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Invited Review

Enteral and parenteral therapy in inflammatory bowel disease

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INTRODUCTION

The centuries old concept of interaction between diet and disease holds true in inflammatory bowel disease (IBD). Different underlying mechanisms responsible for beneficial effects of dietary modifications have been described. In IBD both disease and patient-related factors, including malnutrition from poor dietary intake, increased protein losses, and disease activity, may necessitate dietary modifications. These manipulations range from dietary exclusions to dietary formulations administered through normal oral, modified enteral, and parenteral routes. Comparative studies and prospective trials in favour of such modifications are a source of ongoing debate and research at present. In Crohn's disease, a dietary role in achieving disease remission has also been studied. Dietary therapy like other treatment modalities does not achieve a universal beneficial effect in all IBD patients.

MECHANISMS OF ACTION

The aetiology of inflammatory bowel disease is unknown and considered to be an imbalance between various environmental, genetic and immunological factors. Use of enteral diet is based on the hypothesis that elemental (a solution of amino acids, glucose, short chain triglycerides, with minerals and vitamins) and partially hydrolysed "peptide" diets reduce inflammation. A potential role of malnutrition and dietary repletion affecting immunological and inflammatory responses in IBD has been described.[1] In one of the earlier studies, a role or food-based antigens mediating through altered permeability of gut mucosa was suggested.[2] In this controlled trial biochemical and clinical parameters of 21-patients with acute exacerbation of Crohn's disease improved on elemental diet and response was equivalent to steroids. Other putative mechanisms may be related to alterations in the fatty acids constituents of normal diet that may work as a possible inflammation-modulating agent. Favourable dietary alteration may then lead to formation of eicosanoids, such as less active leukotriene B5 rather that leukotriene B4. Short chain fatty acids also work as metabolic fuel for epithelial cells and cell integrity is severely affected by their absence. Dietary factors are also known to directly or indirectly influence digestive enzymes, intestinal motility, and bowel flora.

Disease activity can be assessed using various parameters including symptoms scoring, endoscopic radiological, and histological changes. Assessment of functional changes is dependent on intestinal permeability, leukocytes migration, protein loss, and measuring acute phase proteins. Interpretation of disease activity and symptom scoring may not show a consistent relationship and is a major factor influencing correct interpretation of the role of various therapeutic modalitites. The results of published trials on the role of dietary treatments are also not immune to such factors.

NUTRITIONAL SUPPORT IN IBD

Nutritional support in IBD can be justified on functional, psychological, and possible anti-inflammatory grounds. To some extent, malnutrition in both complicated and uncomplicated disease may be attributed to psychological effects, which are reversed on nutritional support.[3] Improvement in disease parameters often precedes correction of nutritional parameters and may be

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related with a fundamental primary role in addition to nutritional effects.[4] For consideration of nutritional therapy, IBD patients can be divided into groups on the basis of age, underlying disease state (type and activity), and site of anatomical disease involvement. Depending on these categories a decision can be made on the most appropriate form of dietary supplementation.

1. Ulcerative Colitis: Results of clinical trials generally suggest that the majority of the patients with ulcerative colitis do not derive benefit from dietary modifications. In a prospective, randomized trial in colitis patients, McIntyre et al were not able to demonstrate clinical benefit from the use of parenteral nutrition.[5] Both trial arms received intravenous steroids while fourteen of the 27-patients required urgent surgical intervention. A possible aetiological role of mild related antigenic mechanism suggested by Wright et al, and other investigators in a small minority of patients with ulcerative colitis might justify dietary exclusion.[6,7] Generally, a therapeutic role for entral or parenteral diets is not proven in ulcerative colitis and use is only limited to maintenance or improvement of nutritional status where appropriate.

2. Crohn's disease in children: Growth retardation is one of the important manifestations of childhood Crohn's disease. This most probably results from a combination of factors including chronic nutritional depletion and steroid therapy. A positive dietary therapeutic response has been demonstrated in clinical trials with increased energy intake leading to increased growth rates in growth-retarded children.[8] In a group of 7 patients with Crohn's disease, a mean increase in growth velocity from 1.8 cm/yr to a mean of 6.2 cm/yr was observed by increasing calorie intake from 1535 kcal/day to 2493 kcal/day.[9] Use of semi-elemental peptide-based diets in children results in significant improvement in disease activity and leads to a reduction in steroid dose with concomitant increase in height and weight velocity.[10] One of effective way of improving nutrient consumption is to pass a fine nasogastric tube each night and infuse liquid food during sleep. This technique appears cost-effective and results comparable to elemental diets have been achieved.[11] The role of elemental therapy in childhood Crohn's disease as a primary treatment modality is attractive, as it offers the possibility improving growth and nutritional status without serious side effects.

