Inflammatory bowel disease (IBD) affects over 1 million people in the USA and approximately 2 million in Europe\(^1,2\). While Crohn's disease (CD) and ulcerative colitis (UC) affect mainly adults, approximately one in four of those affected present in childhood or adolescence\(^3\). Although effects on an individual's nutritional status are common in both adults and children with IBD, malnutrition and nutritional deficiencies may be particularly problematic in children who are experiencing these inflammatory disorders during a critical period of growth and development. Malnutrition can occur in IBD secondary to decreased intake and malabsorption, both at the time of diagnosis and during treatment. Other nutritional complications, such as bone mass deficits and growth failure, can occur as a result of the disease process or the treatments used during its management (see Figure 1).

**Growth failure**

Linear growth and BMI are two markers of nutritional status in children. In the pediatric IBD population, growth failure is a frequent occurrence and can manifest as delayed onset of puberty and delayed skeletal maturation\(^4\). Growth impairment in children with IBD ranges between 13 and 58%, and is more commonly seen in CD than in UC\(^5-9\). This disease complication can continue on into adulthood since as many as 20% of children with CD may not achieve their adult height potential\(^10\). The etiology of growth failure is multifactorial. Linear growth impairment may be related to poor energy intake, stool losses and malabsorption, increased nutritional needs, exposure to corticosteroids and the growth-inhibitory effects of the inflammatory process itself (Figure 1). Recent evidence has shown that children with CD have decreased fat-free mass 2 years after diagnosis, even in those patients with clinical improvement, suggesting that weight gain was mainly due to an increase in the fat mass compartment. This finding makes a normal BMI an unreliable marker of normal body composition in patients with CD\(^11\). Body composition throughout the disease course is an area of IBD research that would benefit from further study.

Increasing evidence points to the involvement of cytokines in the inflammatory pathway playing a key role in IBD-associated growth stunting that is independent of undernutrition. IL-6, a cytokine with a central role in multiple immune system reactions, activates transcription protein 3 (STAT3) via the IL-6 receptor subunit (beta)\(^2\)\(^12\). IL-6 is increased in the intestinal lamina propria and serum of newly diagnosed pediatric IBD patients\(^13\). IL-6 has also been shown to correlate with mucosal inflammation in pediatric-onset CD and increased serum levels of IL-6 have been correlated with clinical relapse\(^14\). These pediatric studies allow for evaluation of IL-6 levels in newly diagnosed patients, thereby reflecting absolute cytokine production without the effects of longstanding inflammatory disease or immunomodulatory therapies that may alter cytokine production. Recent studies suggest that an IL-6-mediated decrease in plasma IGF-1 inhibits growth and that Northern European children with CD having a specific IL-6 polymorphism have a greater prevalence of growth retardation compared with other IL-6 genotypes\(^15,16\).

It is well recognized that corticosteroids, still frequently used to induce remission in CD and UC, are associated with a decrease in linear growth. Administration of exogenous corticosteroids creates a state of functional growth hormone deficiency and shifts the cellular differentiation of mesenchymal stem cells away from osteoblasts and toward adipocytes\(^17\). Growth in prepubertal children may be impaired by even relatively small doses of daily prednisone (3-5 mg/m\(^2\))\(^18-20\). Treatment with budesonide is associated with better preserved bone mineral density (BMD) compared with prednisolone\(^21\). At present, there is no solid evidence that occasional, short-term use of corticosteroids to induce remission in CD is detrimental to long-term growth. However, minimization of recurrent or long-term use of corticosteroids is an important management strategy, with studies showing that the addition of thiopurine immunomodulators and anti-TNF-[alpha]\(^2\)\(^2\) agents can decrease the need for corticosteroids in children with CD\(^22-25\). It should be noted, however, that while the pediatric gastroenterology community has attempted to minimize corticosteroid exposure over the last two...
decades, a recent multicenter study of children with newly diagnosed CD demonstrated persistence of growth delay over 2 years despite improvement in disease severity.\textsuperscript{[26]}.

