Nutrition as primary and supportive therapy

Gastrointestinal Clinic, Groote Schuur Hospital and University of Cape Town
T A Winter, FCP (SA), PhD

Malnutrition, and its consequences, is a major problem facing the developing world today. World Health Organisation (WHO) figures indicate that 28% of all children under 5 years of age are underweight, 35% are stunted, and 8% are wasted.[1] In 1987 the Nordic Conference on Environment and Development estimated that 500 million people in the world were undernourished.[2] The problem, however, is not restricted to the developing world, with a number of studies reporting that up to 50% of hospitalised patients in developed countries may be nutritionally depleted.[3-8] This is likely to affect a variety of disease states and management protocols adversely. It is therefore essential that malnutrition be recognised and managed, particularly in ill patients. Record of height, weight and food intake should be standard practice in medical records.

Although nutritional support is unlikely to benefit patients with terminal disease, or those who are well nourished, in others it is likely to improve recovery rates, reduce complications and reduce hospital stay.[9] This would have an overall effect of reducing hospital costs.[10] Furthermore, dietary therapy has been shown to play a primary role in the treatment of conditions such as coeliac disease, irritable bowel syndrome, inflammatory bowel disease and atopic conditions.

Nutrition as supportive therapy

The importance of adequate nutrition in the maintenance of health, and the interrelationship between a poor nutritional state and disease, was appreciated by Hippocrates in the fifth century BC, when he wrote in his *On Ancient Medicine*:[11]

'Wherefore, I say, that such constitutions as suffer quickly and strongly from errors in diet, are weaker than others that do not; and that a weak person is in a state very nearly approaching to one in disease; but a person in disease is the weaker, and it is, therefore, more likely that he should suffer if he encounters anything that is unseasonable ... Whoever pays no attention to these things, or, paying attention, does not comprehend them, how can he understand the diseases which befall a man? For, by every one of these things, a man is affected and changed this way or that, and the whole of his life is subjected to them, whether in health, convalescence, or disease. Nothing else, then, can be more important or necessary to know than these things.'

During the typhus epidemic of 1842, Robert Graves speculated that the high mortality associated with the condition may have been related to the then current practice of bleeding, purging and starving fevers.[12] He abandoned this practice, and rather gave his patients food and drink. The fall in mortality was dramatic, and when questioned regarding the reasons for his success he stated:

'Gentlemen, these results are due to good feeding ... . When I am gone, you may be at a loss for an epitaph for me. I give it to you in these words: "He fed fevers".'

A number of studies have confirmed the positive effects of nutritional support in hospitalised patients. Bastow *et al*.,[13] using overnight nasogastric feeding, demonstrated a significant reduction in median rehabilitation time with a trend to lower mortality in women with a fractured femur, and Delmi *et al*.[14] showed that the clinical benefits of supplementary feeding in patients with a fractured femur persisted 6 months after injury. A study by Larsson and colleagues[15] of 501 elderly patients randomly allocated to receive oral supplements or ward diet alone clearly demonstrated the benefits of enteral supplementation in reducing mortality and duration of hospital stay. In all these studies, however, the beneficial effects of feeding were more pronounced in those patients who were initially malnourished, and this has been confirmed in subsequent reviews of the nutrition literature.[16]

Despite the early enthusiasm for peri-operative

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parenteral nutrition and optimistic predictions, subsequent studies have been less convincing. A multicentre Veterans Affairs trial[17] involving nearly 500 patients randomised to receive either peri-operative total parenteral nutrition (TPN), or the normal ward nutrition, showed similar overall 30-day postoperative complication rates (25.5% v. 24.6%). In fact, more infectious complications occurred in the TPN group. However, on further analysis, patients who were mildly or moderately malnourished received no benefit from peri-operative TPN, whereas overall complication rates were lower in those who were severely malnourished. Similar results were achieved in a study by Sandstrom and co-workers,[18] who demonstrated that overall the practice of peri-operative nutrition resulted in more septic complications.

