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Exclusive Enteral Nutrition: A Nutritional Approach to Crohn's Disease



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Nutritional therapy (exclusive enteral nutrition) was first established as a valid and effective treatment for active Crohn's disease over three decades ago. The benefits of this therapy have been confirmed and further defined in recent studies. The benefits of this therapy, which are especially efficacious in children, include the induction of remission, superior rates of mucosal healing and nutritional improvements. Recent studies have further validated this therapy and have provided information about the mechanisms by which this therapy acts.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two chronic inflammatory bowel diseases (IBD). CD and UC are classified and defined on the basis of certain endoscopic, radiologic and histologic features (1). Whereas UC involves the colon with superficial acute and chronic inflammatory changes,

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CD can involve any part of the gastrointestinal tract. Particular findings of CD include full-thickness acute and chronic inflammation, skip lesions and non-caseating granulomata.

These are life-long conditions and both have relapsing and remitting courses. A number of therapies involving medical, surgical and nutritional options are available and are utilized for CD and UC. Unfortunately, with the exception of colectomy for UC, none of the currently available therapies lead to cure of IBD. The aim of these management options, therefore, is upon managing and controlling the inflammatory processes, resolving symptoms, and preventing complications. Therapeutic choices require an evaluation

of patient specific factors, such as disease location and severity, and also therapy-related factors, such as the side-effect profile and expected benefits. Although new options continue to be developed, such as biological therapies, these too may result in significant side effects and complications.

To date there is no evidence to support the use of nutrition as primary therapy for UC. However, an increasing body of literature does support nutrition in the management of Crohn's disease. A nutritional approach to the management of CD has great merits, as it permits control of inflammation, resolution of symptoms and optimization of growth, especially through childhood. Furthermore, nutritional therapy for the management of CD leads to high rates of mucosal healing, which is now recognized as a key outcome variable in the management of CD. This paper reviews nutritional management of CD and introduces this modality to practitioners.

NUTRITIONAL CONSEQUENCES OF CD

Both CD and UC can impact adversely upon the nutritional state of the patient. In children, almost 90% of individuals have a history of weight loss at diagnosis (2). Weight loss is also seen in at least 50% of children with UC. Loss of weight is also commonly seen in adults at the time of diagnosis with CD.

Weight loss is likely related to decreased intake, consequent to factors including the anorexic effects of pro-inflammatory cytokines, early satiety, and reluctance to eat due to consequent abdominal pain (3). Malabsorption and increased energy expenditure may be additional contributory factors. This weight loss or impaired weight gain can lead to impaired height growth, as well as pubertal delay and psychological consequences in children and adolescents. Interruption to pubertal growth patterns may result in impaired adult height acquisition. In addition, IBD is associated with a number of micronutrient deficiencies (3). Most common of these are iron and vitamin D deficiency—others include vitamin B₁₂, folate, vitamin K and calcium. Due to the potential adverse nutritional impact of CD, particular attention to nutrition and growth is vital in the broad management of IBD, especially in children.

NUTRITIONAL THERAPY

A nutritional approach to therapy for CD is known as exclusive enteral nutrition (EEN). This involves the administration of a liquid diet (formula) exclusively, with cessation of normal diet for the period of EEN. The formula may contain whole proteins (polymeric) or modified proteins (e.g. elemental). In most protocols, EEN is provided for six-to-eight weeks, but it may be extended for longer periods in some institutions. EEN has proven roles in the management of CD, but has not been shown to have a role for the management of UC (2).

Enteral nutrition (EN) can also be provided as supplementary drinks, in addition to usual diet, but this likely has predominantly nutritional benefits. EEN, however, clearly has many benefits beyond the nutritional benefits alone.

EEN was first considered as a distinct management option around 30 years ago. Several case reports and series published in the 1970's suggested that enteral formulae might be efficacious in active CD by diminishing gut inflammation (4–7). These observations led to the performance of a small RCT involving 21 adults with active CD (8). These patients were randomized to treatment with either standard therapy with oral corticosteroids or to receive EEN (using an elemental formula) for four weeks. Treatment with the elemental diet was shown to be similarly effective to steroids in inducing clinical remission as defined by the investigators, but the EEN group showed significantly greater increase in hemoglobin and albumin than patients in the corticosteroid treatment arm.

A number of clinical studies have been conducted over the decades since this RCT, with both adult and pediatric populations studied (summarized in nine). For example, in a recent randomized control trial (RCT) that included 37 Italian children, the response to EEN was very similar to that seen in a group treated with steroids (79% for EEN and 67% for steroids: $p = 0.40$) (10). EEN resulted in a reduction of the serum inflammatory markers ESR and CRP, whilst albumin levels corrected. The mean score of the Pediatric CD Activity Index (PCDAI) also fell from 38.1 ± 10 to 6.53 ± 1.4 .

