Inflammatory bowel disease: nutritional implications and treatment

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The two main types of inflammatory bowel disease seen in clinical practice are ulcerative colitis and Crohn's disease. The nutritional implications of these two conditions can be considered together. Treatment of the two conditions, particularly from the nutritional point of view, require separate considerations. The clinical and pathological features of the two conditions differ. Ulcerative colitis is a non-specific inflammatory disease, predominantly mucosal, extending proximally from the anal region of the colon to a varying degree. Ulcerative colitis may be confined to the rectum, so-called proctitis; involve the rectum and sigmoid colon, procto-sigmoiditis; extend towards and to the splenic flexure, left-sided colitis; or beyond the splenic flexure to the transverse colon, sub total colitis; or finally it could involve the entire colon, total colitis. The disease process does not involve the small intestine. Crohn's disease, on the other hand, may affect any part of the gastrointestinal tract from the lips to the anal margin, although ileo-colonic disease is still the commonest presentation, accounting for two-thirds of cases. In about 20% of patients, inflammation appears limited to the colon; the remainder consists chiefly of patients with ileal disease alone or proximal small bowel involvement (Farmer *et al.* 1985). Pathological features include chronic inflammation involving all layers of the bowel wall, often associated with granulomas and deep fissuring ulceration. Crohn's disease, unlike ulcerative colitis, is often discontinuous with clearly demarcated, inflamed areas separated by normal bowel. Mucosal ulcers may be superficial or deep and the coincidence of fissures with transmural inflammation involving the serosa leads to adhesions, inflammatory masses with mesenteric abscesses and fistula with adjacent organs. The serosa is often opaque and fibrous and extends into the adjacent mesentery which contains enlarged fleshy lymph nodes and dilated lymphatics. The transmural inflammation may be continuous or in a form of multiple lymphoid aggregates. Giant cell 'sarcoid-like' granulomas are diagnostic but are only found in 60% of patients. Granulomas are commonly adjacent to the serosa. Discrete aphthoid-like 'ulcers' overlying lymphoid follicles are often seen in apparently normal mucosa at some distance from obvious disease.

Nutritional status of patients with inflammatory bowel disease

Any patients with ulcerative colitis or Crohn's disease can become severely wasted during an acute unremitting attack of the disease. Chronic undernourishment, however, probably occurs more commonly in Crohn's disease than in ulcerative colitis (Harries *et al.* 1982*a*,*b*,*c*). Several factors can lead to protein–energy malnutrition (Reilly *et al.* 1976). These include a poor nutritional intake, malabsorption (due either to active disease or previous resection, or bypass) and protein losses through the colon or small bowel (Beeken *et al.* 1972). Rates of body protein synthesis and breakdown have both been found to increase in direct proportion to disease activity (Powell-Tuck *et al.* 1984*a*,*b*). It is of interest that many of the complications of severe inflammatory bowel disease, e.g. poor wound healing, muscle wasting, depressed tumour and cellular immunity and increased susceptibility to infection commonly occur in undernourished patients with other conditions. It seems reasonable to speculate, therefore, that

nutritional depletion *per se* may be a major cause of these features particularly in patients with inflammatory bowel disease, since many can remit with nutritional therapy (Harries *et al.* 1983).

The manifestations of protein–energy malnutrition in inflammatory bowel disease

A common clinical manifestation of protein–energy malnutrition in inflammatory bowel disease is weight loss. Anthropometrically this has been shown to occur as a consequence of a reduction in fat stores (Powell-Tuck, 1986) as well as reductions in muscle bulk (Heatley, 1986). Although the clinicians will recognize individual exceptions, weight loss is usually more common in patients with Crohn's disease than in those with ulcerative colitis; thus, when Harries *et al.* (1982*a*) surveyed a group of outpatients with ulcerative colitis they found no significant difference in their anthropometry compared with controls. Weight loss frequently occurs, however, in patients requiring hospital admission on account of acute exacerbations (Goligher *et al.* 1968; Powell-Tuck, 1986), weight loss occurring in up to 62% of the patients in the former series (Goligher *et al.* 1968).

Early studies documented weight loss in 70–80% of patients with Crohn's disease (Van Patter *et al.* 1954; Dyer & Dawson, 1973; Mekhjian *et al.* 1979). In contrast to ulcerative colitis, weight loss has been documented in patients with Crohn's disease receiving treatment as outpatients (Harries *et al.* 1982*a*; Lanfranchi *et al.* 1984; Heatley, 1986). Weight loss can be particularly marked in hospitalized patients with acute exacerbations of Crohn's disease, particularly in those with diffuse disease (Dyer, 1970).

