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Review Article

Understanding Crohn's Disease

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Abstract

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is a chronic inflammatory disorder that can affect any part of the gastrointestinal (GI) tract and typically causes symptoms such as abdominal pain, diarrhea, and eating disorders. CD can manifest at any age, with up to a quarter of cases diagnosed in childhood. In recent years, the incidence of CD has been increasing in many countries. For example, recent data from Australia show a tenfold increase in the incidence of CD in the first decade of the 21st century. Other reports also demonstrate an increase in the incidence of CD in various countries and indicate that the disease often manifests at a younger age. The most accepted hypothesis for the pathogenesis of CD is that uncontrolled inflammation in the GI tract is a consequence of a dysregulated immune response to environmental triggers in individuals with a genetic predisposition [1]. Environmental factors include diet and intestinal microflora. Some nutritional factors, such as breastfeeding in infancy, have a protective effect, while others (such as a high-fat diet) are associated with increased risk.

Kew Words: crohn's disease; gastrointestinal tract; pathogenesis

Introduction

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is a chronic inflammatory disorder that can affect any part of the gastrointestinal (GI) tract and typically causes symptoms such as abdominal pain, diarrhea, and eating disorders [1]. CD can manifest at any age, with up to a quarter of cases diagnosed in childhood. In recent years, the incidence of CD has been increasing in many countries. For example, recent data from Australia show a tenfold increase in the incidence of CD in the first decade of the 21st century [2]. Other reports also demonstrate an increase in the incidence of CD in various countries and indicate that the disease often manifests at a younger age [3]. The most accepted hypothesis for the pathogenesis of CD is that uncontrolled inflammation in the GI tract is a consequence of a dysregulated immune response to environmental triggers in individuals with a genetic predisposition [1]. Environmental factors include diet and intestinal microflora. Some nutritional factors, such as breastfeeding in infancy, have a protective effect, while others (such as a high-fat diet) are associated with increased risk. The development of Crohn's disease in children and adolescents is typically associated with weight loss and can lead to impaired linear growth and delayed puberty. Therefore, treatment of Crohn's disease in this age group requires close attention to nutrition, frequent weight and height measurements [1,4]. Exclusive enteral nutrition allows for remission and optimization of nutrition after diagnosis. Enteral nutrition involves the administration of a liquid dietary formula over a period of time as the only method to promote remission [4]. Enteral nutrition has virtually no side effects and ensures a high rate of mucosal healing. However, like all other currently available treatments for Crohn's disease, enteral nutrition does not lead to a cure.

Crohn's disease is characterized by acute and chronic inflammatory changes in any part of the gastrointestinal tract. Crohn's disease can be distinguished from ulcerative colitis by the location of the disease, the extent of intestinal wall involvement, the focal nature of the lesions, and the presence of noncaseating granulomas [5]. Crohn's disease in childhood is usually extensive, often involving the entire intestine; in more than half of children, the lesion is located proximal to the terminal ileum [1,6]. The initial signs of Crohn's disease may also include perianal, perioral, or extraintestinal manifestations. Many children diagnosed with Crohn's disease experience classic symptoms: diarrhea, abdominal pain, and weight loss. However, others may experience less obvious symptoms, such as lethargy, isolated joint symptoms, or oral abnormalities. Many studies show that almost all children with Crohn's disease have a history of either weight loss or plateauing in weight gain: in some studies, these features are observed in over 85% of children [1,7]. This likely reflects early satiety or abdominal discomfort after meals. Circulating proinflammatory cytokines [e.g., tumor necrosis factor-α] also contribute to anorexia [8]. Due to weight changes, some children may also experience disturbances in linear growth. These changes in normal growth patterns may exist many months before diagnosis, sometimes preceding the onset of any specific gastrointestinal symptoms [9]. Measuring weight, height, and body mass to assess growth is essential in making a diagnosis. Also important is reviewing the growth history and interpreting linear growth in the context of familial growth patterns. Once a diagnosis is made, close attention to growth patterns and linear growth velocity is required to ensure adequate growth is achieved and subsequently maintained.