One meta-analysis combined the data from five pediatric studies (incorporating 147 patients with CD)

and demonstrated that EEN had superior efficacy over steroids in the induction of remission in CD (11). A recent Cochrane meta-analysis published in 2007, which included predominantly adult data, arrived at the conclusion that EEN was effective in the induction of remission of active disease, but that it was less effective in comparison to steroids (12). These reviews, however, highlighted the many other benefits of EEN, including its positive nutritional effects and the lack of toxicities as seen with drug therapies.

ROLES OF EEN IN ACTIVE CD

Induction of remission is the primary role of EEN in individuals with active CD. Numerous additional benefits are also demonstrated: these include mucosal healing, nutritional improvements, and reduced bone turnover.

EEN is demonstrated to lead to mucosal healing, which is increasingly recognized as an important outcome for long-term disease control. Mucosal improvements were seen in a group of 29 children managed with EEN who underwent repeat colonoscopy around eight weeks after the start of therapy (13). Along with improved endoscopic severity scores, reductions in pro-inflammatory cytokines and elevations of anti-inflammation cytokines were noted. A recent study conducted in 28 Japanese adults managed with EEN demonstrated endoscopic healing in 44% of the subjects, whereas endoscopic improvements were seen in 78% of the group (14). In their recent RCT mentioned above, Borelli, et al (10) demonstrated convincingly that EEN leads to enhanced mucosal healing. Children in this study, who were randomized to receive EEN or steroids, underwent endoscopic assessments prior to therapy and again 10 weeks later. Seventy-four percent of the children managed with EEN achieved mucosal healing, whereas just 33% of the subjects treated with steroids had mucosal healing ($p < 0.05$).

EEN results in a number of nutritional benefits (15–17), which can have special relevance in children and adolescents. Studies have examined serum markers of nutrition (such as Insulin-like growth factor (IGF)-1), as well as anthropometric markers as outcome measures indicating the nutritional impact of this form of therapy. EEN can lead to prompt improve-

ments in weight (18) along with rapid increases in IGF-1 (19,20). Weight gains are also linked with increased height and enhanced height velocity (15,16). Interesting, these changes do not always correspond directly with changes in serum or mucosal inflammatory markers, suggesting that EEN may act via multiple coincident mechanisms. An animal study also illustrates that anti-inflammatory effects led promptly to improvements in IGF-1, with interleukin-6 being critical in this response (21).

Whitten, et al (22) demonstrated changes in markers of bone turnover in children managed with EEN. In this prospective cohort, EEN led to a reduction of a marker of bone breakdown and increased levels of a marker of bone formation. Together these changes suggest that EEN may have beneficial effects on bone metabolism, which is likely consequent to altered levels of pro-inflammatory cytokines.

ROLE OF EN IN PREVENTION OF RELAPSES OF CD

The literature from pediatric and adult studies does support a role for ongoing EN in the maintenance of remission and prevention of relapse. A report from Toronto demonstrated the benefits of providing regular feeds in addition to normal diet (23). In these children, overnight NG tube feeds with elemental formula were provided in combination with normal diet through the day. This intervention resulted in prolonged remission. Using a different approach, investigators from another Canadian center showed that disease remission could be maintained by giving enteral formula as intermittent intensive periods of exclusive feeds via NG tube (24).

Ongoing enteral formula may help to maintain remission and delay the requirement for further therapy, such as corticosteroids (25). Another approach to maintenance of remission using a nutrition approach includes the provision of supplementary oral formula in combination with a normal diet throughout the day (18). With this approach a daily supplement of between 500 and 1000 mLs of polymeric formula is recommended, in conjunction with normal meals. This therapeutic strategy may also be used in combination with maintenance medical therapy, but may be limited

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by compliance. Further detailed analysis and study is required to demonstrate the short and long-term benefits of this management approach in children.

Several recent adult studies from Japan also show that oral supplements of formula in addition to an ongoing standard diet can be beneficial (26,27). One report in adults with CD illustrates that maintenance enteral nutrition can have a role in prevention of relapse (28). In this study, 51 patients with CD in remission were randomized to receive either half their calories in the form of an elemental formula along with normal diet or to have an unrestricted normal diet (with no additional supplements) for up to two years. Although 22 of these patients had entered remission after a defined period of EEN, others ($n = 25$) had received parenteral nutrition, five had undergone a surgical procedure ($n = 5$) and one had received corticosteroids. The treatment group had a much lower rate of relapse (34%) than the free diet group (64%). The multivariate hazard ratio was calculated as 0.40 (0.16-0.98). Interestingly, this study was halted before the planned end of the study period, due to the interim analyses by the monitoring board that defined a significant benefit for the use of ongoing formula due to the difference in relapse rates. One caveat to the Japanese EN studies in general, is that the use of concomitant medication is virtually universal—and while most papers report similar use amongst treatment and control groups, this is a potential confounding factor in the interpretation of the results of these studies.

