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doi:10.3748/wjg.14.4420

World J Gastroenterol 2008 July 21; 14(27): 4420-4423
World Journal of Gastroenterology ISSN 1007-9327

LETTERS TO THE EDITOR

Nutritional therapy for active Crohn's disease

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Received: April 26, 2008 Revised: July 7, 2008
Accepted: July 14, 2008
Published online: July 21, 2008

Abstract

Nutritional therapy for active Crohn's disease (CD) is an underutilized form of treatment in adult patients, though its use is common in the paediatric population. There is evidence that nutritional therapy can effectively induce remission of CD in adult patients. Enteral nutrition therapy is safe and generally well tolerated. Meta-analysis data suggest that corticosteroids are superior to nutritional treatment for induction of remission in active CD. However, the potential side effects of such pharmacotherapy must be taken into consideration. This review examines the evidence for the efficacy of elemental and polymeric diets, and the use of total parenteral nutrition in active CD.

Key words: Crohn's disease; Nutrition; Dietary; Treatment; Steroids

Peer reviewer: Dr. Rafiq A Sheikh, Gastroenterology/Hepatology, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento 95831, United States

Smith PA. Nutritional therapy for active Crohn's disease. *World J Gastroenterol* 2008; 14(27): 4420-4423 Available from: URL: http://www.wjgnet.com/1007-9327/14/4420.asp DOI: http://dx.doi.org/10.3748/wjg.14.4420

TO THE EDITOR

Nutritional therapies studied for the induction of remission in active Crohn's disease (CD) include enteral nutrition (EN), and total parenteral nutrition (TPN). EN by means of a polymeric diet can be given *via* the nasogastric or per oral route. Compliance tends to be greater with polymeric nutrition support than with an elemental diet, as the feed is considered more palatable. Polymeric diets provide nitrogen in the form of whole protein, and carbohydrates as hydrolysates of starch. Fat is most often provided as medium chain fatty acids. Fiber is commonly added to polymeric feeds though there is little evidence to suggest that it has a substantial positive or negative effect in hospitalized patients[1]. Elemental diets contain nutrients in simple forms (such as amino acids, simple carbohydrates, fats, vitamins and minerals) requiring little or no digestion to take place prior to absorption.

The theory behind the mechanism of action of an elemental diet is multi-factorial. Malnutrition can have effects on immune function and wound healing, as well as psychological and cognitive effects. Improvements in wound healing by ensuring a good nutritional status would theoretically lead to enhanced mucosal healing. Increased gut permeability has been implicated in the pathophysiology of CD. This is thought to relate to abnormalities in the tight junctions between enterocytes allowing an increase in luminal antigen uptake-potentially a factor contributing to increased inflammatory activity[2]. Treatment with an elemental diet has been shown to decrease intestinal permeability[3]. The incidence of CD dramatically increased in the twentieth century[4]. This coincides with many changes in our daily lives, including changes in our dietary intake. As elemental diets involve the ingestion of specific substances, it may be that pro-inflammatory antigens are avoided. The normal commensal bacterial population of the gut may play a role in the development of inflammation in CD, though the mechanism is unclear. In experimental animal models, inflammation does not develop in mice reared in a sterile environment[5]. An early study suggested the amount of bacteria per gram of faeces was reduced in patients on an elemental diet, though there is no consensus on this issue[6]. The constituents of an elemental diet are primarily absorbed in the proximal small bowel-proximal to the most commonly affected sites of inflammation in CD. The reduction in the workload of digestion and absorption, and a reduction in peristalsis and digestive tract secretions may also play a role[7]. In general, elemental diets contain a low proportion of fat compared to polymeric or normal diets. A recent Cochrane review concluded that there is a non-significant trend towards greater efficacy with

very low fat and long-chain triglyceride elemental diets compared to standard elemental diet regimes[8].

High quality randomised controlled trials looking at the use of nutritional therapy for the management of acute CD are difficult to perform. There have been very few studies where the remission rate with nutritional therapy is as low as that seen in the placebo arm of drug trials in active CD. So, if we accept that nutritional treatments have an effect, then the question arises as to the magnitude of this effect. According to some studies, remission rates may be as high as 84% with the use of an elemental diet[9]. The Cochrane review (2007) of enteral feeding in active CD provides us with very useful meta-analysis data[8]. As found in previous meta-analyses, the Cochrane review concluded that steroids have superior efficacy to enteral nutrition in inducing remission[8]. The exact role of enteral nutrition (EN) in adults to treat active CD is therefore undefined.

