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REVIEW

Role of diet in the management of inflammatory bowel disease

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Abstract

Many studies have looked at connections between diet, etiology, signs and symptoms associated with inflammatory bowel disease (IBD). Although these connections are apparent to clinicians, they are difficult to prove qualitatively or quantitatively. Enteral feeding and polymeric diets are equally effective at bringing about remission in Crohn's disease (CD). Parenteral feeding is also effective, although none of these methods is as effective as corticosteroid therapy. However, enteral feeding is preferred in the pediatric population because linear growth is more adequately maintained *via* this route. Exclusion diets in patients brought into remission using an elemental diet have been shown to maintain remission for longer periods. Studies that aim to isolate culpable food groups have shown that individuals react differently on exposure to or exclusion of various foods. The commonly identified food sensitivities are cereals, milk, eggs, vegetables and citrus fruits. Studies that have looked at gut mucosal antigen behavior have shown higher rectal blood flow, in response to specific food antigens, in those with CD over healthy subjects. Exclusion of sugar shows little evidence of amelioration in CD. Omega 3 fatty acids show promise in the treatment of IBD but await larger randomized controlled trials. Patients frequently notice that specific foods cause aggravation of their symptoms. Whilst it has been difficult to pinpoint specific foods, with advances in the laboratory tests and food supplements available, the aim is to prolong remission in these patients using dietary measures, and reduce the need for pharmacotherapy and surgical intervention.

Key words: Crohn's disease; Ulcerative colitis; Exclusion diet; Elimination diet

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INTRODUCTION

The etiology of inflammatory bowel disease (IBD) is considered multifactorial. Genetic, infective and environmental theories exist, as well as those centered around host immunity, intraluminal gut flora, food allergies and hypersensitivity[1].

Whilst pharmacological therapy plays a major role, many patients prefer to control their symptoms by the most conservative means possible. Our aims in IBD therapy are to downregulate inflammation, and reduce the incidence of relapse and the healing time.

Dietary therapy encompasses dietary modifications suggested by physicians and those that patients make autonomously. The putative mechanisms of action are due to bowel rest, provision of nutrients, alteration of bowel flora or alteration of antigenic stimuli. The gastrointesti-

nal flora and its interaction with nutritional factors has a huge impact on the environment, especially in genetically predisposed individuals. Nutrients as components of cell structure or antigens can induce inflammatory mediator expression and suboptimal levels of nutrients, which may have an impact on tissue repair and other cellular processes[2]. Other reviews have concluded that nutrients that tend to affect the immune responses of the host (n-3 fatty acids, antioxidants) are likely to play a role in the treatment of IBD[3].

In this review, we examine the literature for dietary interventions in IBD, such as exclusion/elimination diets, enteral nutrition and total parenteral nutrition (TPN), and review the evidence that they induce and/or maintain remission in patients with IBD.

METHODOLOGY

PubMed, Cochrane and MEDLINE were searched using the broad key words Crohn's disease (CD), ulcerative colitis (UC) and IBD cross-referenced with exclusion diet, elimination diet, diet therapy and nutritional therapy. The results were limited to human studies and those available in English. They were not limited by the type or size of the trial. The search identified 503 papers of interest. When the titles were reviewed, 315 were found to be of interest by two independent reviewers. If there was any doubt, the papers were included. The 315 abstracts were reviewed again by the same two reviewers, out of which 104 were found to be relevant. These 104 were scrutinized for dietary evidence but only 38 of these had a dietary focus or provided evidence for it. Eighty-five secondary references were reviewed by abstract, of which, 45 were obtained and studied. Of these, 10 provided relevant evidence which was included in the review.

INDUCTION OF REMISSION IN CD

Elemental/polymeric diets

Elemental diets were chanced upon as a therapeutic option for CD patients when they were used to bolster their nutritional status and reduce inflammation[4]. Liquid feeds are thought to work by reducing mucosal antigen exposure, partly due to the nature of the feed and partly to faster transit times. They also alter the fecal flora, which causes local immunomodulation downscaling, which enhances nutritional status and allows relative bowel rest[5].