In addition to changes in weight and height, malnutrition and uncontrolled inflammation also lead to delayed pubertal development. [8] In past generations, the cumulative impact of these growth disturbances typically resulted in reduced final adult height. Therefore, assessment of pubertal status in adolescents and calculation of bone age are important aspects of the ongoing treatment of children with celiac disease, beginning at diagnosis. Micronutrient deficiencies are also observed in children with celiac disease. While iron and vitamin

D deficiencies are most common, vitamin B12, zinc, and selenium levels may also be low. [10] Although the nutritional consequences of celiac disease may be most pronounced at diagnosis (when inflammation is uncontrolled before treatment), these adverse effects can also occur at any subsequent stage. Given that celiac disease can have adverse nutritional consequences in children, it is not surprising that close attention to nutrition is a critical aspect of patient management. Enteral nutrition plays a significant and vital role in reversing many of the negative nutritional consequences of celiac disease in children and achieving remission [4]. Although the primary focus of enteral nutrition is on inducing remission and initial disease control, other benefits may also follow. Furthermore, continued maintenance enteral nutrition after initial enteral feeding may contribute to the maintenance of remission [11,12].

Several studies published over the past 15 years have demonstrated the efficacy of enteral nutrition in children with active Crohn's disease. Generally, enteral nutrition induces remission in approximately 85% of patients. A meta-analysis of pediatric studies found that enteral nutrition produced an equivalent response to corticosteroids in children with active Crohn's disease. [13] One Australian study involving 34 children demonstrated clinical remission in 84% and biochemical remission in 76%, with 58% experiencing an early endoscopic response. [14] A portion of this group also underwent small bowel imaging (magnetic resonance enterography) before and after enteral nutrition: three of these 14 children demonstrated complete transmural healing.

A recent Spanish study evaluated the treatment outcomes of 40 children receiving enteral nutrition. [15] In an intention-to-treat study, remission occurred in 80% of children after 6–8 weeks of enteral feeding. Of the 34 children who completed the full course of enteral feeding, 32 (92.1%) achieved remission. A retrospective study conducted in the Netherlands assessed the outcomes of enteral feeding in 77 children [16]. Of the children who completed the course of enteral feeding, 71% achieved complete remission, and 26% achieved partial remission. The researchers noted that important factors determining outcome in this series included disease localization in the ileum or ileocolic pouch and low nutritional status at baseline.

Mechanisms and Clinical Consequences of Malnutrition in Children with Crohn's Disease