TRIALS COMPARING ELEMENTAL DIET TO CORTICOSTEROIDS

A number of studies have been conducted looking into the efficacy of elemental diets in CD patients. Riordan *et al*[9] studied 136 patients with active CD. An elemental diet was introduced and all other CD treatments discontinued. The intention was to give an elemental diet for 2 wk, though 31% of the patients did not tolerate the diet for more than 1 wk. Of the 78 remaining patients, 84% achieved disease remission after a 14-d treatment course. The group was then split into 38 patients receiving a tapered course of prednisolone and advice on healthy eating, and 40 patients receiving placebo instead of steroid-this 'diet' group was asked to introduce one new food each day and exclude foods that worsened symptoms. There was a median remission of 3.8 mo in the steroid group compared to 7.5 mo in the diet group.

Gorard *et al*[10] compared 22 patients given an elemental diet (4 wk treatment) to 20 patients receiving prednisolone (0.75 mg/kg daily for 2 wk followed by reducing doses). All participants were CD patients requiring hospitalisation for an acute flare of the disease. Nine of the twenty-two patients (41%) in the diet arm of the trial withdrew because of intolerance. Disease activity was measured using a simple disease activity index. The reduction in disease activity was similar between the diet (score of 4.8 reducing to 1.7) and prednisolone (score of 5.3 reducing to 1.9) groups. In addition to this, similar reductions in C-reactive protein, and increases in serum albumin concentration were found. The probability ratio of remaining patients in remission was, however, much lower in the diet group. At 6 mo, this probability was 0.67 after steroid compared to 0.28 after elemental diet.

TRIALS COMPARING POLYMERIC DIET TO CORTICOSTEROIDS

Many trials involving polymeric and enteral diets in CD have been conducted in children, due to the perceived need to avoid corticosteroids, to alleviate the additional risk of growth failure. Day *et al*[11] looked at 27 children with active CD (15 new diagnoses, 12 with known disease). They gave a polymeric feed as the exclusive source of nutrition for 6-8 wk either per oral or *via* a NG tube. No other medical therapy was used at that time. Twenty-four of the twenty-seven children completed the 6-8 wk course, while the other three did not tolerate enteral feeding. At the end of the treatment period, 80% of the newly diagnosed patients and 58% of the known-CD patients had entered remission. The CD remained inactive in all of the newly diagnosed patients with entered remission, over the mean 15.2-mo follow-up period.

Borrelli *et al*[12] conducted a trial comparing polymeric diet to corticosteroids in 37 children with active treatment in naïve CD patients. The study period was 10 wk, and after this time 15 of the 19 children (79%) receiving a polymeric diet had remission compared to 12 of the 18 patients in the corticosteroid group (67%). The differences were not statistically significant. An additional interesting aspect of this trial was that mucosal healing was assessed by endoscopy with histology at weeks 0 and 10. The proportion of children with mucosal healing was significantly higher in the polymeric diet group (74%) than in the corticosteroid group (33%).

The use of a polymeric diet in adult patients with CD has also been studied. Gonzalez-Huix *et al*[13] conducted a randomised controlled trial comparing adults with acute CD receiving 1 mg/kg per day prednisolone (n = 17) followed by a reducing course, to those on a polymeric diet and no medication (n = 15). The polymeric feed was given *via* a fine-bore NG tube and no other nutrition allowed. The polymeric diet patients went back to a normal diet after clinical remission was achieved. Of the seventeen patients in the steroid group, fifteen entered remission after a mean time of 2 wk. One patient had an intestinal perforation requiring surgery, and the others entered remission after being started on a polymeric diet. Of the 15 patients in the polymeric diet group, 12 entered remission after a mean time of 2.4 wk. Of the 3 treatment failures, one improved when steroids were given, and the other two were said to have failed as they did not enter remission after 4 wk on the polymeric feed. Patients from both arms of the trial were started on oral 5-ASA preparations prior to discharge. The cumulative probability of relapse during the follow-up period was higher after steroid treatment than after polymeric diet though this did not reach a statistical significance.

There is some evidence to suggest that the amount and type of fat in polymeric feeds may have an impact on its efficacy in CD patients. Gassull *et al*[14] hypothesised that a polymeric diet rich in monounsaturated fatty acids (MUFA) would be more effective in inducing remission in active CD patients than an identical diet but with polyunsaturated fatty acids (PUFA)-precursors of some inflammatory cytokines. They randomised 62 patients with active CD to either one of these diets for no longer

than 4 wk, or to 1 mg/kg per day prednisolone. The steroid group reacted as expected from previous studies with a 79% remission rate. However, the diet group did not fare as well. Only 20 % in the MUFA group entered remission, while 52% in the PUFA group achieved this target. These results were quite the opposite of those expected. Leiper *et al*[15] conducted a randomised trial in 54 patients with active CD. They received a polymeric diet with either high or low long-chain triglyceride (LCT) content. A staggering 39% of patients withdrew from the trial within 3 wk because of an inability to tolerate the diet, which was offered by either the oral or nasogastric route. Of those completing the trial, the response rate was 46% for the low LCT group and 45% for the high LCT group, respectively, thereby demonstrating no significant difference in efficacy with differing fat composition.