**Bone health**

Osteopenia or low BMD, defined as less than one standard deviation from the mean on dual-energy x-ray absorptiometry (DXA) scans, is reported to affect up to 50% of adult IBD patients.\textsuperscript{[27]} Compared with adults, children have an accelerated rate of bone growth and accumulation of skeletal mass. However, multiple investigators have demonstrated by DXA scanning that the prevalence of low BMD in children with IBD is also high.\textsuperscript{[28-31]} Sylvester \textit{et al.} reported that, compared with a healthy population, children with CD have lower BMD even at the time of diagnosis.\textsuperscript{[32]} In this same cohort of children with CD, there were decreased markers of bone turnover (serum osteocalcin, bone alkaline phosphatase and carboxy-terminal propeptide of type I collagen) when compared with normal ranges for age-matched subjects, suggesting that inflammatory cytokines play a role in the decreased bone turnover and low BMD. Low BMD correlates with elevated serum IL-6, which has been shown to activate osteoclasts.\textsuperscript{[33]} It has been proposed that elevated serum IL-6 and low BMI may be candidate markers for screening DXA, but further studies are needed to validate these markers as predictors of decreased BMD.\textsuperscript{[32]} Other investigators have compared a cohort of children with CD and age-matched controls using peripheral quantitative computed tomography, which provides a 3D estimate of cortical and trabecular BMD. This technique also provides a measure of muscle and fat cross-sectional area. There were substantial deficits in trabecular BMD, cortical bone geometry and muscle observed at the time of diagnosis. Cortical defects persisted, even with improvement in muscle mass. Bone loss was not associated with glucocorticoid use.\textsuperscript{[34]}

As previously mentioned, improvement in BMI in children with CD may result from gains in fat mass, rather than lean body mass. Investigators have suggested that deficits in fat-free mass could hinder the normal acquisition of bone mass in children with CD because of the lack of necessary mechanical strain involved in this process.\textsuperscript{[11]} Furthermore, lack of acquisition of normal bone mass during childhood may increase the risk of fractures later in life.

While low BMD has been associated with increased risk of fractures, a demonstrated risk of fractures associated with IBD remains unclear.\textsuperscript{[35]} In one study, there was no statistically significant difference in the prevalence of fractures in children with IBD compared with their healthy siblings.\textsuperscript{[36]} A population-based study of adults with IBD demonstrated no increased fracture risk when compared with age- and sex-matched controls, whereas another study showed a modest increased risk of hip fracture in patients with IBD (risk ratio 2.85 in CD, 1.49 in UC).\textsuperscript{[37,38]} In a study of 293 adults with CD who underwent DXA scans, subjects with bone density T scores of less than -1 subsequently underwent thoracolumbar spine x-rays.\textsuperscript{[39]} Of these patients, 22% had osteoporotic vertebral fractures and, surprisingly, 88% of those with fractures were asymptomatic. A total of 35% of patients with evidence for vertebral fractures were less than 35 years of age. Therefore, perhaps more patients experience asymptomatic fractures than are fully appreciated.

A technical review from the American Gastroenterological Association recommends obtaining a DXA scan on any adult IBD patient with prolonged corticosteroid exposure (>3 months of corticosteroid exposure or repeated courses), low-trauma fracture, hypogonadism or who is a postmenopausal female or male older than 50 years of age.\textsuperscript{[40]} The International Society for Clinical Densitometry released a position paper in 2008 with recommendations that DXA measurement be part of a comprehensive skeletal health assessment in children and adolescents with potential secondary bone diseases due to chronic inflammatory diseases.\textsuperscript{[41]} At present, there are no specific published recommendations regarding DXA screening and repeated testing in pediatric patients specifically with IBD. Many experts recommend that pediatric patients with CD (but not UC unless there has been significant corticosteroid exposure) undergo a baseline DXA at diagnosis, have a repeat DXA scan annually if BMD is low, maintain adequate calcium and vitamin D levels with supplementation if needed and participate in regular weight-bearing exercise (see Figure 2).
Micronutrient deficiencies

A recent study evaluating 54 adults with CD and 25 healthy controls highlighted the importance of evaluating micronutrient status in individuals with IBD. Even in clinical remission, more than 50% of patients with CD had low plasma concentrations of multiple vitamins and minerals [42].

Iron

Iron deficiency is a common nutrient deficiency found in adult and pediatric IBD and has been reported in 52-73% of adult patients [43,44]. In a prospective epidemiologic study of newly diagnosed pediatric IBD patients, the mean hemoglobin was found to be low for age at 11.8 g/dl (UC) and 11.9 g/dl (CD) [45]. Iron deficiency may occur as a consequence of malabsorption, intestinal bleeding or dietary restrictions. Diagnostic criteria for iron deficiency depend on the individual's present level of inflammation. In patients without biochemical evidence of inflammation, serum ferritin should be greater than 30 µg/l. However, in the presence of inflammation the lower limit of serum ferritin consistent with normal iron stores is 100 µg/l. In patients with a serum ferritin between 30 and 100 µg/l, a combination of iron deficiency and anemia of chronic inflammation (or anemia of chronic disease) is probable [46].

Anemia of chronic inflammation may be influenced by inflammatory cytokines, such as TNF-[alpha] and hepcidin. Hepcidin is a circulating peptide hormone that is induced by inflammation (specifically the cytokine IL-6). When hepcidin increases, it acts on enterocytes to internalize and degrade ferroportin, an enterocyte iron transport protein. In this way, inflammatory cytokines may act to block iron transport and absorption at the intestinal level. Pediatric patients with active CD were shown to have impaired iron absorption and elevated IL-6 levels compared with patients with inactive disease [47].