The inflammatory process in Crohn's disease can extend throughout the small intestine, impairing nutrient absorption and processing [17]. However, a number of other factors contribute to the development of malnutrition in congenital bowel diseases [18]. One of the main factors determining malnutrition in congenital bowel diseases is decreased food intake. The active phase of the disease often leads to decreased appetite due to the appearance of abdominal symptoms (abdominal pain, diarrhea, vomiting, and nausea) [19]. Moreover, the inflammation itself (e.g., via TNF-α and IL-6) can cause decreased appetite through catabolic effects and hypothalamic weight regulation [20]. Furthermore, some of the most commonly prescribed medications can cause nausea, vomiting, and/or anorexia [21]. Finally, some patients and/or their parents believe that certain foods may worsen or even trigger their symptoms. Therefore, they tend to modify their diet, eliminating the perceived harmful triggers, in order to control their disease. According to a recent European study, the most frequently contaminated foods are cereals (29%), milk (28%), vegetables (18%), and fruits (11%) [22]. This behavior may have detrimental consequences on nutritional status [42]. The intestinal epithelium can be easily damaged by intestinal inflammation [23]. Impaired epithelial transport and loss of mucosal integrity are closely associated with malabsorption. Indeed, impaired epithelial function leads to changes in ion transport, which subsequently causes fluid and electrolyte loss [19]. Furthermore, intestinal mucosal inflammation leads to chronic blood and protein leakage [19]. Surgery is also associated with impaired absorption of macro- and micronutrients [19]. Bowel resection may cause accelerated intestinal transit and diarrhea, thereby reducing the contact time of luminal contents with the mucosal surface. Finally, there are conflicting data regarding resting energy expenditure. Resting energy expenditure reflects the energy requirements of an individual at rest [25]. Elevated REE is thought to contribute to the increased caloric requirements in patients with active congenital bowel diseases. However, the latter issue remains controversial, as some studies have documented a positive correlation between REE and disease activity [26], while others have not found it [27]. Impaired linear growth may be the first symptom in up to 46% of children and adolescents with Crohn's disease [28,29]. The prevalence of malnutrition and growth failure has decreased significantly over the past few decades among patients with congenital bowel diseases [28,30,32]. However, regardless of treatment modality, impaired linear growth and underweight still affect a significant proportion of children with Crohn's disease [32]. Underweight at diagnosis is associated with worse disease outcomes [33]. Children with Crohn's disease have altered body composition compared to healthy controls [34,35]. Thangarajah et al [53] conducted a systematic review to determine the alterations in non-bone tissue compartments in children with congenital bowel diseases. The results of the review showed that children with Crohn's disease have lower lean mass compared to healthy subjects [34]. In a recent prospective study, Ward et al. [36] enrolled 73 children with newly diagnosed Crohn's disease to evaluate the impact of bowel disease on musculoskeletal health. The authors reported that total lean body mass (z-score −2.5, SD 1.1, $p < 0.01$) was low for age and sex. Furthermore, jump mechanography demonstrated low muscle strength [36]. Interestingly, children and adolescents with congenital bowel diseases exhibit chronic lean body mass deficits despite weight restoration and asymptomatic disease [37,38]. Persistent lean body mass deficits negatively impact metabolic homeostasis, physical activity, and bone mass accumulation along with bone architecture, and are known to increase the risk of infections [39,40]. Moreover, muscle mass deficiency is also known to negatively impact some specific outcomes associated with bowel disease. In a retrospective study of 68 patients with congenital bowel diseases, Holt et al. [41] reported that lower skeletal muscle areas at the start of TNF-α administration were associated with a shorter time to loss of response. Despite advances in medical therapy, a significant number of patients require surgical intervention during the course of their disease [42]. Unfortunately, malnutrition is a common clinical feature of children and adolescents referred for surgery. The long duration of the disease, along with persistently active mucosal inflammation and the side effects of multiple lines of drugs, contribute to malnutrition in these patients. Malnutrition may have a detrimental effect on the postoperative course. In a retrospective study of 161 patients with Crohn's disease undergoing elective ileocecal resection, poor nutritional status was independently associated with an increased risk of postoperative septic complications [43]. Recently, Ryan et al. examined the clinical consequences of decreased lean body mass [44]. Despite the enormous heterogeneity in the assessment of sarcopenia, in a systematic review, the authors demonstrated that lean body mass deficiency can predict the need for surgery in patients with congenital bowel disease and is also associated with a higher rate of major postoperative complications [44].

Macronutrients

Macronutrients include proteins, carbohydrates, and lipids. Children and adolescents with celiac disease appear to have similar nutritional needs to their healthy peers. However, data from several studies examining protein requirements in children and adolescents with celiac disease suggest that protein requirements may be increased during active disease phases. Protein breakdown has been shown to be reduced after surgical bowel resection in children with active celiac disease. Furthermore, one small study of 15 children with celiac disease who underwent metabolic assessment immediately before and after the first infliximab infusion found that TNF-α therapy reduced proteolysis and improved protein balance in patients receiving parenteral nutrition. These data suggest that protein intake may be increased by 25% during active phases of the disease to reduce protein loss. To date, no study has demonstrated different carbohydrate and fat requirements in children with celiac disease.

