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Nutrition in Pediatric Inflammatory Bowel Disease

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Approximately 25% of patients with inflammatory bowel disease (IBD) have the onset of their disease within the first 2 decades of life. Malnutrition is frequent in patients with IBD, especially those with Crohn's Disease (CD). Various micronutrient deficiencies also contribute to morbidity in these patients. Liquid nutrition is frequently utilized to manage the group of patients with malnutrition. In pediatric CD, there is considerable evidence to support the use of polymeric formula as exclusive nutrition to induce remission in newly diagnosed patients, as well as in those with relapses. Exclusive enteral nutrition is an attractive alternative to corticosteroids in patients with CD. There is no evidence for using exclusive enteral nutrition for inducing or maintaining remission in patients with UC. We review the nutritional aspects of patients with IBD and the use of liquid enteral nutrition for remission induction in pediatric patients with IBD.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract that are included under the common terminology inflammatory bowel disease (IBD). They are chronic, lifelong diseases with frequent relapses and remissions and with wide variations in clinical manifestations. In CD, inflammation can affect any part of the gastrointestinal tract, whereas in UC, inflammation is typically limited to the colon. This partly explains why patients with CD have more nutritional issues than patients with UC. Patients with IBD are prone to a diverse array of complications stemming from the disease process itself. Two complications that are specific to pediatric IBD are growth failure and pubertal delay.

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Malnutrition and Growth Failure in IBD

About 25% of patients with CD and UC present before the age of 18 years (1). Malnutrition is present in up to 85% of patients with CD (2). In a population-based study of pediatric CD, growth retardation and severe malnutrition were present in 9.5 and 32% of children at diagnosis respectively, and despite a significant catch-up, were still observed in 6.9 and 15% of children at 6 year follow-up (3). In contrast, only 3-10% of children with UC have growth abnormalities at diagnosis (4). Studies evaluating the final adult height in patients with pediatric-onset CD have demonstrated a significant failure to reach target adult height in up to 22% of

patients (5). Pubertal growth disturbances are seen in about 25% of boys with CD (6). No pubertal delay is identified in patients with UC (7). There are several causes of undernutrition and growth failure in IBD (Figure 1).

Deficiencies of minerals, trace elements, and vitamins are common in CD. These reflect chronic blood loss (iron deficiency), chronic diarrhea (hypomagnesemia and zinc deficiency), and malabsorption and losses from small bowel involvement (deficiencies of vitamin B_{12} and other micronutrients). Vitamin D deficiency is highly prevalent in IBD and has also been implicated in the pathogenesis of IBD (6).

With the introduction of newer treatment modalities including biologic agents, it has been suggested that these agents positively influence growth and nutrition in patients with IBD. However, growth delay appears to persist, despite improved disease activity associated with the frequent use of immunomodulators and biologic agents (8).

Assessment of Nutrition and Growth

Standard growth charts are available to graph height, weight, body mass index (BMI), and height velocity such that an individual child's measurements can be compared with normative data. Each patient's measurements can be represented as a percentile or a standard deviation score or z-score, which represents a quantitative deviation from the reference population mean for same age and gender. Target height calculation using mid-parental height should be documented at the initial visit. An individual patient should follow the same percentile and same z-score throughout life. Some deviation is expected at puberty (with early and late pubertal growth spurts).

A definition of growth impairment in terms of a static height measurement may be misleading, since it is influenced by parental height and pubertal status. A patient may be normally short; conversely a previously tall child may not have grown for 2 years but may still be of average stature for age and gender. Serial measurements showing a fall from higher to lower percentiles and height velocity expressed as a z-score for age and gender should be used to define growth faltering. Height velocity z-score for age and gender is the most sensitive parameter to recognize impaired growth. One of the drawbacks of height velocity is that normal standards for height velocity throughout childhood are based on height increments during

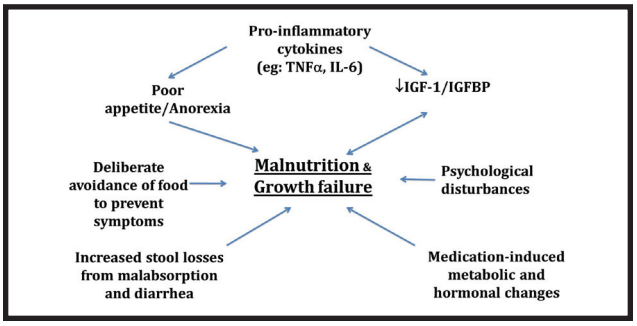

Figure 2. Pathogenesis of Malnutrition and Growth Failure in Inflammatory Bowel Disease. Key: TNFα tumor necrosis factor-alpha, IL-6: Interleukin-6, IGF-1: Insulin like growth factor-1, IGFBP: Insulin like growth factor binding protein