3. Anatomical disease distribution: In IBD, severe malabsorption can results from insufficient absorption of electrolytes and nutrients from the gut. Malabsorption in Crohn's disease is dependent on the anatomical site and extent of small bowel involvement. Patients with major jejunal resection suffer from sodium and water losses and are helped by sipping glucose-sodium drinks. A shortened small bowel, from major intestinal resection in continuity with functional length of large intestine, leads to excessive fat entering the colon. This leads to inhibition of water absorption causing liquid diarrhea. Steatorrhea, in turn, results in increased oxalate absorption and consequent formation of calcium oxalate renal stones. Enteral and parenteral nutrition can be considered as an option in these patients.

4. Disease activity in Crohn's disease: Disease activity in acutely sick patients with Crohn's disease leads to marked losses of body weight and lean body mass. In acute inflammation there is depressed anabolism with depressed gains in lean body mass. Christie et al recorded a significant loss of physiological impairment (20-40%) along with 35% loss of body protein stores in malnourished patients with acute Crohn's disease).[12] Physiological parameters including muscle weakness evident on respiratory function tests, grip strength tests, and other measures improved significantly on nutritional supplementation. Controlled trials in young patients with chronic Crohn's disease also demonstrate marked benefits of increased calorie intake. Additional intake of small volumes of liquid diet is recommended at appropriate intervals during the day and at bedtime.[4]

ENTERAL AND PARENTERAL THERAPY IN IBD

Enteral diets are subdivided into various types depending on the major constituents, including proteins, carbohydrates and fats. The main types include elemental, peptide-based and polymeric diets. Both enteral and total parenteral nutrition (TPN) have been used as primary therapy in IBD. A large number of controlled trials comparing the efficacy of these formulae to normal diet and steroids have been conducted in patients with Crohn's disease. Fears of potential complications, such as mucosal atrophy and higher incidence of bacterial translocation from the intestinal mucosa of patients receiving TPN, have not been substantiated.[13] Similarly, liver function abnormalities resulting from the use of TPN appear transient and reversible after cessation of TPN.[14,15]

a) Total parenteral nutrition in ulcerative colitis

Role of TPN as primary therapy in ulcerative colitis is not supported on the basis of available data. However, use of TPN is supported as an adjunctive therapy in acute exacerbation, malnourished patients, and during the perioperative period (Table 1).[5,16-22] Randomised controlled trials assessing various disease parameters indicate con-

Table 1. Total parenteral nutrition in ulcerative colitis

Reference	Patients	Comments
Reilly et al, 1978[16]	34	All ulcerative colitis patients required colectomy
Elson et al, 1980[17]	10	7-patients required colectomy within one month, only one remained symptoms free
Dickenson et al, 1980[18]	36	All receivied steroids, no therapeutic response in TPN group
Jernerot et al, 1985[19]	12	Some benefit in moderate disease, none in severe colitis
McIntyre et al, 1986[5]	27	14-patients required urgent surgery, no differences between TPN and oral diet groups
Sitzmann et al, 1990[20]	22	All received medical treatment including steroids, 17-patients required colectomy
Gonzoles-Huix et al, 1993[21]	42	Similar efficacy in enteral and parenteral groups (less complications in enteral group)
Seo et al, 1999[22]	11	Control steroids and diet, study group TPN+steroids. No significant differences

TPN=total parenteral nutrition

flicting results and can be criticized for the small number of patients included. Jernerot et al reported a series of 158-patients with ulcerative colitis who received 204 courses of TPN therapy.[19] Remission rates of 55.7%, 86.9% and 91.8% were obtained in severe, moderate, and mild disease respectively.

The positive effects of TPN reported from non-controlled studies are not confirmed by the controlled trials. Owing to the geterogeneity of the results, it is difficult to compare published data. In terms of remission rates and need for operative intervention, TPN had more side-effects than, and no advantage over, total enteral nutritions (TEN).[23] A beneficial role for TPN in decreasing morbidity in pre-operative, malnourished patient has been suggested from meta-analysis. However, post-operative use was shown to increase complication rates.[24,25]

b) TPN in Crohn's disease

The goals of TPN regimens in Crohn's disease are to maintain nutritional status, induce remission, and avoid disease complications. Contrary to ulcerative colitis, TPN has a well-recognised role in the management of Crohn's disease (Table 2).[20,22,27-33] Guidelines on the use of TPN in Crohn's disease differ slightly in paediatric and adult populations.[34] Use of TPN is well-justified in adult patients with acute exacerbation, high-output fistulae, high-grade obstruction, and in cases of failure of enteral treatment. In paediatric patients, short bowel syndrome and growth failure can be considered as additional indications for the use of TPN.