Micronutrients

Iron

Iron deficiency and iron deficiency anemia are common clinical manifestations of congenital bowel diseases in children. According to the World Health Organization definition of anemia, its prevalence at diagnosis reaches 78% in the pediatric bowel disease population. Moreover, anemia affects up to 42% of children with congenital bowel diseases one year after diagnosis, and is reported to be more common in the pediatric population than in adults, both at diagnosis and during follow-up. Anemia in children has a complex and multifactorial pathogenesis, but the most common etiology is a combination of iron deficiency anemia and anemia of chronic disease . In particular, iron deficiency anemia has been noted as a leading cause of anemia in children with intestinal diseases. Some reports have shown that despite achieving clinical remission, a significant number of children with IBD develop anemia during a one-year follow-up. These findings suggest that anemia is an important comorbidity for children with intestinal diseases and that it may not resolve without specific therapeutic interventions. When dealing with a child with congenital intestinal diseases and anemia, the first therapeutic approach should include providing a balanced and varied diet with iron-rich foods, as well as improving the absorption of dietary iron (i.e., combining non-heme iron sources with ascorbic acid-rich foods or avoiding combinations with foods that may impair iron absorption). The next step in case of persistent iron deficiency anemia is the administration of iron supplements. The choice between oral and parenteral iron administration is not always straightforward. Oral iron preparations have the relative advantage of eliminating the need for infusions and, therefore, a scheduled hospital visit, as well as greater availability and lower cost compared to parenteral preparations. However, there are concerns regarding their well-documented gastrointestinal side effects and the possibility of adding a symptomatic burden to those of congenital bowel diseases. Indeed, intolerance is a common finding, leading to discontinuation in up to 50% of patients. Moreover, some authors suggest that oral iron preparations may negatively affect intestinal inflammation. More recently, a new oral iron preparation, iron maltol, consisting of a single iron ion (Fe^{3+}) chelated with high affinity to three maltol molecules, has been shown to be safe, effective, and well tolerated in patients with iron deficiency anemia and congenital bowel disease who have reported poor tolerability of other oral iron preparations. Oral preparations have also been associated with changes in gut microbiota. However, in a recent prospective, controlled, open-label study, Rampton et al demonstrated that oral iron supplementation did not increase disease activity in adolescents and adults with congenital bowel disease over a 6-week period. Therefore, oral iron supplementation may be used in children and adolescents with milder anemia and inactive disease. In addition to oral iron compounds, various intravenous formulations are available as therapeutic options for iron deficiency anemia in patients with congenital bowel diseases. While historically high molecular weight intravenous iron compounds were burdened with significant levels of side effects and hence were underutilized due to safety concerns, the introduction of low molecular weight formulations has resulted in a significant reduction in side effects. Various studies conducted in children and adolescents with congenital bowel diseases have reported high efficacy of intravenous iron formulations with relatively low rates of side effects. Mamula et al. reported their retrospective experience with intravenous iron dextran administration in 70 children with congenital bowel diseases. The authors observed a significant increase in Hgb levels, by an average of 2.9 g/dL. Hypersensitivity reactions were rare, with only 9% of patients experiencing infusion reactions, none of which were severe [86]. Furthermore, Powers et al reported their retrospective experience with intravenous ferric carboxymaltose in children with congenital bowel disease who had poorly responded to oral iron supplements. Among the 72 patients included in the study, a median increase in Hgb was recorded and 3.2 g/dL, and only seven children (16%) reported minor adverse reactions to the infusion. Intravenous iron preparations are effective and well tolerated. Their use should be considered in children with bowel disease with moderate to severe forms of anemia and in those patients who do not tolerate or do not respond to oral iron compounds.

Vitamin B12 and Folate

Vitamin B12 status can be assessed by measuring serum B12 levels or, more accurately, by measuring methylmalonic acid and homocysteine levels. Ileal disease or resection may mediate vitamin B12 malabsorption, placing patients with Crohn's disease at risk of deficiency. Other proposed mechanisms of vitamin B12 deficiency include small intestinal bacterial overgrowth, decreased intake, increased physiological demands, and protein-losing enteropathy. A systematic review including 3,732 patients from 42 studies concluded that Crohn's disease without ileal resection (or with resection less than 20 cm) does not increase the risk of B12 deficiency. A recent systematic review analyzed eight studies that examined vitamin B12 status in children with congenital bowel diseases. The authors noted an overall low incidence of B12 deficiency in the study population. One study reported that ileal or ileocolic resection increases the risk of abnormal serum vitamin B12 concentrations. According to the latest ESPGHAN working group guidelines, vitamin B12 screening should be performed in all patients with a history of ileal or ileocolic resection and in patients with suspected vitamin B12 malabsorption. If stores are depleted, patients should receive intramuscular injections.