12-month periods. It is recommended that height velocities be calculated over intervals no shorter than every 6 months. A height velocity z-score of -2 over a 12-month period equates to a reduction in height z-score of approximately 0.3 to 0.4. It should be noted that BMI may not be a reliable marker of nutrition status in pediatric IBD; it does not reflect alterations in body composition (i.e., decreased skeletal muscle). Thus, BMI can underestimate malnutrition in patients with inflammatory bowel disease (9). Recent evidence has shown that children with CD have decreased fat-free mass 2 years after diagnosis, even in those patients with clinical improvement (including weight gain), suggesting that weight gain was mainly due to an increase in fat mass.

Impaired linear growth is defined by at least one of the following criteria: (10)

1. Height z-score at diagnosis or subsequently significantly less than expected height z-score
   - Difference between observed height z-score and predicted height z-score using the 'Mid-parental Heights' formula is >2.0 OR
   - Difference between observed height z-score and the 'pre-illness' height z-score is >1.0
2. Current height z-score significantly less than height z-score at diagnosis or reduction in height z-score since diagnosis is < 0.75

Assessment of pubertal status by Tanner staging should be an integral part of nutrition and growth assessment in patients with IBD. Self-assessment using line drawings and written descriptions of Tanner stages have been validated in children with CD (11). In girls, menarchal status should also be ascertained. Females enter the adolescent growth spurt relatively early in

puberty, while in males it occurs late (Tanner 4). The growing phase could be considered final once they have entered Tanner stage 5 and they have demonstrated less than 0.5 cm linear growth in 12 months.

Laboratory parameters including hypoalbuminemia should not be used to monitor nutrition status. Albumin levels correlate inversely with the inflammatory status rather than with the nutrition status (12). In this sense, albumin is better used as a barometer of disease activity.

NUTRITION SUPPORT IN IBD

Similar to many other chronic illnesses, the primary goal of nutrition in IBD is to prevent and treat undernutrition, correct micronutrient deficiencies, promote growth and development, and improve quality of life. In addition, enteral nutrition (EN) is utilized to induce and maintain remission in CD.

Nutrition Support in CD Patients with Malnutrition and Growth Impairment

Malnutrition is very common in patients with CD. Caloric intake in growth-impaired CD patients is reported to be 54% of that recommended for children of similar height age (13).

Undernutrition as well as growth failure cannot be treated with nutritional counseling alone (14). Supplemental liquid nutrition (oral or enteral) in addition to their regular diet improves nutritional status and eliminates some of the consequences of undernutrition. Improvement of nutrition often leads to improvement in general well-being and thus may improve the quality of life. Supplementing a higher proportion of calories, as liquid EN is also known to help in maintaining remission and preventing relapses (see the section on EN in maintaining remission). Regular polymeric formulas should probably be utilized purely for nutritional rehabilitation because of better tolerance. In older children and teens not tolerating oral feeds, consideration should be given to short-term (4-6 weeks) nasogastric tube placement. With supplemental nutrition and appropriate treatment of inflammation, most patients improve within a few weeks and start consuming adequate calories through a regular diet.

There is no significant relationship between resting energy expenditure (REE) and disease activity (15). Though prediction equations are not accurate in determining calorie needs in IBD patients (16), Hill, et al recommend using the Schofield equation for pediatric IBD patients (17). *Regardless of the method used to determine needs, it is important to closely monitor patients' weights, feeding tolerance and disease symptoms after beginning EN therapy.*

Enteral Nutrition as a Primary Therapy in CD

The beneficial effects of nutritional therapy in inducing remission were observed in the 1970's when parenteral nutrition (PN) and bowel rest were commonly used to treat patients with CD. A number of clinical trials that followed in the 1980s showed that an elemental diet was as effective as corticosteroids in inducing remission in CD (18). Peptide-based and polymeric liquid diets were subsequently introduced to reduce osmotic load, thus allowing better tolerance. The rates of remission induction are equal with elemental, semi-elemental and polymeric diets (19-21). Polymeric diets are more palatable and the need for enteral administration of formula is less (22). There are insufficient data to support the use of specialized formulas (fat modified, ω-3 fatty acids, glutamine and arginine, TGF-β enrichment) for inducing remission.