Compliance may be poor as elemental diets are not known for their palatability and are often delivered *via* a nasogastric tube, whereas the polymeric drinks are far more palatable. Several trials and meta-analyses have shown no significant difference in the efficacy of elemental diets over polymeric diets[6,7].

Elemental diets offer a cheaper way of bringing about remission and without the side effect profile of TPN. In both adult[8] and pediatric populations, elemental[9] and polymeric[10] feeds have been shown to be as effective as corticosteroid therapy in treating active CD. However, a Cochrane review by Zachos *et al*[11] has shown, in a meta-analysis, that enteral nutrition is not as effective as steroid therapy for inducing remission.

However, enteral therapy for CD has its role in selected cases, in particular, in children in whom steroids may cause growth retardation[12]. Food exclusion with liquid diet is very difficult to maintain, therefore, these are rarely long-term solutions. Unfortunately, a staged return to normal feeding often leads to relapse.

Exclusion diets

The East Anglia Multicentre Controlled Trial showed that various food intolerances were perceived in individual patients, and among the more common were cereals, dairy produce and yeast[13]. This work looked at the use of exclusion diets as an intervention in active CD. The exclusion diet was based around daily reintroduction of a single food type. If it caused diarrhea or pain, it was eliminated. All patients were treated initially with an elemental diet, and those who attained remission followed a reduced prednisolone course or the exclusion diet pathway. Jones *et al*[14] have shown that maintenance of remission, by identification and avoidance of food intolerances, is possible, often without pharmaceutical adjuncts. Testing for these sensitivities has proven difficult, because testing shows a large number of sensitivities in unselected populations, which are of doubtful clinical significance[15]. Jones *et al*[14] have tested a diet rich in unrefined carbohydrate against an exclusion diet. Seven out of 10 patients on the exclusion diet stayed in remission for 6 mo, while none of those on the carbohydrate-rich diet remained in remission. Pearson *et al*[16] have conducted a study of 42 CD patients after induction of remission by elemental diet. Single foods were investigated using open and double blind rechallenge over 5 d. Fourteen patients dropped out due to flare-ups that were thought to be unrelated to food, and caused by inability to comply with the regimen. Twenty of the remaining patients identified food intolerances and eight did not. This research group has concluded that food intolerance is not as frequent as claimed in other studies, and that it is variable in its intensity and occurrence.

Parenteral feeding in CD

TPN allows bowel rest while supplying adequate calorific intake and essential nutrients, and removes antigenic mucosal stimuli. However, TPN is expensive, invasive and has a number of side effects. TPN has been shown to bring about remission in CD[17,18]. Müller *et al*[18] have found that, in 30 consecutive complicated CD patients, 3 wk of TPN as an inpatient followed by an additional 9 wk at home, during which time, no medication or oral intake was allowed, 25 patients avoided surgery. These patients returned to work and needed no further medication and ate normal meals subsequently. In a prospective randomized controlled trial (RCT), 51 patients with active CD refractory to medical treatment were treated with TPN and nil by mouth, defined formula diet *via* a nasogastric tube, or partial parenteral nutrition[17]. Clinical remission was

obtained in 71% of the patients on TPN, 58% on enteral feeding, and 60% on partial parenteral feed.

Enteral vs parenteral feeding

There has been controversy regarding the enteral *vs* parenteral route for feeding in patients with IBD. Comparison of TPN against elemental diet in a group of 36 patients showed no significant difference in the number of days to remission, the drop in Crohn's disease activity index (CDAI) score, the erythrocyte sedimentation rate (ESR), or albumin[19]. However, in other studies that have agreed with this finding, neither was proven to be as beneficial as corticosteroids, except one study in a pediatric population[20]. In that study, Sanderson *et al*[20] entered 17 children into an RCT, in which eight were given an elemental diet for 6 wk *via* a nasogastric tube, and seven were given adrenocorticotrophic hormone injections and oral prednisolone and sulfasalazine. The elemental diet was equally effective at improving the Lloyd-Still disease activity index scores, C-reactive protein (CRP), ESR and albumin. The elemental diet was markedly better at maintaining linear growth. Whilst strong evidence exists supporting the primary use of enteral feeding in children with CD[21], it is not commonplace in the treatment of adults.