There is conflicting evidence that bowel rest made possible by parenteral nutrition simultaneously improves symptoms and inflammation in Crohn's disease.[29-31,35,36] In a comparative, controlled trial, Greenberg et al were able to achieve clinical remission in 71%, 58% and 60% patients with active Crohn's disease treated by TPN, defined enteral formula diet and partial parenteral nutrition respectively.[31] Anatomical distribution of Crohn's colitis appears to influence the response to TPN. Although, specific data is lacking, patients with Crohn's

Table 2. Controlled Trials of total parenteral nutrition in Crohn's disease

Reference	Patients	Remarks
Elson et al, 1980[27]	20	13-patients showed improvement of disease markers
Muller et al, 1983[28]	30	Surgery avoided initially in 25-patients, majority relapsed within 4-years
Lochs et al, 1983[29]	10	80% remission rates
Jones et al, 1987[30]	19	84% TPN and 89% EN achieved remission
Greenberg et al, 1988[31]	51	Remission rates TPN=71%, EN=58%, and OD=60% (all patients maintained on steroids)
Sitzmann et al, 1990[20]	16	13-patients avoided surgery over 4-years period
Furukawa et al, 1997[32]	71	Remission rates, TPN=62%, EN=77% (Retrospective analysis)
Kobayashi et al, 1998[33]	9	Superior remission rates for TPN compared to EN, PM
Seo et al, 1999[22]	12	Only one patient required surgery, marked improvement of inflammatory markers

TPN=total parenteral nutrition, E=enteral nutrition, OD=oral diet, PM=polymeric diet

colitis respond less well to TPN and bowel rest than those with ileal involvement or ileocolitis. In patients with extensive intestinal resection, a useful role of TPN has also been described.[37,38]

Growth retardation and delayed puberty are well-known manifestations of Crohn's disease in 20-35% of children. Along with other anti-inflammatory medications a role for TPN is suggested in these individuals.[39]

The long-term effects of TPN on disease outcome remain controversial. Zitzmann et al reported significant long-term differences in disease behaviour and outcome among patients with ulcerative colitis and Crohn's colitis treated with TPN.[20] Disease recurrence post-TPN appear mild and promptly respond to standard medical treatment.[40] In certain situations, home parenteral nutrition may be justified, but important associated risks include septicaemia and venous thrombosis. These are reported to be more common in younger age groups and in patients with Crohn's disease.[41] On the other hand, quality of life issues are worth consideration and generally favourable results are achieved for IBD patients in younger age groups.[42]

ENTERAL NUTRITION IN IBD

The efficacy of enteral nutrition as primary and adjunctive therapy has been demonstrated in patients with IBD and is well established in Crohn's disease. Apart from elemental diet, other enteral formulae with different absorption properties, including peptide-based and polymeric diets, have been tried. In peptide-based diets a nitrogen source is provided in the form of di- or tripeptides due to their better absorption, tolerability, and cost-effective properties. Comparing the role of various factors on remission rates achieved by two forms of nutritional therapy, Furukawa et al did not find significant differense in remission rates achieved after 4-weeks of enteral (77%) and parenteral nutrition (62%).[32] A recent prospective, randomized, controlled Japanese study found that short-term treatment with enteral nutrition induced clinical remission in about two-thirds of patients, irrespective of the fat content of the nutrient formula.[43] Controlled trials comparing these diets to steroids therapy have produced conflicting results.[44-47] Results of randomized trials do not show and advantage of parenteral over any enteral nutrition.[29-31] Moreover, with enteral diets remission can be achieved more economically and with fewer complications. Fell et al adopted a modified approach in a group of adolescent patients by adding active transforming growth factor β 2 (TGF-β2) and achieved significant clinical and biochemical remission.[48] Results of this prospective, cohort study need confirmation from further randomized controlled trials.