In children with Crohn's disease, protein–energy malnutrition may present with stunted growth and delayed linear growth (McCaffery *et al.* 1970; Burbige *et al.* 1975; Layden *et al.* 1976; Grand *et al.* 1977; Kelts *et al.* 1979). As mentioned previously, poor nutritional intake, malabsorption, protein-losing enteropathy and increased rates of body protein breakdown are the major factors in inflammatory bowel disease that lead to protein–energy malnutrition (Reilly *et al.* 1976; Gassull *et al.* 1986).

Protein metabolism

In some patients with inflammatory bowel disease, nitrogen intake and faecal losses are the major determinants of N metabolism. With regard to N intake this may be slightly diminished in outpatients with 'inflammatory bowel disease'. However, food intake in severely ill patients with inflammatory bowel disease, for example those with acute colitis, sub-acute obstruction, sepsis or fistulas, may be severely compromised or lost entirely. Faecal losses of N in inflammatory bowel disease are variable, ranging from normal to low in mild disease to about 6·5 g/24 h in severe colitis (Powell-Tuck, 1986). In some patients N balance is not determined by differences between intake and faecal loss of N, for example intra-abdominal abscess formation can be associated with large urinary losses of N (Clark & Lauder, 1969). Moreover, increases in whole-body protein synthesis and breakdown, as estimated by the method of Waterlow *et al.* (1978), correlate with disease activity (Powell-Tuck *et al.* 1984*a*). These latter findings have illustrated how changes in whole-body protein turnover in inflammatory bowel disease are not due to local tissue changes but to a more generalized effect, probably on several tissues within the body (Powell-Tuck, 1986). The protein metabolism of the various tissues of the body will, thus, respond to the various differing stimuli which may occur in inflammatory bowel disease.

Fat and carbohydrate absorption

Steatorrhoea is found in Crohn's disease but not ulcerative colitis, and in the former patients the overall incidence is about 30% (Dyer, 1970; Smith & Balfour, 1972). Bile acid metabolism may be disturbed in extensive Crohn's disease as well as in patients who have had intestinal resections, and this may result in lumen concentrations of bile acid below the critical micelle concentration with resultant steatorrhoea. The extent and severity of small bowel disease may determine the degree of steatorrhoea in Crohn's disease, and the extent of any surgical small bowel resection will also influence the degree of steatorrhoea.

Dietary carbohydrate is normally assimilated in the proximal small intestine (Silk & Dawson, 1979). Small intestinal assimilation of dietary carbohydrate is not now thought to be as complete as previously imagined; unabsorbed carbohydrate passes into the colon where it undergoes bacterial fermentation to volatile fatty acids and gas. Carbohydrate assimilation has not been extensively studied in Crohn's disease or ulcerative colitis. In the light of recent work highlighting the importance of butyric acid as an energy substrate for the colonocyte, further research in this area is clearly indicated, possibly even in regard to the pathogenesis of inflammatory bowel disease.

Haematinic deficiency

Of patients with Crohn's disease, 25–50% have iron deficiency (Hoffbrand *et al.* 1968) and up to two-thirds of patients with ulcerative colitis have Fe deficiency (Driscoll & Rosenberg, 1978). Folic acid depletion probably occurs in about one-third of patients with inflammatory bowel disease and usually varies with active disease (Hoffbrand *et al.* 1968; Heatley, 1986). Diminished vitamin B_{12} absorption occurs in between half and two-thirds of patients with Crohn's disease and may be due to different factors (Heatley, 1986). Deficiency is present, however, in only about one-third of untreated patients with active disease (Heatley, 1986).

Mineral and vitamin deficiencies

Recent research has highlighted the importance of magnesium deficiency, particularly in Crohn's disease (Hessov *et al.* 1982). Zinc deficiency also occurs in association with Crohn's disease in up to 40% of patients (McClain *et al.* 1980; Sturniolo *et al.* 1980; Fleming *et al.* 1981). Various deficiency states affecting both water-soluble and fat-soluble vitamins have been reported in patients with Crohn's disease (Harries & Heatley, 1983). The relevance to the clinical condition has not been well documented.

The need for nutritional therapy

It is clear from the previous discussion that malnutrition is common in patients with active inflammatory bowel disease, especially Crohn's disease, and a wide range of nutritional disturbances can be identified, particularly in patients with Crohn's disease. Early recognition of deficiency is appropriate so that replacement therapy can be prescribed. It is important to appreciate that nutritional defects may have important subtle effects, thus Fe and Zn deficiency can be associated with impaired immune competence (Dowd & Heatley, 1984), and specific nutrients like Zn (McClain *et al.* 1980) and potassium and calcium deficiencies will influence protein metabolism. The case for focusing attention on nutritional deficiencies in inflammatory bowel disease is thus a clear one. Currently there is a good deal of interest centring around the hypothesis that nutritional therapy support in inflammatory bowel disease might constitute primary rather than supportive therapy. The ensuing text discusses this hypothesis. It should be

appreciated, however, that the aims of investigators have been to assess the effect of nutritional support administered either as a supplement to normal food (dietary supplements or enteral feeding) or as the only means of nutrient intake (enteral or parenteral nutrition).