Omega-3 fatty acids

Shoda *et al*[22] have noted that the gradual replacement of n-3 polyunsaturated fatty acids with n-6 polyunsaturated fatty acids results in an increased incidence of CD. This implies that there is the potential to modulate immune responses by altering the ratio of polyunsaturated fatty acids in favor of n-3 rather than n-6[23]. Meister and Ghosh have shown that fish-oil-enriched enteral diet, when incubated with intestinal tissue from 11 subjects with IBD and four controls, reduced inflammation modestly in CD and significantly in UC[24]. Inflammatory improvement was assessed by analyzing the interleukin (IL)-1 receptor antagonist/IL-1β ratio. The greater the ratio, the less inflamed the tissue. A systematic review of the effects of n-3 fatty acids in IBD by MacLean *et al*[25] has identified 13 controlled trials that investigated the effects of n-3 fatty acids. The results were mixed but in the three studies that looked at steroid requirements, this was found to be reduced. However, this was statistically significant in just one of these studies[26].

MAINTENANCE OF REMISSION IN CD

Exclusion diets

Jones has looked at exclusion diets for the maintenance of remission of CD and has shown that, in personalized exclusion diets, 62% of the patients maintained remission at 2 years and 45% at 5 years, with no other medical intervention[19]. This was compared to the European Cooperative Crohn's Disease Study in 1984 in which the placebo arm of the study had no patient who maintained remission after 2 years of follow-up[27].

A Cochrane review of the maintenance of remission in CD has suggested that larger, high-powered controlled trials are required to confirm current hypotheses relating to diet and maintenance of remission[28]. Trials of diet against azathioprine and infliximab also have been suggested to investigate quantitative effects of nutritional supplements and their impact on cost-effectiveness and quality of life.

Enteral feeding

Enteral feeding has been shown to have a role in preventing relapse in inactive CD patients (predominantly in children)[29], but the effect has also been observed in a Japanese study of adult CD patients[30]. Esaki *et al*[31] have demonstrated in a trial of 145 patients with CD (mostly induced into remission with TPN) that, under maintenance with elemental/polymeric nutrition, the risk of recurrence was lower in those with small bowel rather than large bowel involvement.

DIETARY MANAGEMENT IN UC

Maintenance of remission in UC

UC does not seem to be ameliorated by bowel rest and elemental diets in the same way as CD is[32-34]. However, patients still express concern about specific food types, and there does appear to be an association with a western diet[35]. In a study that has investigated self-reported food intolerance in chronic IBD, patients with CD and UC have reported that they felt intolerant to specific dietary triggers and restricted their diet accordingly[36]. The same study has shown that the pattern and frequency of food intolerance did not differ between CD and UC patients. This has been reinforced by work from our own group that has investigated food intolerances detected by measuring IgG4 antibodies to specific food antigens[37,38]. There is no evidence to support the use of elemental/polymeric feeding in the treatment of UC[12,23].

Omega-3 fatty acids

Omega-3 fatty acids derived from fish oils have been shown to be of benefit in a double-blind RCT that looked at patients with distal UC. That study found that the group treated with 3.2 g eicosapentaenoic acid or 2.4 g docosahexaenoic acid daily had significantly better clinical and sigmoidoscopic scores compared with the control group who took sunflower oil, after 3 and 6 mo. This supports the idea that omega-3 oils suppress natural cytotoxicity[39].

ADDITIONAL DIETARY FACTORS

Fiber

Dietary fiber has been investigated as a means of increasing short-chain fatty acid (SCFA) production. IBD has been linked with impaired SCFA production. SCFAs are mainly produced by the anaerobic bacterial fermentation of undigested carbohydrates and fiber polysaccharides.

In 1995, Galvez *et al*[40] reviewed a number of studies that concluded that dietary fiber confers clinical benefits in patients with IBD because it maintains remission and reduces colonic damage. This is thought to occur by increasing SCFA production and by altering the gut flora towards predominantly non-pathogenic bacteria.

Fats

The properties of omega-3 fatty acids have been discussed elsewhere in this review. Other studies have revealed an inverse correlation between the percentage of energy derived from long-chain triglycerides and the efficacy of enteral feeds in achieving remission[41,42].

