Nutrition in Crohn Disease

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Abstract and Introduction

Abstract

Nutrition plays an important role in the pathogenesis, treatment, and morbidity of Crohn disease. Approximately two thirds to three fourths of hospitalized patients with active disease and one fourth of outpatients with Crohn disease are malnourished. Malnutrition, which can be present even when Crohn disease is in remission, can affect growth, cellular and humoral immunity, bone density, and wound healing. Decreased nutrient intake, malabsorption, drug-nutrient interactions, anorexia, and protein-losing enteropathy can all contribute to the protein-calorie malnutrition and other specific nutrient deficiencies seen in Crohn disease. Therefore, by preventing and correcting nutrient deficiencies, nutritional therapy is an important component in the overall management of patients with Crohn disease.

Introduction

Crohn disease (CD) is a chronic transmural inflammatory disorder of the gastrointestinal tract of unknown cause. Since Drs. Crohn, Ginzburg, and Oppenheimer were initially credited with describing Crohn disease in 1932, weight loss has been recognized as a predominant feature of the disease.[1] Many subsequent studies have demonstrated that nutrition and nutritional deficiencies are important factors in the pathogenesis, treatment and morbidity of CD. Malnutrition can be present even in patients whose disease is quiescent. In one representative study of outpatients with CD, 11 of 47 (23%) patients had abnormalities indicating protein-energy malnutrition.[2] Significant deficiencies of vitamins, minerals, and trace elements can also exist in patients with CD, whether they are inpatients or outpatients[3-7**] (Table 1).

Causes of Malnutrition in Crohn Disease

Malnutrition, a broad term that refers to faulty or inadequate nutritional status, can be determined by insufficient dietary intake, poor appetite, muscle wasting, and weight loss.[8] Malnutrition in CD is often multifactorial in origin and frequently insidious in its onset. Several factors may contribute to a patient's malnutrition, including anorexia; drug-nutrient interactions; malabsorption; and increased fluid, electrolyte, and blood loss from the gut. Anorexia is often the most prominent cause of malnutrition,[9] which can result from increased levels of tumor necrosis factor (TNF)-, interleukin-1, and other cytokines.[10, 11] Patients also may have inadequate intake of nutrients secondary to fear of abdominal pain and diarrhea after eating. Deficiencies in zinc, copper, and nickel have been associated with altered taste sensation, leading to a cycle of decreased oral intake, and causing further malnutrition and mineral deficiencies.[5, 12, 13] Even metronidazole, which is used in the treatment of CD, can produce a metallic taste and exacerbate a patient's anorexia.

Medications used regularly in the treatment of CD also can augment nutritional deficiencies. Corticosteroids suppress calcium absorption in the small intestine,

increase calcium excretion by the kidneys, and alter protein metabolism. Sulfasalazine decreases folate absorption. Antibiotics alter gut flora and can affect vitamin K metabolism. Many medications (eg, sulfasalazine and 5-aminosalicylic acid) can be associated with nausea and vomiting, thus limiting nutritional intake.

Malabsorption can be another cause for malnutrition in patients with Crohn disease. Approximately one third of patients with CD have small intestine involvement. The absorptive surface area of the small intestine in CD may be limited by the degree of inflammation present. Small bowel resections also physically decrease the absorptive surface area. Ileal resections can result in vitamin B12 deficiencies and bile salt malabsorption; the lack of bile salts can lead to fat and fat-soluble vitamin deficiencies. Ileocecal valve resections can result in bacterial overgrowth causing malabsorption.[14]

The intestinal inflammation seen in CD is often associated with exudative protein losses; the degree of protein loss correlates with the severity of disease activity.[15] Inflammation also produces a catabolic response, which is probably a cytokine-mediated event, resulting in a negative nitrogen balance. To achieve a positive nitrogen balance, patients with CD require higher protein intake than the general population without a known gastrointestinal disorder.