COCHRANE COLLABORATION REVIEW OF ENTERAL NUTRITION THERAPY FOR THE INDUCTION OF REMISSION IN ACTIVE CD

There have been four meta-analyses looking at the use of enteral nutrition therapy in comparison to steroids to induce remission in active CD patients. Overall, each of these meta-analyses showed steroids to be more effective than enteral nutrition strategies. However, when two large trials were excluded because of the concomitant use of other medicines in the steroid arm, both enteral nutrition and steroids were seen to have an equal efficacy. A recent review from the Cochrane Collaboration studied the results from trials comparing different types of enteral nutrition (EN) to each other, and trials comparing the use of EN to steroids[8]. When looking at differences between diet formulations used to treat patients with acute CD, they performed a meta-analysis which included data from 188 adult patients treated by elemental diet and 146 patients given a polymeric diet. No significant difference was found in the results achieved between elemental and polymeric diets.

Sub-group analysis showed no difference between formulae with high fat *versus* low fat content. Differences in the amount of fat in the form of high *versus* low long-chain triglyceride were also shown not to be significant. Meta-analysis of trials comparing enteral feeding to corticosteroids compared data from 192 enteral nutrition patients *versus* 160 patients treated with steroid, which revealed a pooled odds ratio of 0.33 favouring steroid treatment.

TOTAL PARENTERAL NUTRITION AS A TREATMENT FOR ACTIVE CD

Controlled trials of total parenteral nutrition (TPN) in CD patients are few and far between. Greenberg *et al*[16] conducted a trial in 51 patients with active CD. They were randomised to either TPN and nil by mouth (n = 17), partial parenteral nutrition (PPN) and supplementary nutrition with a liquid feed of a defined formula *via* a NG tube (n = 19), or PPN and supplementary normal food (n = 15). Remission occurred in 71% of patients on TPN, in 58% of patients on the PPN/defined formula diet, and in 60% of patients on PPN/normal diet. Of those achieving remission, the chance of successfully remaining in remission at one year was 42%, 55%, and 56%, respectively. The differences were found not to be significant. The total bowel rest achieved through TPN was therefore not thought to be of importance.

DISCUSSION

There is a disappointing lack of quality studies on the use of TPN in active CD patients. It is difficult to find a place for TPN as a treatment for active CD. The efficacy of TPN does not seem to be greater than that suggested by other trials of EN or steroids. TPN is known to be associated with an increased risk of adverse events, such as sepsis, although perhaps it has a place in patients intolerant to both EN and steroids. The value of TPN in malnourished patients with intestinal failure due to CD is beyond doubt.

There would seem no logical reason to choose EN over steroids for the vast majority of our patients. The European Society for Parenteral and Enteral Nutrition published guidelines in 2006 on the use of enteral nutrition in gastroenterology[17]. They suggested that a role could be found for EN in active CD in the following circumstances: steroid intolerance, patient refusal of steroids, EN in combination with steroids in undernourished individuals, and in patients with an inflammatory stenosis of the small intestine.

EN plays a greater role in children with active CD. In this group of patients, EN has been shown to have an efficacy equal to steroids. Therefore, it would seem perfectly reasonable to prescribe EN instead of steroids in the hope of avoiding steroid side-effects, including deleterious effects upon growth and development of children. The use of corticosteroids increases the risk of permanent growth failure in children, and 20%-30% will become adults with an abnormally short stature whether or not they are exposed to prolonged courses of steroids[18].

The nutritional status in those with acute CD is important. Differences are seen between patients in an active phase of disease and those in remission. Weight loss is found in up to 75% of patients hospitalized with an exacerbation of CD, with a negative nitrogen balance present in more than 50%, whereas the majority of patients in remission are of normal nutritional status[17]. The role of nutritional therapy in the maintenance of a good nutritional status in CD patients is important, especially as the condition itself will predispose to malnutrition.

When EN is to be used, the type of formula does not make any difference to the efficacy. Polymeric diets are less expensive and more palatable than elemental

diets, and therefore it would seem reasonable to suggest that there is no place for the elemental diet.

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S- Editor Zhong XY **L- Editor** Wang XL **E- Editor** Yin DH