Sugars

A high intake of sugar has been shown to be linked to CD in a number of trials, hence its possible etiological role has led to therapeutic trials of sugar avoidance[43]. Most of these trials also have promoted a high fiber intake. The only trial to look solely at sugar avoidance has shown no statistically significant benefit[44].

ANTIGENIC RESPONSE TO FOOD

Van den Bogaerde *et al*[45] have published a trial in which the reactivity of peripheral lymphocytes to food, yeast and bacterial antigens was studied. They found that 23 out of 31 patients with CD responded to one or more antigens, compared to five out of 22 in the control group. They also correlated *in vitro* sensitization and *in vivo* changes with histological and blood flow changes. Skin testing and rectal exposure to six food antigens and saline were tested in 10 patients and 10 controls. The results showed that CD patients demonstrated *in vitro* and *in vivo* sensitization to food antigens and this was gut specific[46].

Levo *et al*[47] have shown that patients with IBD have higher serum concentrations of IgE. They also have shown that the levels are higher still in those with active disease over those in remission. However, this difference is not statistically significant. In 1998, another study was performed to investigate food-specific IgE as well as IgG, and IgE anti-IgE autoantibodies using serum from normal subjects, patients with CD and those with food allergies. They found that food-specific IgE was not detected at all in the CD group but they did have higher levels of IgG and IgE anti-IgE autoantibodies. They concluded that, even if IgE is an autoantigen in CD, it is not thought to take part in the pathophysiology of the adverse food reactions commonly reported by the patients[48].

Western diets are more strongly associated with CD[35]. There are several theories as to whether this may relate to the increased intake of sucrose, refined carbohydrate, and omega-6 fatty acids, and reduced intake of fruit and vegetables. Urban diets contain large quantities of microparticles such as natural contaminants like dust, and food additives which may be antigenic. CD patients allocated to a low microparticle diet experienced a reduction in disease activity and in steroid requirement compared to a control group on a normal diet[49].

The Table 1 lists the reviewed studies that have investigated dietary exclusion and sensitivity to foods.

SUMMARY

Although many studies have looked at diet therapy and IBD, mixed opinions exists as to the importance that food intolerance plays in the pathophysiology of IBD. In those that have looked at food sensitivity, this was done using different methods. Riordan *et al*[13] have observed sensitivity to corn in seven patients; wheat, milk and yeast in six; egg, potato, rye, tea and, coffee in four; and apples, mushrooms, oats and chocolate in three. Ballegaard *et al*[36] have found sensitivity, using questionnaires, to vegetables (particularly onions and cabbage), fruits (apples, strawberries, and citrus fruits) and to meat (especially beef). Van den Bogaerde *et al*[45] have shown in a case-control study using lymphocyte proliferation that, out of 31 CD patients, 16 reacted to cabbage and peanuts, 14 to cereals, 13 to milk, and nine to citrus fruits.

As observed by Hunter[50], epidemiologists tend to look at statistical relationships that lead to studies of sugar, sweet, coke and chocolate intake because patients with CD eat and drink more of these substances than control subjects. Clinicians focus on the foods that patients associate with their symptoms and therefore avoid. As a result, exclusion diets have tended to concentrate more on dairy products, cereals and yeast. Other work is being carried out on polyunsaturated fatty acids, especially omega-3 oils, and their anti-inflammatory effects.

Current elemental and polymeric diets have a role to play in the management of CD, particularly in children. Exclusion diets are of use particularly for maintenance of remission. TPN is of value and has been shown to be as effective as elemental diets, but none have proven as effective as corticosteroid therapy. However, TPN remains a crucial method for administering nutrition in patients with severe disease, who are not able to tolerate enteral feeding.

Despite early ideas about the involvement of sugars in the etiology of CD, the omission of sugar has not been found to be of benefit. Omega oil has shown promising results, particularly in reducing inflammation in UC, and to a lesser degree, in CD.