Nutritional Assessment

When assessing a patient, it is important to conduct a detailed physical examination and elicit a thorough history. The subjective global assessment is a method of qualitatively assessing a patient's nutritional status. With this method, the patient is classified as generally well nourished, moderately malnourished, or severely malnourished, based on the patient's weight loss, dietary intake, gastrointestinal symptoms, CD activity, functional capacity, muscle mass, subcutaneous fat, edema, and ascites[16] (Table 2). The subjective global assessment has been shown to be reproducible among observers, with better than 80% agreement when two independent observers assessed the same patient.[16, 17]

As can be seen, both the history and physical examination are of paramount importance; however, laboratory studies also are integral components to the assessment of a patient's nutritional status when assimilating data regarding the cause of the patient's malnutrition. Anemia is common in CD and its cause is often multifactorial. It can be difficult to determine if the patient has an iron-deficient anemia or an anemia of chronic disease. In both, iron is low, but the ferritin concentration can be increased independently of iron status by infectious, inflammatory, malignant, and other disorders. The total iron-binding capacity (TIBC or transferrin concentration) can be useful in distinguishing between the two causes of anemia. In uncomplicated iron deficiency, the TIBC increases and in the anemia of chronic disease the TIBC decreases. A combined microcytic and macrocytic anemia can be present, as is seen in some patients with CD who are deficient in vitamin B12 or folate. Vitamin B12-intrinsic factor complex is absorbed in the last half of the small intestine, but the greatest density of intrinsic factor receptors is in the distal ileum; hence, patients with ileal resections will require vitamin B12 parenterally (intramuscularly or intranasally). Sulfasalazine competitively inhibits the jejunal folate conjugate enzyme, often producing folate malabsorption and requiring concurrent oral folate supplementation.[6] Even patients not taking sulfasalazine should be considered for folate supplements as a result of frequent poor dietary intake of folate. Additionally, data exist to suggest that folate supplementation conveys protection against the development of colorectal cancer in patients with inflammatory bowel disease (IBD).[18-20]

Osteoporosis and Vitamin D Deficiency

Osteoporosis represents a major public health problem, accounting for more than 1.5 million bone fractures in the United States each year.[21] The estimated national direct expenditures (hospitals and nursing homes) for osteoporotic and associated fractures was estimated to be $17 billion in 2001 ($47 million each day).[21] An average of 24% of patients with hip fracture 50 years of age and older die in the year following their fracture. The dual energy x-ray absorptiometry (DEXA) scan is commonly used in diagnosing osteoporosis. The T-score refers to the number of standard deviations (SD) above or below the mean for a young adult population (corresponding to peak bone mass); a World Health Organization (WHO) report formulated diagnostic ranges for osteoporosis based on T-scores. A T-score within one SD of the norm is considered to be within normal limits. A T-score that is 1.0 to 2.49 SD less than the norm is defined as osteopenia, and a value greater than 2.5 SD indicates the presence of osteoporosis. The Z-score refers to the number of SD above or below the mean for an age-matched population. Use of the Z-score can conceal normal age-related loss, thereby underestimating fracture risk.

Osteoporosis is a common extraintestinal complication of IBD. The prevalence of osteopenia is between 40% and 50% and the prevalence of osteoporosis is between 5% and 36% for patients with IBD.[22-26] The underlying inflammatory process in CD may play a significant role in the induction of osteopenia in these patients.[27] In CD, the principal cytokines released by the inflammatory cells of the intestine are TNF-, interferon-, and interleukin-6. These cytokines, particularly TNF-, stimulate osteoclast activity disproportionately, resulting in an imbalance in the regulation of bone metabolism. Additional risk factors for osteoporosis include corticosteroid use, decreased oral intake,[28] small bowel resection,[26] low body mass index,[29] malabsorption, and vitamin D deficiency.[30, 3] Of these, one of the most significant risk factors appears to be corticosteroid usage.[24-26, 32] Patients with IBD on corticosteroids experience a 6.2% annual loss of total bone mass compared with only 0.9% annual loss of total bone mass in patients not using corticosteroids.[33] It is estimated that one quarter to one half of patients on long-term glucocorticoids will experience bone fractures.[34]