ENTERAL FORMULATIONS AND IBD

A chance finding of disease improvement from the use of elemental diet in Crohn's patients being prepared for surgery led to further evaluation through randomized, controlled trials. Elemental diets are shown to be comparable to steroids in achieving remission as a primary therapy for Crohn's disease (Table 3).[2,8,49-55]

A meta-analysis of 5-clinical trials on 147-patients by Heuschkel et al found enteral nutrition a better choice as first-line therapy in children with active Crohn's disease.[56] They found no differences in efficacy between steroids and enteral nutrition. A short course of entral diet is shown to be equivalent to and in some cases superior to the conventional treatment modalities in remission

Table 3. Controlled trials comparing elemental therapy and steroids

Reference	Pantients (n)	Duration (days)	Outcome/Remission rates (%)	
			Elemental	Steroid
O'Morain et al, 1984[2]	21	28	81	80
Saverymuttu et al, 1985[49]	32	10	94	100
Seidman et al, 1986[8]	18	21	78	68
Hunt et al, 1989[50]	29	28	100	100
Okada et al, 1990[51]	20	42	80	11^
O'Brien et al, 1991[52]	16	28	62.5	All included were steroid refractory
Gorard et al, 1993[53]	42#	28	4.8→ 1.7*	5.3→ 1.9*
Ruuska et al, 1994[54]	19	77	80	78
Papadopoulou et al, 1995[56]	58	42	83	64

^ All patients in steroid group had severe disease, # 41% patients were intolerant of elemental diet, *Reduction in disease activity

induction and maintenance in Crohn's disease.[54]

Nutritional support has been suggested as an effective and safe alternative to chronic steroid therapy in steroid-dependent IBD patients. Verma et al reported complete withdrawal of steroid therapy in 43% of steroid-dependent patients.[57] Similarly, use of prolonged home elemental therapy appears safe and effective compared to drug therapy in remission induction and maintenance.[58] Absence of proper guidelines on the use of home enteral and parenteral nutrition emerged as one of the main issues in a survey of 2525 (44% Crohn's disease) patients receiving such therapy.[59]

Compliance is one of the major issues associated with the use of elemental diet and dropout rates ranging from 10-41% have been reported.[53] To evaluate such factors, oral and nasogastric administrations have been compared in IBD patients and results of a survey supported elemental diet as a well-tolerated mode of therapy.[60] In an interesting study, Anstee et al reported use of percutaneous gastrostomy for enteral nutrition in 9-patients with Crohn's disease, who were unable to tolerate oral therapy.[61] Results of this and other similar trials do support use of this modified administration route in special situations.[62] Patients with small bowel disease somehow tend to do better than patients with Crohn's colitis.[55,63]

From the results of individual trials, peptide-based, and polymeric (containing whole protein, polysaccharides, and fat) diets do not appear as effective as elemental diet in remission induction in IBD (Table 4).[36,45,46,64-70] As indicated earlier, interpretation of results is difficult because of the large number of variable factors. A meta-analysis of trials by Griffiths et al showed significantly inferior results from peptide-based enteral diets compared to steroids and found no differences between elemental and non-elemental formulae.[71]

CONCLUSIONS

Enteral and parenteral nutritions do not have a primary therapeutic role in the management of ulcerative colitis. As with any other debilitating medical or surgical condition their use is justified for malnourished patients to improve and/or maintain nutritional status. Use of TPN is best limited to carefully selected patients where enteral nutrition has either failed or is contraindicated.

Elemental, peptide-based and hydrolysed enteral formulae are shown to be effective in inducing and maintaining remission both in childhood and adult Crohn's disease. Generally, results tend to favour the use of elemental diets, which can be administered by normal oral or modified routes in selected patients. Similarly, TPN is effective both as primary and adjunctive therapy in Crohn's disease.

Steroids are easy to administer and remain treatment of first choice in most centres. However, enteral therapy has a better safety profile with comparable efficacy to steroids.

The environmental factors, including diet, have a major role in the aetiology of IBD and development of a disease-specific diet with possible addition of disease-modifying, growth promoting agents may be a target for future research.

Table 4. Trials comparing various enteral formulae

Reference	Diet	No of patients	Remission (%)
Middeton et al, 1991[45]	PM v ED	29	87 v 92
Royall et al, 1994[46]	PM v ED	40	75 v 84
Giaffer et al, 1990[64]	PM v ED	30	36 v 75
Raouf et al, 1991[65]	PM v ED	24	82 v 78
Rigaud et al, 1991[36]	PM v ED	30	73 v 66
Park et al, 1991[66]	PM v ED	14	71 v 29
Mansfeild et al, 1992[67]	HD v ED	35	47 v 42
Mansfield et al, 1995[68]	PM v ED	44	36 v 36
Akobeng et al, 2000[69]	PM (G) v PM	18	44.4 v 55.5
Verma et al, 2000[70]	PM v ED	21	55 v 80

PM=polymeric diet, ED=elemental diet, PM (G)=glutamine enriched polymeric diet, HD-hydrolysed diet

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