CONCLUSION

IBD has a multifactorial etiology but food sensitivity/intolerance appears to play a role, and the culpable foods vary on an individual basis. Techniques to identify food intolerance require refining. Progress has been made by looking at factors such as IgG4 responses to food antigens, but a large expanse of work exists in trying to determine people's food sensitivities and the degree to which these affect disease activity. Without further research, it remains unclear whether dietary manipulation will continue to have a role solely in symptom control, or

Table 1 Reviewed studies looking at dietary exclusion and sensitivity to foods

Ref.	Trial type	No. of patients	Diets compared	Findings	Outcomes/measures	GRADE rating
Voitk *et al*[4]	Retrospective	13	Elemental diet	Patients with UC. Showed improved weight and positive nitrogen balance	Weight, nitrogen balance and nutritional state	1D
Borrelli *et al*[10]	Open RCT	38	Oral steroid *vs* polymeric feed only	Clinical remission comparable (67% steroid group, 79% polymeric group). Significantly improved histological and endoscopic scores in the polymeric group	Clinical remission, histological and endoscopic scores at 10 wk	1A
Riordan *et al*[13]	Multicentre double blinded RC	136	Exclusion diet *vs* steroid treatment	Patients were maintained in remission on exclusion diets	Hemoglobin, albumin, ESR, CRP, remission rates over 2 yr	1A
Jones *et al*[14]	Controlled trial	20	Unrefined carbohydrate rich diet *vs* exclusion diet	7 out of 10 on the exclusion diet remained in remission for 6 mo *vs* none of the other group	Clinical remission	
Pearson *et al*[16]	Prospective cohort	42	Food intolerances after remission induced with enteral feeding	20 patients identified food intolerances and eight did not. 14 did not complete the study	Food intolerances were found in CD but were variable and short-lived	2C
Greenberg *et al*[17]	RCT	51	TPN *vs* formula diet *via* NG *vs* partial parenteral and oral food	Clinical remission in 71% of parenteral group, 60% of partial parenteral group and 58% defined formula group	Relapse rates, weight, albumin, arm circumference, triceps skinfold thickness	1B
Jones *et al*[19]	Randomised	36	TPN *vs* elemental for induction of remission in CD	Both were successful with no significant differences. Elemental diet was cheaper, safer and simpler	CDAI, ESR and serum albumin	2B
Sanderson *et al*[20]	RCT	17 children	Elemental *via* NG for 6 wk *vs* high dose steroids	Elemental feed equally effective in children to high dose steroids. Linear growth better in elemental group over 6 mo	Lloyd-Still score, ESR, CRP, albumin, linear growth and body weight	2A
Wilschanski *et al*[29]	Retrospective	65	Nasogastric supplemental feeding	Continued nasogastric feeding post resumption of normal diet maintained remission for longer and showed improved linear growth	Relapse rate, linear growth	1D
Esaki *et al*[31]	Retrospective	145	Enteral *vs* non enteral (where enteral applies to elemental or polymeric feeds)	Enteral feeding showed a lower relapse rate than non-enteral	Rate of relapse based on CDAI scores	1D
Axelsson *et al*[33]	Cohort	34	Elemental diet for IBD refractory to improvement on high dose steroids	31 had been on high dose steroids prior to trial. 15 went into remission on elemental feed alone. 6 achieved remission with introduction or increase in prednisone dose	Serum iron, transferring, albumin, creatinine clearance, ESR, urea clearance, fecal volume, number of bowel movements	1B
Ballegaard *et al*[36]	Questionnaire	130		Sensitivity was commonly reported to vegetables (40%), fruit (28%), milk (27%), meat (25%) and bread (23%). No differences were found between the UC and CD groups		1C
Brandes *et al*[44]	RCT	20	Refined sugar rich *vs* refined sugar excluded	The sugar rich diet was stopped in 4 patients due to flare-ups. In those with mild disease there were no detrimental effects in either group	CDAI	2B
Van den Bogaerde *et al*[45]	Case-control study	31 CD, 22 controls	Peripheral lymphocytes were incubated with food and bacterial antigens	Lymphocyte proliferation to all food and bacterial antigens was higher in CD patients than controls	Lymphocyte proliferation	1C
Van den Bogaerde *et al*[46]	Case-control study	10 CD, 10 controls	Skin testing and rectal exposure to 6 food antigens	CD patients had significant in vivo and in vitro sensitization to food antigens which is gut specific	*In vivo* - rectal blood flow. *In vitro* - lymphocyte proliferation	1C

whether complete remission may be possible using these methods in combination with pharmacological agents.

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