Two meta-analyses have concluded that EN is as effective as corticosteroids at inducing a remission (21, 23). In the current European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, EN is recommended as a first line therapy for inducing initial remission in CD in children (14). Even though, there have been no studies comparing EN to placebo due to the ethical considerations, the benefits of EN can be demonstrated by comparing the EN response rates (53% to 80%) to usual placebo response rates (18% to 42%) in clinical trials (18,24).

With the current move towards achieving mucosal healing to avoid long-term consequences of CD, it becomes even more imperative to use EN for remission induction. Two pediatric studies report mucosal healing rates between 44% and 74% on exclusive EN (25,26), and there is also a rapid reduction in pro-inflammatory cytokines in children receiving exclusive EN for active CD (27). This provides further evidence that nutrition therapy in this situation is providing more than simply an optimal calorie intake and is presumed to be due to low antigenicity of sterile formulas.

Nutrition therapy appears to be more effective in newly diagnosed patients (28). The clinical response rate to nutrition therapy may be influenced by disease location (29). The response rate with macroscopic ileal involvement can be as high as 82-91%, and falls to

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50% with isolated colonic involvement. There is no reason to withhold nutrition therapy from those with colonic disease, but these observations suggest a lower threshold for switching to an alternative if a prompt response is not seen. EN can also be beneficial with symptom improvement in patients with small bowel narrowing and can be utilized in patients with perianal fistulizing CD (30). It can also be used as an adjunctive therapy to immunomodulators and biologic agents in refractory CD patients.

The duration of exclusive EN utilized for the purpose of inducing remission varies among studies from 6 to 10 weeks (Table 1). As yet, there is no conclusive evidence for the use of EN to maintain remission in children with CD.

Limitations of Enteral Nutrition

There are no contraindications to using EN therapy for inducing remission in CD. Limitations include bloating, nausea, diarrhea and early satiety. Other rare side effects are transient elevation of transaminases (31) and refeeding syndrome. There have been 3 case reports (32,33) of refeeding syndrome in CD patients started on EN. It is common in those with severe malnutrition (those with body weight <70% of ideal body weight) and preexisting electrolyte imbalances. Correcting any underlying electrolyte imbalances and advancing the calories slowly over 3-4 days can prevent refeeding syndrome.

Mode of Administration

Similar remission rates (75% vs 85%) can be obtained using EN administered either as fractionated oral or continuous enteral feedings (34). In patients with CD, who need long-term nutritional support, gastrostomy tubes can be placed and utilized safely (35,36).

MICRONUTRIENTS

Subclinical micronutrient deficiencies are common in pediatric IBD patients. Deficiencies are seen more often in children with CD versus UC. A wide variety of micronutrient deficiencies including those of vitamins A, D, E and K, folate, beta-carotene, magnesium, selenium, zinc, and iron have been described in IBD patients. As with growth failure, there are multiple factors that lead to micronutrient deficiencies. Contributors to deficiencies include inadequate intake, malabsorption and disease activity. Intakes of vitamins and minerals in adults with CD are below the recommendations for virtually all micronutrients, especially folate, calcium and vitamins C and E (37). In this article we will focus specifically on folate, calcium, vitamin D and iron

Table 1. Exclusive Enteral Nutrition in a Newly Diagnosed Crohn's Disease Patient

- 16-year-old female with Crohn's Disease with 15% weight loss over past 3 months
- Ht: 165 cm (50-75th %ile). Wt: 45 kg (10th %ile). BMI: 16.5 (3rd %ile)
- Estimated needs (Schofield equation): 2000 calories/day
- Plan: Use 1.0 calorie/mL standard, intact-protein formula by mouth/via nasogastric tube
- To avoid refeeding syndrome, begin by providing 50% of estimated needs for 1-2 days, advance to 75% of estimated needs for 1-2 days then advance to goal
- Goal is 1920mL of polymeric formula daily. In addition to formula, patient can have water, Pedialyte®, calorie-free flavored water and clear, hard candy
- Evaluate weight, tolerance and symptoms after 2-3 weeks. If patient is responding, exclusive EN should be continued for 6-8 weeks