An international working party recently developed guidelines for the diagnosis and management of iron deficiency and anemia in adults with IBD [46]. While oral iron supplementation has been the mainstay of therapy for iron deficiency anemia in IBD, there are no reliable data to indicate one compound over another and the optimal dose of oral iron for adults has not been established. Typically used oral formulations include ferrous sulfate, gluconate and fumarate, each of which contains different amounts of elemental iron. In children who have mild-to-moderate iron deficiency, the recommended dosage is 3 mg/kg/day [48]. For severe iron deficiency, 4-6 mg/kg/day in two-to-three divided doses is recommended.

The oral method of iron delivery may be limited by poor absorption, particularly during the time of acute intestinal inflammation. Although Gisbert et al. demonstrated that oral ferrous sulfate was well-tolerated and effective in adults with IBD, in other studies up to 20% of patients report intolerance with oral iron preparations [49,50]. Erichsen et al. suggested that administration of oral ferrous fumarate to patients with CD may deteriorate plasma antioxidant levels and increase symptoms of diarrhea, abdominal pain and nausea [51]. Using mouse models, investigators have shown detrimental effects of oral iron on intestinal inflammation and the production of proinflammatory cytokines [52-54].

Intravenous iron sucrose appears promising as a more effective alternative to oral iron and has been cited as the preferred route of iron supplementation in adults with IBD because it is more effective, better tolerated and improves quality of life to a greater extent than oral iron supplements [46]. Absolute indications for intravenous iron in adults with IBD include the following: severe anemia (<10 g/dl), intolerance or inappropriate response to oral iron (lack of hemoglobin increase by at least 2 g/dl or failure to attain normal level within 4 weeks of treatment), severe intestinal disease activity, concomitant therapy with an erythropoietic agent or patient preference [46]. A randomized prospective open-label multicenter study of 46 adult IBD patients with anemia compared weekly intravenous iron sucrose infusions with daily oral iron sulfate [55]. Intravenous iron sucrose was administered at a dose of 7 mg/kg per dose for 6 weeks, while the oral iron group received iron sulfate 100-200 mg/day for 6 weeks. A comparable increase in hemoglobin was observed for both groups, but only iron sucrose led to a rise in serum ferritin. Five patients discontinued oral iron sulfate owing to intractable
gastrointestinal side effects, whereas only one patient had to stop iron sucrose owing to a side effect (nausea, facial rash and peripheral edema during the first infusion). Another multicenter study of adults with iron deficiency who had not previously responded to oral iron demonstrated a good response to iron sucrose. Administration of erythropoietin with iron sucrose resulted in additional benefit in raising hemoglobin levels [56].

Ferric-carboxymaltose (FeCarb) is a novel intravenous iron preparation that can be given in a single dose over 15 min, as opposed to 60-210 min with iron sucrose. FeCarb has been shown to be safe and effective over 12 weeks and to be comparable and 'noninferior' to ferrous sulfate [57]. Treatment-related adverse events occurred in 28.5% of the FeCarb and 22.2% of the ferrous sulfate groups, with discontinuation of study medication owing to adverse events in 1.5 and 7.9%, respectively.

**Vitamin B12**

Vitamin B12 (cobalamin) is a water-soluble vitamin that is essential for proper functioning of the nervous system, and for carbohydrate, protein and fat metabolism. Vitamin B12 binds to a specific receptor and is absorbed through the ileal mucosa. While patients with ileal CD may be at particular risk for vitamin B12 deficiency, the unaffected small bowel may have the capability to adapt and increase its ability to absorb vitamin B12 [58]. In a study of over 200 adults with CD and 40 with UC, using a two-step competitive binding technique to determine serum B12 levels, the prevalence of an abnormal vitamin B12 serum concentration was found to be 18.4 and 5%, respectively [59]. In this study, prior ileal or ileocolonic resection was an independent risk factor for a low B12 level. Duerksen et al. showed that in 56 patients with CD, the length of ileal resection correlated with an abnormal Schilling test result. Patients with less than 20 cm of resected ileum were not at risk for vitamin B12 malabsorption, whereas patients with resections from 20 to 60 cm were at risk [60]. Patients who have undergone restorative proctocolectomy are at increased risk for vitamin B12 deficiency. Of 171 adult patients undergoing this procedure, a quarter had low serum vitamin B12 [61]. In this study, 94% of patients with a low serum vitamin B12 level had a normal Schilling test and were negative for bacterial overgrowth by hydrogen breath test. There are no recent data on the incidence of vitamin B12 deficiency in children with CD.