Folate (vitamin B9) levels can be measured in serum or, more precisely, in red blood cells (RBCs), as well as indirectly by measuring serum homocysteine levels. Studies in adult patients with celiac disease have shown the incidence of folate deficiency to be between 20% and 30%. Data in children are limited. However, folate deficiency appears to be rare in children with celiac disease. According to ESPGHAN guidelines, children should receive additional folic acid supplements (1 mg daily or 5 mg weekly) when treated with methotrexate (MTX), as it acts by inhibiting folate uptake into cells.

Dietary Fiber

Dietary fiber is a complex group of indigestible cell wall components [45]. Fiber is able to withstand the acidic environment of the stomach and is not metabolized by human intestinal cells. In the colon, dietary fiber serves as a substrate for fermentation by the intestinal microbiota. This process produces byproducts such as short-chain fatty acids [46]. The major short-chain fatty acids (acetate, butyrate, and propionate) have been shown to exert several beneficial effects on the host, including providing energy to colonic epithelial cells and reducing inflammation in IBD [47]. Restricted dietary

fiber intake is associated with increased bacterial consumption of intestinal mucus, potentially contributing to inflammation [48]. Dietary fiber intake in children with congenital bowel diseases has been shown to be suboptimal compared with healthy controls [49] or to meet recommended intake levels, regardless of whether the patient has active or inactive disease [50]. According to the latest recommendations of the IBD Nutrition Group, there is currently no evidence to support restricting dietary fiber intake in patients without intestinal strictures or obstruction [51].

Nutritional Therapy

Nutrition status is one of the most important factors determining both clinical and surgical outcomes in patients with celiac disease [52]. From this perspective, identifying, preventing, and correcting nutritional deficiencies can be considered as important a therapeutic intervention as selecting appropriate pharmacological strategies. Indeed, malnutrition and impaired linear growth may indicate active disease, and their restoration should be considered a treatment goal [53].

The impact of disease location on outcomes in published studies has varied.

One study conducted in the UK showed a marked difference between colonic disease (response rate of 50%) and ileal or ileocolic disease (remission rates of 92% to 83%, respectively) [54]. In contrast, a subsequent study conducted in Scotland involving 114 children found that children with isolated terminal ileal disease had a lower remission rate, but site did not influence outcome

[55].

Until now, little attention has been paid to the impact of factors such as disease location or severity on individual patient outcomes. One study showed that an early reduction in faecal calprotectin levels was associated with a response to enteral nutrition (EN) at one month [56]. Further evaluation of faecal markers or other specific indicators may allow the development of predictive algorithms that will lead to more individualized use of enteral nutrition in children. Enteral nutrition may play a role in the perioperative period in children with Crohn's disease. Preoperative nutritional support may promote weight gain and improve nutritional parameters (eg, serum albumin), leading to improved surgical outcomes. Extensive data from clinical trials conducted in Japan also demonstrate the benefits of enhanced nutritional support in the postoperative period. These studies showed that the use of enteral nutritional support to provide up to 50% of caloric requirements in adults with surgically induced remission delayed relapse in these patients [57,58]. Few significant side effects are observed with EN [59]. Some children may experience nausea or loose stools at the beginning of treatment, while others may experience constipation. A transient increase in liver transaminases was noted in one case series [60], but was not observed in a second series [26]. Refeeding syndrome after EN has also been reported [62,63]. Three children reported in these reports had moderate/severe malnutrition, placing them at increased risk of developing refeeding syndrome. Therefore, when initiating enteral feeding in children with significant malnutrition, a standardized approach should be used to identify those at increased risk and initiate enteral feeding slowly and cautiously, while closely monitoring electrolytes. Recent data highlight the importance of mucosal healing as a key indicator of treatment efficacy in children with Crohn's disease. Several studies have shown a discrepancy between clinical improvement in patients with active disease and the absence of endoscopic changes, especially after treatment with corticosteroids [64,65]. Although improvement in patient well-being is a useful and compelling marker of disease control, the role of mucosal healing as a predictor of the long-term burden of Crohn's disease has become increasingly evident [64]. A significant challenge in documenting mucosal response to therapy is the need for repeat endoscopy, often in patients who have experienced significant clinical improvement in their symptoms after treatment. Several studies in recent years have documented important endoscopic, histological, and biological data before and after the introduction of enteral nutrition in children with Crohn's disease, providing invaluable evidence to further support the use of this therapy as a primary means of achieving disease remission. An English-language case-control study found a 79% clinical remission rate in children with Crohn's disease after an eight-week course of enteral nutrition. Furthermore, improvements in median endoscopic and histological scores were observed after treatment in both the ileum and colon. Of particular significance were the reduction in interferon-γ mRNA levels in the ileum and the increase in transforming growth factor-β1 mRNA levels, while in the colon, interleukin-8 mRNA decreased after treatment. Several studies have shown early mucosal healing with enteral feeding 8–10 weeks after initiation of therapy. Furthermore, EEN was consistently superior to corticosteroids in achieving mucosal healing in cases of active Crohn's disease when the two different treatment modalities were directly compared. Perhaps most encouragingly, early mucosal healing as a result of EEN leads to improved outcomes at one year, particularly in terms of reduced rates of endoscopic recurrence, hospitalizations, and the need for anti-TNF agents. However, as a consequence, a weak initial mucosal response after a course of EEP can be considered as an indicator of a more severe course of the disease, which may require earlier use of other treatment methods.