As with the studies of enteral nutritional support, the parenteral nutrition studies indicate that nutrition supplementation only benefits those patients who are nutritionally deplete, and particularly in the case of parenteral nutrition, overzealous feeding is likely to be harmful. Nutritional support, both enteral and parenteral, is expensive and it is therefore important to target those patients most likely to benefit to ensure maximum efficacy of the practice.

Nutrition as primary therapy

Adverse effects of dietary components are well documented, and diet has been implicated in the aetiology of atopic conditions such as eczema and asthma, although the incidence in asthma is low.[19-22] The irritable bowel syndrome may also be associated with certain foods.[23] The difficulty in clinical practice is to identify the specific agent responsible for the symptoms, and then to endeavour to exclude it from the diet. This generally involves skin testing, radio-allergosorbent tests (RASTs), or the implementation of exclusion diets, which have been reasonably well standardised. Should the patient show a satisfactory response to the exclusion diet, the various food components are then reintroduced in an attempt to identify the responsible agent/agents.

Coeliac disease is a clear example of a dietary component (gliadin) causing an abnormal immunological response in the gut, resulting in an inflammatory attack on mucosal structures and villous atrophy. Treatment is avoidance of all gliadin-containing foods such as wheat and rye.

Inflammatory bowel disease, particularly Crohn's disease, is often associated with malnutrition, and this is likely to have an adverse effect on the healing process. Several studies have shown that nutritional intervention is beneficial as supportive therapy in active disease, and that the time-honoured 'bowel rest' is not a prerequisite to healing.[24-27] Specific diets and dietary products may also have a primary effect in the management of inflammatory bowel disease. Elemental diets, where the nitrogen source is in the form of amino acids, and semi-elemental diets, where the protein is hydrolised to peptides having chain lengths of between four and five amino acids, have been shown to be effective in inducing remission in active Crohn's disease, with the added benefit of nutritional support.[28-30] Presumably these diets work by reducing antigenic stimulation to the gut, thereby allowing the inflammatory process to downregulate. Unfortunately, they tend to be unpalatable, usually requiring administration via a nasogastric tube. Patient acceptance and compliance, particularly on a long-term basis, is therefore likely to be extremely limited. Furthermore, the effects of these diets appear to be restricted to the short term, and recurrence rates of up to 100% at 1 year have been reported.[31] Studies with peptide-based diets (semi-elemental) have produced conflicting results. Trials have indicated that peptide-based diets may be similar to elemental diets,[32,33] but inferior to steroids[34] in inducing remission. Studies with polymeric diets have indicated that they may be as effective as elemental diets,[31,35,36] raising questions of the mechanisms by which dietary therapy exerts its effect in Crohn's disease. Interpretation of the individual trial remains difficult, however, owing to a number of variables including sample size, composition of enteral feeds, disease site and extent and outcome measures. Meta-analysis has indicated that steroids remain significantly better than enteral nutrition in inducing remission in active Crohn's disease, particularly when peptide-based diets are administered.[37] Enteral diet therapy, however, may be of particular value in children and in patients where steroid therapy is contraindicated, in undernourished patients, and in preparation for surgery.

Arachidonic acid metabolites have been implicated in the pathogenesis of chronic inflammatory conditions such as inflammatory bowel disease. Both Crohn's disease and ulcerative colitis have been associated with increased levels of leukotriene B4, a potent chemo-attractant in the intestinal mucosa. Fish oil n-3 fatty acids compete with arachidonic acid, with the subsequent production of prostaglandins of the 3 series, and leukotrienes of the 5 series. These are less inflammatory, and are associated with altered cytokine function with suppression of the production of interleukin 1 and tumour necrosis factor.[38] Several studies have now indicated that diets high in fish oil are associated with a decreased risk of cancer in general, and colon cancer in particular,[39,40] and that dietary therapy with fish oils is effective in the management of inflammatory bowel disease.[41-43] A study by Belluzzi *et al.*[44] reported impressive results in the maintenance of remission in patients with Crohn's disease, with 56% of their fish-oil group still in remission after 1 year, compared with 26% of their control group.[41-44] It should be noted that fish oils have a rather unpleasant taste, and that patients often

complain of side-effects such as nausea, halitosis, and diarrhoea. Better absorption of the new enteric-coated preparations, as used in the Belluzzi study, allows the use of much smaller doses. Frequency of side-effects is therefore reduced and compliance improved.