Until recently, vitamin B12 replacement therapy was only available by intramuscular injection. However, cyanocobalamin is now available in oral tablet form. A meta-analysis showed that, in adults, high doses of oral vitamin B12 (1000 and 2000 µg) were as effective as intramuscular administration in achieving hematological and neurological responses [62]. These studies have not been performed in children nor specifically in patients with CD.

**Folate**

Folate is a water-soluble B vitamin that has been shown to prevent DNA damage and cell injury, which can lead to different types of cancer. Folate deficiency may be associated with tumor growth in IBD [64]. Folate supplementation, regardless of folate level, had been recommended for patients with UC to decrease the risk of dysplasia and colon cancer [65]. However, more recent evidence challenges previous data, with two large studies showing an association between folate supplementation and increased cancer outcomes and overall mortality, as well as an increased colorectal cancer risk [66,67]. Thus, while folate deficiency should be avoided, there may be detrimental effects to oversupplementation when folate levels are normal. Further study in this area is needed to clarify the risk-benefit ratio for supplementation.

Adult patients with IBD have had reportedly normal or low levels of folate when compared with non-IBD controls [68,69]. By contrast, children with newly diagnosed, untreated IBD were found to have higher red blood cell folate and whole-blood folate concentrations than in controls [70]. The explanation for these findings in children is unclear.
Some medications used to treat IBD may affect folate metabolism. Methotrexate is an inhibitor of dihydrofolate reductase, thereby inhibiting the production of folate, which is needed for purine synthesis. There are no published guidelines regarding folate supplementation in patients with CD who are receiving methotrexate. However, looking to the rheumatology literature, a meta-analysis showed that routine folic acid supplementation had no major effect on variables reflecting disease activity in rheumatoid arthritis, but did reduce gastrointestinal-related side effects. Data from one randomized controlled trial demonstrated that supplementation with folic acid or folinic acid might require a small increase in dose of methotrexate to maintain the same efficacy. Sulfasalazine is a competitive inhibitor of folate absorption and some studies have suggested a correlation between folate deficiency and sulfasalazine therapy. Mesalamine preparations are now used much more frequently than sulfasalazine for the treatment of UC and, since these medications do not affect folate absorption, coadministration of this vitamin is not necessary.

**Vitamin D**

Vitamin D is essential for normal absorption of calcium from the intestine and for normal bone mineralization. Vitamin D deficiency had previously been defined as a 25-OH vitamin D (25OHD) level of less than 11 ng/ml. However, recently, there has been increased awareness of the epidemiologic association of vitamin D deficiency with many chronic diseases, and current expert opinion has proposed that minimum acceptable serum levels should be increased to at least 20 ng/ml. Although a lower limit of 20 ng/ml for 25OHD levels is considered indicative of vitamin D sufficiency in children, data in adults suggest a somewhat higher cutoff on the basis of studies that reported impaired calcium absorption and suboptimal parathyroid hormone levels at 25OHD levels of 32 mg/ml. Thus, a lower limit of 32 mg/ml is increasingly becoming more accepted as the lower limit of normal for 25OHD levels in adults. More studies are needed to determine if the lower limit of normal also needs to be raised in children and adolescents. A recent review of the National Health and Nutrition Examination Survey III revealed that changing the definition of vitamin D deficiency from less than 11 to less than 20 ng/ml increased the prevalence of vitamin D deficiency in adolescents from 2 to 14%.

Crohn’s disease and UC have been associated with hypovitaminosis D in adults. In a study of children with CD, vitamin D deficiency (defined as serum 25OHD concentration <38 nmol/l or <15 ng/ml) was found in 16% of patients and was associated with the winter season, African-American background, CD confined to the upper GI tract and the magnitude of lifetime exposure to glucocorticoid therapy. Another study of 130 children with IBD reported the prevalence of vitamin D deficiency (serum 25OHD <15 ng/ml) to be 36.4%. Serum 25OHD concentration was not associated with either lumbar spine BMD Z score or serum parathyroid hormone concentration. Unfortunately, both of these studies lacked a control group. Further data are needed to determine if vitamin D deficiency is specifically increased in children with IBD compared with the normal population and to determine the long-term consequences of this deficiency.

The role of vitamin D status in IBD-related bone disease and fracture risk is unclear. Poor vitamin D status has been shown to correlate with a lower baseline BMD in a population of adults and in newly diagnosed adult patients with IBD. The dietary intake of calcium and vitamin D in premenopausal women with IBD has been shown to be less than the recommended amounts, but was not a predictor of low BMD. While serologic levels of 25OHD were not measured in this study, this evidence suggests that poor intake of vitamin D is probably not responsible for low BMD in IBD patients.