Nutritional supplements

There is little scientific information supporting the use of dietary supplements in the treatment of inflammatory bowel disease. In one study Harries *et al.* (1983) showed that supplementing a normal diet with an orally administered whole protein-based enteral diet resulted in a significant improvement in anthropometric measurements and immune variables in patients with Crohn's disease. No information is available as to whether such an approach influences the natural history of the disease. In general, most clinicians advocate a high-energy high-N intake, particularly in severely malnourished patients with Crohn's disease (Clark, 1986). That the administration of nutritional support via the enteral route improves the nutritional state in inflammatory bowel disease was further confirmed by Gassull *et al.* (1986). These authors studied twenty-three patients with Crohn's disease and twenty-three patients with ulcerative colitis, all admitted to hospital with acute exacerbations of their disease. Although nutritional support in their study was without effect on patient outcome, the percentage of patients requiring intravenous albumin infusion was significantly less in the group fed enterally than in the control group.

Nutritional support as primary therapy

Parenteral nutrition. There are two main theoretical benefits of total parenteral nutrition in inflammatory bowel disease: nutritional effect and bowel rest (Matuchansky, 1986). The nutritional effects include stimulation of protein synthesis, both at the systemic and local (intestinal) level, resulting in stimulation of cell renewal and healing processes together with correction of vitamin and trace element deficiencies. The nutritional effects also include stimulation of systemic, mainly cellular, immunity. Bowel rest remains one of the major expected beneficial effects of parenteral nutrition despite the fact that there is no statistically confirmed benefit. Bowel rest implies interference with digestive secretion and motility, interference with antigenic (chemical, dietary and bacterial) stimulation of the intestinal mucosa from the lumen, interference with mucosal permeability and vascular supply as well as interference with trophic effects of intestinal hormones. The expected consequences of these interactions include a decrease in local inflammatory and infectious processes, healing of ulcerated mucosa, decreased output from fistulas, relief of partial inflammatory obstruction, particularly in Crohn's disease, a possibly temporary break in pathogenic interactions between external agent's host genetic receptivity and intestinal cellular immunity.

Parenteral nutrition in ulcerative colitis. In two carefully designed prospective randomized controlled studies, patients with acute exacerbations of ulcerative colitis, all of whom were treated with corticosteroids, received either bowel rest with parenteral nutrition or a standard ward diet (Dickinson *et al.* 1980; McIntyre *et al.* 1986). Parenteral nutrition and bowel rest did not influence the outcome, and one can conclude that this treatment has no primary therapeutic effect in attacks of acute ulcerative colitis.

Parenteral nutrition in Crohn's disease. During the period 1973–84, eighteen papers were published discussing parenteral nutrition in Crohn's disease. Of these only five were prospective (Greenberg *et al.* 1976; Dickinson *et al.* 1980; Elson *et al.* 1980; Loch *et al.* 1980; Muller *et al.* 1983). Only three of these were controlled. This, when taken in conjunction with a heterogeneity of patients in terms of number of patients, extent and

activity of disease, presence or absence of fistulas, duration of parenteral nutrition, type of associated treatments and criteria of remission, makes objective analysis very difficult (Matuchansky, 1986). Matuchansky (1986) concluded that notwithstanding these reservations the effects of parenteral nutrition could be tentatively evaluated provided that influences on activity, natural history of disease, enterocutaneous fistulas and growth retardation were clearly distinguished. In his analysis he concluded that the optimal duration of parenteral nutrition to induce remission was 4–6 weeks. After this time there was little hope of achieving a remission. Small intestinal Crohn's disease was more likely to respond than large bowel disease. The chances of achieving a clinical anatomical remission were higher in steroid-dependent cases than steroid-resistant cases, and the presence of fistulas had a deleterious effect on the chance of achieving a remission. A clinical remission of at least 1 year appeared to be reported on average in 60% of patients with Crohn's disease receiving total parenteral nutrition. In the most recent report available (Greenberg *et al.* 1988) patients with Crohn's disease which was unresponsive to medical management were randomly allocated to three groups and received nutritional support for 21 d: (1) total parenteral nutrition with nothing by mouth, (2) a nasogastrically administered formula, defined and containing whole protein, and (3) partial parenteral nutrition supplying some of the nutritional requirements, with oral foods *ad lib*. Remission of disease was defined as those patients with a modified disease activity score (Summers *et al.* 1979; Milewski & Irving, 1980) of less than 150 on day 21. All patients who remitted were maintained on a dose of 15 mg prednisolone daily and followed up at 1 year. There was no significant difference in outcome between the three groups. This new study, therefore, lays to rest the idea that bowel rest 'achieved with parenteral nutrition' plays a central part in the induction and subsequent maintenance of remission in active Crohn's disease. As has been pointed out by Matuchansky (1986) and Payne-James & Silk (1988), no prospective randomized controlled trial has yet been undertaken to compare parenteral nutrition alone with standard medical therapy in acute Crohn's disease, although it was considered that such a trial may be desirable. The findings of the new study (Greenberg *et al.* 1988) indicate that such a trial is not required. This is because the premise that bowel rest (as achieved by parenteral nutrition) is essential or beneficial in achieving remission of acute Crohn's disease has now been demonstrated to be invalid.