Glutamine is the most abundant free amino acid in the body, and is an important energy source and precursor for purine and pyrimidine biosynthesis for cells having a high turnover rate. This includes cells such as enterocytes and those involved in the immune system. It is also an important source of glucose during periods of starvation. Glutamine has been considered a non-essential amino acid, as human tissues, particularly skeletal muscle and lung, are able to biosynthesise glutamine from glutamate. Although it is the most abundant amino acid, plasma levels rapidly decrease following injury. In metabolically stressed individuals the capacity for producing endogenous glutamine may be overwhelmed, resulting in deficiency.[45,46] This deficiency may subsequently result in derangements of intestinal structure and function, as well as compromising the immune system.[47,48] It has therefore been proposed that glutamine should rather be considered a partially or conditionally essential amino acid.[49]

The role of supplementing glutamine to postoperative and critically ill patients has been investigated in several studies. Ziegler *et al*.[50] demonstrated fewer infections and shorter hospital stay in patients undergoing bone marrow transplants for haematological malignancies, although in their study overall 100-day mortality was unchanged. Griffiths *et al*.[51] subsequently demonstrated significant improvement in 6-month survival in critically ill patients admitted to ICUs receiving glutamine-containing parenteral nutrition. The role of glutamine-enriched enteral nutrition has also been investigated, with a study of patients with multiple trauma demonstrating significant reduction of pneumonia, bacteraemia and septicaemia.[52]

Short-chain fatty acids (SCFAs) are produced by the anaerobic bacterial fermentation of dietary carbohydrate, and fibre within the lumen of the colon. Colonic epithelial cells have been shown to be dependent on the availability of these fatty acids, particularly butyrate, for nourishment and function.[53-56] Lack of these substrates, either due to starvation or diversion of the faecal stream, may lead to mucosal atrophy, reduced absorption of sodium and water, inflammation, and possibly neoplastic transformation.[57,58] Ulcerative colitis has been shown to be associated with both reduced concentration of SCFAs and a decreased ability of the colonic mucosa to metabolise butyrate.[57-61] These findings suggest a causal relationship, and therefore a possible therapeutic role in this condition. Studies have indicated that local irrigation with SCFA-containing enemas may be effective in the management of distal ulcerative colitis, despite the evidence of impaired metabolism.[62-65]

Hydrogen is a further product of anaerobic bacterial fermentation of carbohydrate in the colon. The fate of this also depends on the activity of the bacterial flora. Methanogenic bacteria combine the hydrogen with carbon dioxide to produce methane ($CO_2 + 4H_2 = CH_4 + 2H_2O$). Methane is harmless to colonic cells, and is expelled in flatus, and in the breath. Sulphidogenic bacteria, on the other hand, produce hydrogen sulphide ($SO_2 + 4H_2 = 2H_2S + 2H_2O$), which is toxic to colonic mucosal cells, impairs mucosal integrity by disrupting disulphide bridges, and may also inhibit colonocyte oxidation of butyrate. The activity of sulphidogenic bacteria is dependent on the availability of sulphur in the colon, the chief source being protein in the diet. With adequate supplies of sulphur these bacteria out-compete the methanogenic bacteria for hydrogen.[66] Over 90% of patients with ulcerative colitis have been shown to have significantly greater faecal sulphite levels than do controls[55] and this may have further implications in the pathogenesis of the condition.[67,68] These features argue for a reduction in high sulphur-containing protein in the diets of patients with ulcerative colitis.

Although drug therapy is likely to remain the mainstay of therapy for conditions such as inflammatory bowel disease, the primary and supportive role of diet and dietary constituents is becoming increasingly appreciated. This is resulting in a better understanding of pathophysiological processes operating in a variety of diseases, and is likely to lead to further advances in the management of these conditions.

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