Supplementary EN may also have benefits in preventing postoperative recurrence of CD. A group of adults who had received at least 1,200 kcals of an enteral formula (polymeric or elemental) for the first 12 months following a resection had much lower risk of disease recurrence than a comparison group who were not treated with supplementary feeds ($p = 0.017$) (29). These benefits were particularly evident in patients with penetrating disease and patients without colonic disease. A further Japanese study has shown similar findings (30). In this study 40 patients were allocated to either receive nocturnal elemental feeds in conjunction with a low-fat diet through the day for more than 12 months or to receive a standard diet. The group of 20 adults who received overnight feeds had endoscopic disease recurrence rates of 25% after six

months and 30% after one year. In contrast the group who received just a standard diet had recurrence rates of 40% and 70% after the same time intervals ($p = 0.027$ at 12 months). Further studies evaluating EN in this post-operative role are required before this approach can be considered more widely.

PROTOCOLS FOR THE USE OF EEN

Although EEN has been utilized for many years, there is still no consensus on the best way to administer this therapy. It is clear that EEN needs to be provided as an exclusive diet (with exclusion of normal diet) (31). Differences in the type of formula used, duration of EEN, and the method of EEN delivery are among some of the areas where there is a lack of uniformity in how EEN is delivered. Although the initial studies of EEN employed elemental formulae, subsequent studies have shown that polymeric formulae have the same benefits. Polymeric formulae have a number of advantages, including superior taste characteristics (which permits oral administration in many cases), as well as cost benefits. Despite this, a number of centers use elemental or semi-elemental formulae for the administration of EEN. Examples of the different types of EEN protocol practiced as highlighted by the variations in protocol carried out at the authors' centers.

The protocol in use at Sydney Children's Hospital, Sydney, Australia, involves the exclusive use of a polymeric formula for up to eight weeks (18). Patients take increasing volumes over the first three-to-five days and then take ongoing volumes based upon their expected energy requirements. Most patients drink their required volumes orally, with a small number requiring nasogastric tube insertion. During the period of EEN, medical, nursing and dietetic staff provide close support with frequent support phone calls and regular clinic visits. After the completion of the period of EEN, the child's normal diet is slowly restarted, with one meal introduced every three days.

By contrast, the protocol in use at the IWK Health Centre, Halifax, Canada, involves the exclusive use of a semi-elemental formula delivered by nasogastric tube for up to twelve weeks (32). Full feeds are achieved in the first three days, with initial goal volume based upon expected energy requirements, and

this is adjusted based on discussion between the patient and dietitian over time. While a polymeric formula is occasionally used at initiation of feeds, which might allow oral administration, given concerns about compliance with a sole liquid diet for 10-12 weeks, the practice at the IWK has been to place a nasogastric tube for all patients receiving EEN. After the 10-12 week EEN period, a regular oral diet is reintroduced in no particular order and with no specific restrictions (although an emphasis is placed on a healthy, balanced diet).

The use of other caloric intake during EEN also varies between units (33). Whilst some centers permit only additional water and sugarless gum, others permit small amounts of clear fluids or candy.

MECHANISMS OF ACTION OF EEN

Although EEN was proven as an efficacious therapy for CD almost three decades ago, the mechanism by which EEN exerts its action remains largely unknown. However, several potential mechanisms have been hypothesized. These include reduced gut activity due to the administration of a solely liquid diet, indirect nutritional effects, direct anti-inflammatory effects, or via modulation of the gastrointestinal microflora.

The first of these hypotheses appears to be less plausible due to the fact that polymeric formulae and elemental formulae have similar efficacy. Two studies have demonstrated direct effects of enteral formulae upon epithelial cells, with direct anti-inflammatory effects. Meister, et al (34) showed that exposure of cells to formula lead to an altered ratio between pro-inflammatory and anti-inflammatory cytokines. De Jong and colleagues (35) more recently demonstrated that the addition of enteral formula to epithelial cells stimulated with a pro-inflammatory cytokine (TNF- α) reduced cellular responses, and suggested that this could be due to modulation of intracellular signaling pathways.

In addition to these lines of evidence, several reports have illustrated that EEN administration alters patterns of intestinal microflora. Leach, et al (36) utilized molecular methods to define the patterns of flora in a group of children managed with six-to-eight weeks of EEN. Flora altered during the treatment

period, and alterations remained for up to six months following the commencement of therapy. It is not yet clear, however, whether the alterations in flora then led to changes in bacterial epithelial interactions, or if the modifications in flora are consequent to amelioration of mucosal inflammation and innate immune changes.

CONCLUSIONS

EEN is a well-proven therapy for the management of CD in children and adults. As well as induction of remission, EEN also leads to high rates of mucosal healing, improved bone turnover, and nutritional improvements. EEN also has few side effects, whilst permitting the avoidance or delay of exposure to other therapies such as corticosteroids. This is especially relevant in children and adolescents to avoid the growth-suppressant effects of these medicines, but is also relevant in all ages to avoid the myriad of other steroid related side effects. Further studies are now required to focus on defining the optimal protocol(s) for the administration of EEN, the further roles of EEN and to ascertain the mechanisms of EEN. ■

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