Folate

Folate deficiency has been seen in adults with IBD (38). In newly diagnosed children with IBD, red blood cell folate concentrations were actually 19.4% lower in controls (39). Certain medications interfere with folate metabolism and patients may have inadequate folate intake or may malabsorb folate. For these reasons, folate supplementation is often routinely recommended. There have been concerns regarding increased risk of colorectal cancer with high folate intakes (40). More recent studies have shown that consuming high levels of folate is not associated with increased risk of colorectal cancer (41,42).

A prenatal multivitamin usually contains twice the amount of folic acid found in a standard multivitamin, 800 mcg versus 400 mcg, respectively. It may be beneficial for IBD patients over 8 years to routinely take a prenatal vitamin to decrease their risk of deficiency.

Vitamin D

Serum concentration of 25(OH) vitamin D is the best indicator of vitamin D status. Vitamin-D deficiency is found in 19-35% of children with IBD (43,44). Serum 25-hydroxy vitamin D concentrations are similar in children with CD and UC and do not correlate with lumbar spine bone mineral density (44). Vitamin D levels are lower in children with dark skin and when levels are drawn in the winter (44). A vitamin D level above 32 ng/mL should be considered the goal for children and adolescents with IBD (44).

Vitamin D levels should be monitored annually and patients with deficiencies should receive vitamin D supplementation.

Supplementation with relatively high doses of vitamin D3 has been studied in healthy children. Providing an average of 2000 IU/day of vitamin D3 appears to be safe (45).

Many pediatric IBD programs routinely monitor bone mineral density in children with IBD, either by dual-energy X-ray absorptiometry (DXA) or quantitative computer tomography. Guidelines for the timing and frequency of monitoring in children do not exist. It is important to recognize that the techniques for interpreting DXA scans are different for children than adults.

Calcium

The Institute of Medicine increased the Recommended Dietary Allowances for calcium in some age groups in 2010. Up to 70% of Americans over the age of 2 do not meet the recommendations for calcium intake (46). Patients with IBD sometimes need to avoid milk products because of lactose intolerance, but at times avoid these products unnecessarily. Avoidance of dairy products makes meeting calcium needs especially difficult. A standard multivitamin/mineral generally contains only 100-200 mg of calcium. It is important to assess calcium intakes of children with IBD and recommend a calcium supplement if patients are not meeting their needs. Calcium absorption is highest in doses $\leq$ 500 mg. For example, if a patient requires 1000 mg of calcium through supplements, it is advantageous to provide this as 500 mg twice daily.

Iron

Iron deficiency is common in patients with IBD. Anemia impacts quality of life with symptoms including fatigue and headaches, but is often not aggressively treated. A study of 429 IBD patients found anemia present in 19% of patients and iron deficiency present in 35%. In about 20% of patients anemia was due to iron deficiency, 12% due to anemia of chronic disease and 68% were a result of both conditions. Folate or vitamin B12 deficiencies accounted for less than 5% of causes of anemia (47).

It is common for patients who are anemic at the time of diagnosis to receive therapy to control intestinal inflammation with the expectation that anemia will resolve once the IBD is under control. Pels et al found 'expectant management' to result in slow hematological recovery, showing a need for more active treatment of iron deficiency (48). Oral iron is sometimes poorly tolerated though studies have found it to be no more difficult for IBD patients to tolerate than other patients (49). Finally, gastrointestinal upset is often dose dependent; consider smaller doses more often over the day to improve tolerance. An alternative to oral iron therapy is intravenous infusion of iron. Iron dextran is safe when appropriately used (50) and is more effective at correcting hemoglobin in IBD patients (51).

CONCLUSIONS

Assessment of growth, nutrition and pubertal development should be an integral part of assessing and monitoring patients with pediatric IBD. Height velocity is the earliest and most sensitive marker of growth faltering. Malnutrition should be identified and managed with supplemental nutrition. Patients and families should be encouraged to utilize exclusive EN as a modality of inducing remission in newly diagnosed patients with CD. Identifying and managing micronutrient deficiencies is very important, in particular, ensuring adequate calcium and vitamin D supplementation will improve bone health in these patients.■

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