were non-compliant during the first week (per protocol analysis).[22]

Further, Pinguer et al. observed that a 2-month treatment with EEN in young adults is associated with a high rate of mucosal healing and a distinct gut microbiota composition shift, characterized by a decrease in Faecalibacterium and increased Roseburia and Clostridium species.[23]

Of note, Yang et al. prospectively showed in 41 adult active CD complicated with intestinal fistula/abdominal abscess or inflammatory intestinal stricture that EEN for 12 weeks was effective in inducing early clinical remission, mucosal healing, promoting fistula closure and reducing the size of abscesses.[58] The same group of research confirmed the effectiveness and safety of a 12-week treatment with EEN for active CD in 14 pregnant women, assessed by the decrease in CDAI and serum levels of CPR. Hence, this provides the rationale for a safe and effective alternative to conventional therapeutic strategies to induce clinical remission during pregnancy.[59] A recent retrospective analysis, conducted in 31 adults, described a significant improvement of clinical symptoms and biochemical parameters after a median duration of 4 weeks of EEN in adult patients with complicated CD.[60] It is noteworthy that among different phenotypes of CD, more than 80% patients had either stricturing or fistulizing disease. In addition, the baseline disease activity remained the most important predictor of clinical response to EEN.[60] Xuo et al. retrospectively evaluated 91 active isolated colonic CD patients with a median age of 33 years in order to establish potential factors that might influence the response to EEN.[61] Among the main determining factors, pancolitis resulted in the greatest contribution to the risk of non-response to EEN, followed by lean BMI and colonic lesion features.[61]

A Cochrane metanalysis investigated the effectiveness and safety of EEN as primary therapy to induce remission in CD.[62] A subgroup analysis by age showed a significant difference in remission rates for adults but not for children. Importantly corticosteroids seemed to be superior (73%; 116/158) to EEN (45%; 87/194) in adult patients.[62] Interestingly, there was no statistically significant difference in remission rates between EEN and corticosteroids therapy on a per-protocol analysis while the per-protocol subgroup analysis showed a difference in remission rates for both adults (RR 0.82, 95% CI 0.70–0.95) and children (RR 1.43, 95% CI 1.03–1.97).[62] However, patients receiving EEN were more likely to withdraw due to side effects than those on corticosteroids therapy.

In a pilot clinical trial involving 13 adult CD patients treated with 4-week EEN, Guo et al. investigated the impact of EEN on health-related quality of life.[63] A total of 11 patients (84.6%) achieved clinical remission with a significant improvement in total IBD questionnaire (IBDQ) score and all IBDQ dimensions, including bowel and systemic symptoms, social function, and emotional status after a 4-week treatment of EEN[63] (Table 1).

Perspectives and Barriers to Exclusive Enteral Nutrition

EEN prescriptions should be individualized according to a comprehensive nutritional assessment based on clinical indication assessed by a multidisciplinary IBD team. Major limitation of EEN use in adults is the relatively higher non-compliance rate, than children, mostly in case of longer durations of therapy.[64]

The main determining factors are GI intolerance (diarrhea, bloating, and flatulence) and unpalatability, in particular the monotony of the diet and the taste of polymeric formulas. Notably, the sharing of food and drink with work colleagues, family or friends is an essential part of most social interaction and the use of EEN could limit it. Therefore, personality trait in addition to social context (lifestyle, work or study commitments, and dietitian access), and health professional beliefs in the efficacy of the treatment should be considered before EEN is commenced.[65] Indeed, the compliance to EEN especially in semi-elemental preparation often affects its clinical effectiveness. Sharma et al. reported that among 31 patients, 7 patients (20%) referred intolerance to EEN that had to be discontinued.[60]

According to a national survey conducted by 51 Spanish gastroenterological units, the most important limiting factor for beginning EEN treatment in CD is the low acceptance by the patients due to lack of time and/or allied multidisciplinary staff, such as dietitians, nutritionists, psychologists, to follow-up and support them.[66] In order to determine the best suitable candidates between adult CD patients to treat with EEN, Wall et al. recruited 38 adults aged 16–40 years with newly diagnosed CD or having a flare-up of disease to use EEN for 8 weeks or 2 weeks of EEN followed by 6 weeks of PEN.[67] They assessed the personality traits of participants, by using the conscientiousness subset of the Big Five Inventory.[67] Importantly, adherence to EEN treatment is associated with a greater conscientiousness score compared with the non-adherent CD group, hence EEN should be considered for patients with more conscientious personalities.[67]

Table 1 Main Studies That Have Explored the Use of Exclusive Enteral Nutrition in Adult Crohn's Disease Patients