Enterocutaneous fistulas. There is considerable debate as to the role of parenteral nutrition in the management of enterocutaneous fistulas which complicate Crohn's disease. Some advocate the use of parenteral rather than enteral nutrition as long as there is no distal obstruction, as fistula closure seems to be achieved quicker with parenteral rather than enteral nutrition (Matuchansky, 1986). Others report a more gloomy experience, being able to close fistulas with parenteral or enteral nutrition but commonly find that the fistulas reopen as the patient returns to a normal diet (Clark, 1986).

Growth retardation. Parenteral nutrition has been successfully used to reverse growth failure in children and adolescents with Crohn's disease (Kirschner *et al.* 1981). The realization that the most important factor resulting in impaired growth is an inadequate nutritional intake may stimulate others to provide nutritional support via the enteral route (Rosenthal *et al.* 1983), and parenteral nutrition is now, therefore, considered to be indicated only after treatment with steroids associated with enteral nutrition has failed (Matuchansky, 1986).

Enteral nutrition in Crohn's disease

A new interest in enteral nutrition and Crohn's disease was stimulated by the paper of O'Morain *et al.* (1980). Twenty-seven patients with acute Crohn's disease (thirty-two

acute episodes) were given an elemental diet for 4 weeks. Twenty-nine acute episodes went into remission clinically and biochemically, and at 6 months only six had relapsed. In 1984 the same workers reported the results of a controlled clinical trial comparing prednisolone with an elemental diet in the management of first acute attacks of Crohn's disease (O'Morain *et al.* 1984). The patients were treated for 4 weeks and at the end of this time the improvement in all patients, i.e. clinical, haematological and biochemical, was the same for both treatment groups. Follow-up information after 3 months was not reported. A similarly designed short-term study was performed in children by Sanderson *et al.* (1989). Again similar improvements in disease activity, measured by chemical function as well as weight gain, were seen in both groups.

These exciting findings suggest that at least in the short term, first acute attacks of Crohn's disease can be managed by using nutritional support in the form of a chemically defined elemental diet as primary therapy. It remains to be seen whether subsequent exacerbations can be managed in a similar way, and as yet long-term follow-up is not available. Currently this unit is coordinating a tripartite control clinical trial to study these aspects of the management of Crohn's disease. It should be appreciated that basic physiological research indicates that the nutritional components of elemental diets are assimilated in the proximal small intestine, so that possible benefits of these diets as primary therapy are being achieved as a consequence of 'bowel rest'.

Summary and conclusion

It is clear that the nutritional state of patients with inflammatory bowel disease is often impaired and that the provision of nutritional support results in an improvement in nutritional state of these patients. Improvement in nutritional status can be achieved as effectively with enteral as with parenteral nutrition. The nutritional support appears to have no primary therapeutic effect in patients with ulcerative colitis. With regard to nutritional support in Crohn's disease, parenteral nutrition should be restricted to use as supportive rather than primary therapy. Available information now seems to suggest that most of the benefits of parenteral nutrition in Crohn's disease are related to improvement in nutritional state rather than as primary therapy, and its use should be restricted to treatments of specific complications of Crohn's disease, such as intestinal obstruction, related to stricture formation or short bowel syndrome following repeated resection. The present available evidence indicates that defined elemental diets may have a primary therapeutic role in the management of first acute attacks of Crohn's disease when there is a need to improve the nutritional status of patients with inflammatory bowel disease as an adjunct to primary drug therapy. Enteral nutrition is as efficacious as parenteral nutrition; moreover, it is safer to administer and more cost-effective.

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