One recent retrospective study by Dear et al.[7**] examined the effect of dietary treatment and corticosteroids on bone density in female patients with CD treated with and without long-term steroids. The prevalence of osteoporosis was 15% and of osteopenia was 45% in the cohort studied. Both hip and spine T-scores for all patients were significantly below peak bone mass. However, when compared with age-matched controls, the Z-score, the noncorticosteroid-treated patients did not differ significantly from controls; the mean Z-scores were -0.3 (95% CI: 0.15 to -0.75) and -0.04 (95% CI: 0.42 to -0.5) for the noncorticosteroid-treated groups. In contrast, the spine Z-score for the steroid treated group was -0.98 (95% CI: -0.6 to -1.36). Although the standard, both clinically and in research, is to use the T-score as it correlates best with the absolute fracture risk, the Z-score can be useful in comparing age- and gender-matched controls. This study demonstrates that all patients with CD are at risk for some level of osteopenia or osteoporosis, but that patients who are treated with steroids have a much higher risk of osteoporosis when compared with age-matched controls. This study also shows that patients treated with dietary manipulations that often avoid dairy products and other sources of calcium are not necessarily at an increase risk of developing osteoporosis. However, more studies are needed to determine what the risk of developing osteoporosis is for men with CD.

In their study, Dear et al.[7**] also found a prevalence of vitamin D deficiency between of 8% and 14% in the cohort studied. Vitamin D is a hormone that is a positive regulator in calcium and phosphate homeostasis; it acts on calcium and phosphate levels by increasing their absorption in the small intestine, enhancing their mobilization from bone, and decreasing their excretion by the kidney. These processes maintain calcium and phosphate ion concentrations at levels that are appropriate and are needed for neuromuscular activity and bone mineralization. The intestinal absorption of calcium occurs mostly in the more proximal segments of the small bowel and is dependent on vitamin D-dependent Ca2+-binding protein; calcium is also absorbed in the kidneys by both parathyroid hormone and vitamin D-stimulated mechanisms. Vitamin D is absorbed in the duodenum and jejunum; hence, when the small intestine has been resected in CD, both calcium and vitamin D absorption can be impaired, resulting in muscle weakness and skeletal demineralization.[30] Vitamin D can also be synthesized in the skin from 7-dehydrocholesterol after exposure to ultraviolet B radiation. Interestingly, a recent case report looked at using ultraviolet B radiation to treat a woman with severe intestinal fat malabsorption caused by CD and multiple small bowel resections, leaving her with only 2 feet of small intestine.[35*] She took daily vitamin D supplements and was dependent on total parenteral nutrition, but she continued to be vitamin D deficient and had bone pain and muscle weakness. After 6 months of ultraviolet B radiation treatment, which consisted of 10 minutes in a tanning bed time three times a week, her serum 25(OH) vitamin D level was in the normal range and she no longer complained of bone pain or muscular weakness. After only 4 weeks of treatment, her serum 25(OH) vitamin D level was increased by 357% from 7 to 32 ng/mL, her parathyroid hormone level decreased by 52%, and her calcium level increased from 7.8 to 8.5 mg/dL. Although only one case report, this offers a potential alternative for patients who are not responding to oral and intravenous vitamin D replacement.

Plasma Antioxidants

Although the cause of Crohn disease is unknown, oxidative stress is postulated to be an important factor in its pathogenesis.[36, 37] In CD are seen low concentrations of endogenous antioxidant defenses, increased free radical production by neutrophils and monocytes,[38] and decreased circulating antioxidants, all of which may be contributing to the increased oxidative stress seen.[39**]

Lipid peroxidation is significantly higher in patients with CD than in healthy controls and the level of oxidative stress is independent of disease activity.[40] The colon has relatively low stores of endogenous antioxidants; hence, circulating antioxidants (eg, carotenoids, vitamin A, vitamin E) may be important factors in the prevention of free radical-mediated tissue injury in CD.[41] Low blood concentrations of vitamin A in patients with CD have been shown,[42, 43] and a recent study by D'Odorico et al.[39**] also demonstrated this; vitamin A levels in patients with CD were 1.67 ± 0.1 µmol/L and in controls were 2.7 ± 0.07 µmol/L ($P < 0.0001$). D'Odorico et al.[39**] also measured carotenoid levels and found a statistically significant reduction in blood levels when compared with normal subjects ($P < 0.0001$). Beta-carotene, the carotenoid most reduced in concentration, was decreased by 50% when compared with controls ($P < 0.0001$). Despite these low blood levels of antioxidants, no overt clinical signs of vitamin deficiency were seen in any of the patients. The carotenoids also were decreased significantly more in active than in remission phase CD.