There are no guidelines for the management of hypovitaminosis D in either adults or children with IBD. Cholecalciferol (vitamin D₃) is the natural form of vitamin D, which is synthesized in the skin upon exposure to sunlight. Ergocalciferol (vitamin D₂) is a synthetic product derived from plant sterols/ergosterol. Recent evidence has shown that cholecalciferol is more potent than ergocalciferol and thus should be preferentially used for supplementation. Several studies have examined BMD changes with treatment using supplemental vitamin D, calcium, fluoride and bisphosphonates. In a prospective double-blind placebo-controlled study designed to assess the effects of daily fluoride supplementation (150 mg) in adult patients with IBD plus calcium (1 g) and vitamin D (800 IU) resulted in a significantly increased lumbar spine BMD after 1
The addition of fluoride did not provide further benefit over the placebo group. Another study was designed to assess the efficacy of 2 years of calcium and vitamin D supplementation on the BMD of adult patients with CD, either with or without cyclical oral etidronate therapy. BMD steadily increased in both groups, but without additional effect of the bisphosphonate. Conversely, in a randomized controlled trial of calcium and vitamin D administered alone or in combination with intravenous pamidronate, the addition of pamidronate did significantly increase the BMD after 12 months. Administration of 1000 mg daily of elemental calcium and 50,000 IU monthly of vitamin D₂ for 6 months to children with IBD resulted in no significant improvement in BMD compared with controls with IBD and no intervention. While it may be prudent to supplement patients who are deficient in vitamin D and calcium, the effect of supplemental calcium and vitamin D, as well as bisphosphonates, on BMD and the relation to fracture risk needs further investigation.

**Other fat-soluble vitamins**

Vitamin K is essential for normal bone metabolism and deficiency may contribute to abnormal bone resorption and osteoporosis. Free uncarboxylated osteocalcin has been shown to be a much more sensitive measurement of vitamin K status than prothrombin time, and a high level of circulating uncarboxylated osteocalcin is a sensitive marker for vitamin K deficiency. Schoon et al. showed that adult patients with CD had lower serum vitamin K levels by high-pressure liquid chromatography measurement and that uncarboxylated osteocalcin level was inversely correlated with low BMD. In another study, adult CD patients had a lower oral dietary intake of vitamin K compared with controls and the intake was inversely correlated with elevated markers of bone resorption (uncarboxylated [Glu]-osteocalcin and urine crosslinked N-telopeptides of type 1 collagen).

Investigators evaluated the prevalence of hypovitaminosis A and E in children with IBD compared with age-matched control subjects. Hypovitaminosis A was present in 14.4% and hypovitaminosis E was present in 6.2% of the IBD patients. There was a direct correlation between vitamin A and vitamin E levels and these findings were similar among patients with CD and UC. A striking relationship was noted between disease activity and low levels of vitamins A or E. Further studies are necessary to determine if this represents a true deficiency in this population.

**Zinc**

Zinc, which is absorbed along the length of the small intestine, is a component of over 200 enzymes and is necessary for immune function, DNA and RNA synthesis and gene transcription. Zinc homeostasis is maintained by changes in zinc absorption and endogenous fecal zinc excretion. Zinc deficiency can lead to clinical features of acrodermatitis, alopecia, anorexia, diarrhea and poor growth. Zinc has also been implicated in the regulation of intestinal permeability in animal models of colitis. Griffin et al. reported that fasting serum zinc levels were lower in adolescent CD patients than in controls, with no difference in albumin levels. Adolescents with mild, stable CD had decreased zinc absorption and did not compensate by altering zinc excretion. The clinical effect that zinc deficiency has on CD patients is unknown and requires further study.

**Nutritional interventions to ameliorate intestinal inflammation**

**Exclusive enteral nutrition**

Enteral nutrition is the preferred method of providing nutritional support when patients' needs cannot be met by regular diet and supplementation. The enteral route is preferred over parenteral nutrition owing to decreased cost and potential side effects compared with parenteral nutrition. Enteral nutrition may also be used as a primary therapy for patients with active CD and its role as 'anutritional therapy' has recently been extensively reviewed. Two meta-analyses in children with CD found that exclusive enteral nutrition was as effective as corticosteroids in inducing clinical remission. However, another meta-analysis of six trials indicated a pooled odds ratio of 0.33 in favor of corticosteroid therapy for induction of remission. There were inadequate data from the published reports to perform subgroup analysis by age, disease location or disease year.
duration. No difference in efficacy has been noted between elemental, semi-elemental and polymeric formulas for induction of remission in CD\textsuperscript{[104]}. The fat content of the formula had no effect on efficacy in the treatment of active CD\textsuperscript{[104,105]}.