Authors, Year	Study Design	Study Population	Intervention/Groups	Outcomes	Key Findings
Gassull et al.,[22] 2002	Multicenter, Randomized, Double Blind Clinical Trial	62 active CD patients aged 18–65 years	Patients were enrolled into 3 groups to use for 4 weeks: (1) EEN high in oleate and low in linoleate (2) EEN high in linoleate and low in oleate (3) corticosteroids	Efficacy of two whole protein-based diets with different fat compositions for inducing clinical remission compared with steroids	Clinical remission in adult CD patients is achieved in about 2/3 of cases after 4 weeks of exclusive polymeric enteral diet high in linolate and low in oleate
Yamamoto et al.,[28] 2005	Prospective Study	28 active CD patients with a median age of 28 years	4 weeks of elemental diet	Impact of elemental diet on mucosal inflammation in young adult with CD	Endoscopic healing is obtained in about 40% of CD patients in association with a decline of the mucosal proinflammatory cytokines
Guo et al.,[63] 2013	Non-Randomized Clinical Trial	13 active CD patients aged 18–40 years	4 weeks of polymeric enteral nutrition	Impact of EEN on health-related quality of life in adults with active CD	4-week treatment of EEN significantly improves health-related quality of life
Yang et al.,[58] 2017	Prospective Study	41 complicated CD patients aged 18–60 years	12 weeks of EEN	Efficacy of EEN in adult CD patients complicated with intestinal fistula/abdominal abscess or inflammatory intestinal stricture	12 week-treatment is effective for inducing early clinical remission, mucosal healing, promoting fistula closure and reducing the abscess size
Wall et al.,[20] 2018	Prospective Study	30 active CD patients aged 16–40 years	Patients were recruited into 2 groups to use: 1) EEN for 8 weeks 2) EEN for 2 weeks + PEN for following 6 weeks	Impact of EN on clinical symptoms, nutrition and inflammatory markers	EN is an effective treatment in motivated adult CD patients that may prefer nutritional therapies to corticosteroids for inducing remission
Xu et al.,[61] 2019	Retrospective Study	91 active isolated colonic CD patients with a median age of 33 years	EEN for more than 2 weeks	Factors that influence the response to EEN in isolated colonic CD patients	Pancolitis is the greatest contributor to the risk of non-response to EEN, followed by lean BMI and colonic lesion features in isolated colonic CD patients
Wall et al.,[67] 2020	Prospective Study	38 active CD patients with a median age of 27 years	Patients were recruited into 2 groups to use: 1) EEN for 8 weeks 2) EEN for 2 weeks + PEN for following 6 weeks	Association between adherence to EEN and conscientious personality	Conscientiousness is associated with adherence to nutritional therapy and should be considered
Shukla et al.,[21] 2020	Prospective Study	27 active CD patients with a median age of 45 years	EEN for 6 weeks with a weekly specialist dietetic support	Clinical remission and adherence to EEN treatment	EEN may be achievable for adult CD patients for inducing remission when an additional professional dietetic support is provided

(*Continued*)

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Table 1 (Continued).

Authors, Year	Study Design	Study Population	Intervention/Groups	Outcomes	Key Findings
Yang et al.,[59] 2021	Retrospective Study	14 active CD pregnant women	12 weeks of EEN	Efficacy of EEN for inducing remission in women with a CD relapse during pregnancy	EEN may provide a safe and effective alternative treatment to induce remission in pregnant women
Sharma et al.,[60] 2021	Retrospective Study	31 complicated CD patients with a median age of 34 years	EEN for a median duration of 4 weeks	Efficacy of EEN for inducing remission in complicated CD patients	4 week-treatment of EEN significantly improves clinical symptoms and biochemical parameters of adult patients with complicated CD
Mutsekwa et al.,[65] 2021	Exploratory Qualitative Study	17 active CD patients with a median age of 45 years	Patients who had completed EEN treatment were interviewed	(1) Personal experience of EEN treatment (2) Potential strategies to manage challenges during EEN (3) Potential enablers for adherence to EEN	Support from social networks and health professionals, taste of polymeric formulas, and patients' perceived self-efficacy were strong enablers for adherence

In recent years major progress has been made to mimic EEN and develop several whole-food diets with biologically plausible mode of action. In an attempt to mimic EEN with an ordinary food, a novel diet called CD-TREAT diet, based on the composition of EEN, has been introduced.[15] The advantage of the CD-TREAT diet to EEN is the palatability, which is the limiting factor of EEN in adults. Indeed, a better tolerance of CD-TREAT in a healthy population has been found. After 8 weeks of CD-TREAT diet, 80% (4/5) showed a clinical response and 60% (3/5) of the pediatric CD patients were in remission. However, a limitation is the low study number of only 5 active pediatric CD patients.[15]

A recent study analysed, through individual semi-structured interviews, the adult patient experience with EEN to identify challenges and enablers. Thus, they aid clinicians in the development of strategies to improve patient's adherence.[65] Understanding the balance between efficacy, potential side effects, and patients' compliance is a key point for selecting therapeutic regimes in adults with CD. Health professionals play a crucial role in supporting the patient with motivation to commence EEN and being available to check in/ask questions, setting expectations for what the experience would be like, providing clear guidelines for how to undertake the diet along with strategies for managing the challenges likely to be encountered.[65]

Conclusions

Many difficulties arise in extending the use of EEN in the clinical management of adults with CD. Most difficulties are related to long-term adherence due to taste fatigue and social incompatibility. This has made EEN a largely unacceptable therapeutic strategy in long-term clinical practice of adults with CD. Importantly, an ideal dietary intervention should be palatable, acceptable and compatible with a social/professional life. This determines a high chance of long-term adherence. Hence, large RCTs assessing the efficacy of new potential nutritional interventions are awaited to guide clinical practice and direct future research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the

version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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