Decreased nutritional intake of vegetables and fruit was seen in patients with CD when compared with controls, which may contribute to the decreased

antioxidant levels found in these patients. Other mechanisms also may contribute to reduced plasma antioxidant levels, including malabsorption, increased gastrointestinal losses, and increased vitamin requirements. Further studies are needed to better elucidate the processes that result in the decreased plasma antioxidant levels in CD. Optimal vitamin status with adequate concentrations of antioxidants may improve the clinical course of CD, as patients with CD have higher concentrations of 8-OHdG (a measurement of DNA damage induced by oxygen-derived free radicals) regardless of disease activity or duration.[39**] Although this seems plausible, it still needs to be demonstrated in a prospective randomized controlled fashion.

Long-Chain Triglycerides

An elemental diet (one that is very low in fat and contains primarily l-amino acids) is felt to be effective in inducing remission in patients with CD.[44-48] Although originally believed that elemental diets were equivalent to standard corticosteroid therapy, further studies[49, 50] and a recent meta-analysis[51] have concluded that remission rates with corticosteroids are higher than with elemental diets. The decreased remission rates may be secondary to patients' noncompliance with ingestion of elemental diets, given their unpalatable nature.

Two meta-analyses have shown an inverse correlation between remission rates of a given enteral diet and the long-chain triglyceride (LCT) content in that diet.[52, 53] A recent randomized controlled trial examined this question by giving patients with active CD two whole protein liquid enteral feeds which differed only in their LCT content.[54**] The remission rates were 46% in the low LCT and 45% in the high LCT ($P = 0.99$). This study failed to show any difference in the remission rates between patients treated with high- or low-content long-chain triglycerides. Further studies need to be done to look at the source of fat in the diet or the emulsifiers and stabilizers used in the diets to determine if it is these, and not the LCT content, that influences remission. Regardless, the efficacy of elemental diets depends on the patient's ability to tolerate the feeds for prolonged periods of time.

Butyrate

Butyrate is a short-chain fatty acid produced by bacterial fermentation of dietary fiber and undigested starch in the colon. It is important in maintaining the health and integrity of colonic mucosa,[55] as it provides greater than 70% of the energy supply of the colonocyte.[56] Recently, it was demonstrated that butyrate inhibits the inflammatory response in CD by inhibiting the transcription factor nuclear factor kappa B (NFB) activation in immune cells.[57] NFB is involved in inflammatory and immune responses and regulates TNF. By inhibiting NFB, TNF is downregulated and, theoretically, inflammation will be reduced. Already demonstrated in patients with steroid-resistant CD is marked improvement in those patients treated with monoclonal antibodies to TNF.[58] Although further studies are needed to determine the best method of administering butyrate, it offers promise for an immune modulatory therapy for treating patients with CD. Of note, an oral precursor of butyrate has recently been used in ulcerative colitis and was successful in lowering corticosteroid dose. Further utility in CD might be of special interest.

Conclusions

Malnutrition is commo n in patients with Crohn disease and may have serious potential consequences. The presence of malnutrition is associated with defects in

cellular and humoral immunity, delayed growth, bone disease, and poor wound healing. A detailed history, thorough physical examination, and appropriate laboratory work are integral in diagnosing the cause of the patient's malnutrition so that therapy can be tailored accordingly. Nutritional support, with either elemental diets or parenteral nutrition, has been shown to be efficacious, but remains less effective than steroids in inducing remission in CD. Given the multitude of side effects associated with corticosteroids, alternative therapies are continually being studied, including short-chain fatty acids and elemental diets. Further studies are needed to better elucidate the relationship between nutrition and Crohn disease.

Tables

Table 1. Prevalence of decreased nutritient levels among patients with Crohn disease

Table 2. Subjective Global Assessment (SGA) of nutritional status

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