**Partial enteral nutrition**

Efficacy of partial enteral nutrition for maintenance of remission in adults with CD has not been proven. A Cochrane analysis attempted to review partial enteral nutrition for maintenance of remission in CD, but of 24 studies reviewed, only two met the inclusion criteria and were evaluated\textsuperscript{[106]}. In the first study by Takagi et al., patients in remission with a Crohn’s Disease Activity Index of less than 150 were randomized to consume half of their daily calories as an elemental formula and the remainder of their calories from a regular diet\textsuperscript{[107]}. After a mean follow-up of 11.9 months, nine out of 26 patients in the half elemental diet relapsed compared with 16 out of 25 patients in the regular diet group (odds ratio: 0.3; 95% CI: 0.09-0.94). In the second study by Verma et al., 33 adults with corticosteroid-dependent CD who were in clinical remission were randomized to receive either an elemental formula or a polymeric formula in addition to an unrestricted diet\textsuperscript{[108]}. Treatment success was defined as remaining in remission after complete withdrawal of corticosteroids. After 12 months, eight out of 19 patients on the elemental formula and six out of 14 patients on a polymeric diet achieved treatment success (odds ratio: 0.97; 95% CI: 0.24-3.92). In a trial of children with CD, partial enteral nutrition (consuming 50% of caloric needs from formula and 50% from an unrestricted diet) did not suppress inflammation over a 6-week course, but total enteral nutrition (100% of calories from formula) did result in reduction of diarrhea, increase in hemoglobin and albumin and a decrease in platelets and erythrocyte sedimentation rate\textsuperscript{[109]}.

**Potential advantages of exclusive enteral nutrition therapy**

Despite the inconclusive data in adults for the use of enteral nutrition as therapy to induce or maintain remission in CD, the positive results in children should be highlighted since there is a very narrow window of opportunity to improve growth and pubertal development in children with CD. A difference between adult and pediatric studies of enteral nutrition is the degree of patient adherence to the specialized diets, with greater than 90% adherence often reported in pediatric studies. This difference may account for some of the differences in the efficacy of this treatment method in children versus adults\textsuperscript{[110-112]}. With a demonstrated equivalent efficacy to corticosteroids at inducing remission, exclusive enteral feeding may be a better option for pediatric patients, given the known detrimental effects of corticosteroids on growth and bone development. Particularly in pediatrics, parents may opt for attempting enteral therapy over a more 'top-down approach' owing to concerns about potential serious medication side effects, such as lymphoma.

Exclusive enteral therapy can be taken orally, however, it is often difficult for a child to drink these formulas on a daily basis for weeks at a time. Thus, administration of feeds via a nasogastric tube should be considered, although there are also inherent difficulties with adherence to this type of regimen. Successful initiation and maintenance of exclusive enteral nutrition in pediatric patients is enhanced when the providers involved, such as the physician, dietician and nurse, become experienced in this modality and work together as a team. Additionally, use of small-caliber nasogastric tubes, topical anesthetic gel prior to placement, instructional teaching videos and access to home healthcare services may assist in adherence to prescribed tube feedings. Unfortunately, significant studies in this arena with UC are lacking.

The mechanism of enteral nutrition for decreasing inflammation in CD is unknown, although it is proposed that perhaps enteral nutrition leads to an alteration in cytokines or intestinal bacterial composition\textsuperscript{[113]}. Yamamoto et al. reported that adult patients with CD in remission who received overnight enteral feedings in addition to a low-fat diet during the day had significantly lower mucosal tissue IL-1[beta]\textsuperscript{2}, IL-6 and TNF-[alpha]\textsuperscript{±} levels at the end of 12 months compared with a group of patients without nutritional therapy or dietary restriction\textsuperscript{[114]}. Endoscopic scores at 12 months and clinical relapse rates during the trial were higher in the nonenteral nutrition group. The same group had previously shown a significant decrease in proinflammatory cytokines (IL-1[beta]\textsuperscript{2}, IL-1ra, IL-6, IL-8 and TNF-[alpha]\textsuperscript{±}) within terminal ileum and colon biopsies from patients following 4
weeks on an exclusive elemental diet [115]. In a very small cohort of children with CD treated with exclusive enteral nutrition with a polymeric formula for a mean of 56 days, there was significantly reduced fecal bacterial diversity when compared with stool from healthy children, which correlated with disease activity [116]. Further studies are needed to understand the anti-inflammatory effects of exclusive enteral nutrition.

**Omega-3 fatty acids**

Omega-3 (n-3) fatty acids are incorporated into the walls of inflammatory cells and decrease the concentration of arachidonic acid (n-6), which is the main substrate of COX and 5-lipoxygenase enzymes, known producers of proinflammatory cytokines. Omega-3 fatty acids can be found in some vegetables, but the major source is fish oil. Omega-3 fatty acids have been shown to have an anti-inflammatory effect on animal models of IBD [117-120]. In a small trial of 19 patients with CD and UC, IBD-related joint pain was improved with administration of seal oil that is rich in n-3 fatty acids, when compared with patients who received soy oil, rich in n-6 fatty acids [121]. Adult patients with active CD who received supplementation with omega-3 fatty acids were not found to have a change in peripheral cytokine profiles. However, oral supplementation with omega-6 fatty acid powder caused an increase in proinflammatory cytokines (IL-1[beta], IFN-γ and MCP-1) and a decrease in anti-inflammatory cytokines (IL-4 and IL-5) [122]. A pediatric study of 38 patients randomized into two groups: 5-ASA 50 mg/kg/day plus omega-3 fatty acids or 5-ASA 50 mg/kg/day plus olive oil placebo capsule showed that significantly fewer patients in the omega-3 fatty acid group relapsed at 1 year [123].

Data from a double-blind placebo-controlled study suggesting that adults with CD who received 2.7 g of fish oil could be maintained in remission led to much clinical focus on the use of fish oil supplements [124]. Subsequently, two large multicenter randomized controlled trials have now been performed at 98 centers in Canada, USA, Israel and Europe (Epanova Program in Crohn’s Study [EPIC]-1 and EPIC-2) using a similar product but with very different results [125]. Neither trial showed a significant difference in relapse rate between adults with quiescent CD randomized to receive either 4 g of fish oil daily or placebo. Largely based on the results of these two studies, a Cochrane review has concluded that the existing data do not support treatment with omega-3 fatty acids for maintaining remission in CD [126]. No evidence has supported the use of omega-3 fatty acids for maintenance of remission in UC [127].

**Other potential dietary supplements & approaches**

Polyphenols, such as green tea extract and curcumin, are phytochemicals that are found in food substances produced from plants that may potentially have immunomodulatory effects. Green tea extract (also known as epigallocatechin or EGCG) has been shown to have anti-inflammatory effects on animal models of colitis [128,129]. It has been demonstrated that EGCG acts through modulation and inhibition of NF-κB [130]. However, no human studies have yet been performed with this agent. Curcumin is the major chemical constituent found in turmeric (the principle spice used in curry). Curcumin may also exert anti-inflammatory effects through NF-κB [130]. A number of human studies in children and adults with IBD have shown promising effects. One open-label pilot study showed improvement in symptoms of patients with CD and UC, but this needs further study [133].

At this time, there is no significant evidence in the medical literature to support any particular diet, such as low-fat, low-carbohydrate or gluten-free, in the management of CD or UC. Although the avoidance of insoluble fiber may alleviate abdominal pain or obstructive symptoms in patients with fibrostenotic CD, it should be kept in mind that fiber should be part of a balanced diet. There may be an increased risk for lactose intolerance in patients with CD but this should be assessed on an individual basis [134]. Keeping a food diary may be helpful to associate a particular type of food with symptoms of diarrhea, abdominal pain or flatulence. In general, it is recommended that children and adults with IBD consume a well-balanced diet. Arbitrary dietary recommendations to a patient, such as removing all fiber or dairy products from the diet, without a clear individualized rationale should be avoided as this could adversely impact a patient’s nutritional status and quality of life.
Evaluation of nutritional status in IBD

Monitoring the nutritional status of children and adults with IBD is an essential component of medical care. In children, screening should include measurements of body weight and height with comparisons for age and calculation of the BMI. BMI should also be calculated for adults. It should be kept in mind that BMI does not reflect alterations in body composition (i.e., decreased skeletal muscle). Pre-illness growth points in children are helpful to assess the chronicity of the growth failure and to assess for stunting. Nutritional assessment should include a dietary history and a screen for symptoms, such as oral ulcers or dysphagia, which might be contributing to decreased intake. Regular assessment of nutritional laboratory test results, including 25OHD, calcium, iron, ferritin, total iron-binding capacity, percent iron saturation, zinc, folate, vitamin B12 and fat-soluble vitamins, should be considered (see Box 1).

Minimization of corticosteroid use is critical in pediatrics. This can be achieved with the use of exclusive enteral nutrition, as well as the earlier use of corticosteroid-sparing therapies, such as thiopurine immunomodulators and biologic therapies. Finally, achieving remission of disease, as well as the prevention of growth failure and delayed puberty, is critical in managing pediatric IBD.

As previously mentioned, the American Gastroenterological Association and the American College of Gastroenterology have published guidelines for the selective screening of adults with IBD \[40,135\]. Unfortunately, there are currently no recommendations for performing screening DXA scans in pediatric patients with CD, although some experts propose obtaining a study at baseline and then annually if BMD is low.

Expert commentary

The focus of clinical management of IBD, especially CD, in children has turned toward nutritional interventions and corticosteroid-sparing medication regimens in the attempt to treat intestinal inflammation and reverse growth delay and malnutrition. With a demonstrated equivalent efficacy to corticosteroids at inducing remission in CD, exclusive enteral feeding should be strongly considered a part of medical management for pediatric CD patients.

Five-year view

As has been too often the case in the past, studies in children with IBD continue to significantly lag behind those focused on adults, resulting in a paucity of pediatric-generated medical evidence that can be used to create algorithms - whether for screening purposes or therapeutic management. Given that early and sustained improvements in nutritional health may provide life-long advantages to children with IBD, in addition to potentially decreasing long-term healthcare costs, the medical and funding communities should recognize the importance of well-developed nutritional studies in pediatric IBD.

For children in particular, growth and nutritional consequences may be forefront in the presentation and clinical progression of IBD. Despite the recent introduction of new therapies, such as TNF-[alpha] inhibitors, the nutritional status of many children is impaired secondary to disease complications or medication adverse effects. Some of these complications, such as bone demineralization, can occur in a patient who may be asymptomatic.

With the increased attention that is being given to prevent disease complications, minimize medication exposure and adverse events and improve health maintenance for patients with chronic illness, we anticipate that nutritional issues in IBD will receive significant attention over the next 5 years.

Critical areas for research include evaluating the effects of diet and dietary supplements on the inflammatory pathway and the composition of the intestinal microbiota. Of particular interest is the hypothesis that enteral nutrition leads to an alteration in cytokines or intestinal bacterial composition, which may potentially affect the natural history of disease progression. Further investigation is needed to know whether single or combination
components of the diet are involved in downregulation or modulation of the inflammatory pathway. Additionally, we anticipate that our knowledge regarding the mechanisms by which inflammation affects absorption of macro- and micro-nutrients will probably evolve, as will our understanding of how current treatments affect nutrient absorption. This should enable us to develop nutrient supplements that are packaged in formulations with enhanced absorption and efficacy.

Better methods of assessing nutritional status are needed in order for us to be able to identify earlier either nutritional complications or those who are at increased risk for developing nutritional deficiencies. Investigators have already provided us with data suggesting that children with a specific genetic profile may be at increased risk for growth failure. As the genetic information boom in IBD continues, we expect to be able to better classify both patient disease phenotype and response to therapeutic interventions. More research is needed on bone mineralization to develop more sensitive tools and biomarkers to assess BMD and to establish evidence-based algorithms for interventions.

Box 1. Suggested nutritional assessment and monitoring of the pediatric patient with inflammatory bowel disease.

**History**

*ã¢â‘œ Detailed history

*ã¢â‘œ Recorded dietary history with dietetic evaluation (3-5 days)

**Examination**

*ã¢â‘œ Weight, height, BMI (percentiles)

*ã¢â‘œ Tanner staging

*ã¢â‘œ Growth velocity

*ã¢â‘œ Triceps skinfold thickness

*ã¢â‘œ Mid-arm circumference

**Laboratory analysis**

*ã¢â‘œ Complete blood count

*ã¢â‘œ Erythrocyte sedimentation rate

*ã¢â‘œ C-reactive protein

*ã¢â‘œ 25-OH vitamin D

*ã¢â‘œ Serum albumin

*ã¢â‘œ Serum folate, vitamin B12

*ã¢â‘œ Serum vitamin E, vitamin A, retinol binding protein
*â€ Serum iron, ferritin, total iron binding capacity

*â€ Serum calcium, magnesium, phosphorus

*â€ Serum zinc

*â€ Prothrombin time/international normalized ratio

*â€ Stool guaiac

Key issues

*â€ Growth failure and pubertal delay are common complications of pediatric inflammatory bowel disease (IBD).

*â€ Iron deficiency is common in IBD and newer methods of intravenous delivery may provide a better option for therapeutic intervention in some patients.

*â€ Recent changes in the defined normal ranges for vitamin D insufficiency will probably lead to an increased prevalence of vitamin D deficiency in IBD.

*â€ Low bone mineral density affects children with Crohn'â€s disease (CD) at diagnosis.

*â€ Screening and monitoring guidelines of bone mineral density are needed in children with IBD.

*â€ Exclusive enteral nutrition therapy may be as effective as corticosteroids for the induction of remission for children with CD.

*â€ Existing data do not support the use of fish oil in the maintenance of remission in CD.

**CAPTION(S):**

Figure 1. Multifactorial etiology for growth failure in inflammatory bowel disease.

**References**

Papers of special note have been highlighted as:*â€ of interest *â€*â€ of considerable interest


*â¢* Interesting study demonstrating that low bone mineral density is present at diagnosis in children with inflammatory bowel disease and thus may be impacted by disease-related inflammation.


*â¢ Well-designed systematic population-based study examining the risk of fracture in patients with Crohn'âs disease.


*â¢*⢠Meta-analysis showing possible increased colorectal cancer risk with folic acid supplementation.


Prospective, randomized, placebo-controlled trial demonstrating the lack of efficacy of fish oil to maintain remission in adults with Crohn's disease.


Source Citation