In addition to the anti-inflammatory effect, enteral nutrition also results in significant improvements in nutritional parameters. Early changes after initiation of enteral nutrition include a rapid increase in circulating insulin-like growth factor (IGF-1) levels with a rapid return to control values. Weight increases, with weight gain generally consistent with efficacy. Some reports have also noted early growth recovery throughout the enteral nutrition period. An earlier report showed improvements in weight, lean body mass, and skinfold thickness after 3 and 6 weeks of enteral nutrition. Similarly, a subsequent study conducted in Toronto, Canada, showed improvements in weight and lean body mass after enteral nutrition. Interestingly, this report also noted improved linear growth compared to the height gain observed in ten children receiving corticosteroids over the same time period.

Vitamin D deficiency is a common problem among children with IBD. Some co-authors found that the majority of their cohort of Australian children with Crohn's disease had vitamin D deficiency (<51 nmol/L) or insufficiency (51-75 nmol/L). This report also showed that children with vitamin D deficiency were exposed to higher levels of corticosteroids than children with normal vitamin D levels. However, as expected, the mean serum vitamin D concentration was higher in the group receiving EEN after diagnosis compared with the group receiving corticosteroids.

An eight-week course of enteral nutrition in children with newly diagnosed IBD has been shown to normalize bone markers, indicating greater new bone formation and less bone resorption. Furthermore, a six-week course of enteral nutrition (followed by a two-week course of partial EN) resulted in greater improvement in dual-energy X-ray absorption z-scores compared to a group of Canadian children receiving corticosteroids. Enteral nutrition has also been shown to have a more direct beneficial effect on bone mineral density. A German study clearly demonstrated that bone turnover and muscle mass improved within 12 weeks of starting EEN in children with IBD. The peripheral quantitative computed tomography technique used in this study demonstrated improvement in trabecular density z-scores, normalization of pre-existing high cortical density zscores, and an increase in muscle cross-sectional area. Although enteral nutrition has been well established as a standard and safe therapy for inducing remission in active Crohn's disease, there is marked variability in the use of enteral nutrition, as well as differences in individual protocols. A transatlantic study published in 2003 found that enteral nutrition was routinely used by 62% of European pediatric

gastroenterologists, compared with only 5% in the United States. Subsequent studies found that 12% of North American and 38% of Australian pediatric gastroenterologists routinely used EEN. A recent Swedish report found that 96% of Swedish pediatric units used enteral nutrition as a treatment option for active Crohn's disease, while 68% of respondents routinely used enteral nutrition as initial therapy for newly diagnosed Crohn's disease . The reasons for such marked differences in the routine use of enteral nutrition are not fully understood. Two studies have shed light on the factors influencing the choice of enteral nutrition as the preferred treatment option for celiac disease in children. Routine use of enteral nutrition by Australian pediatric gastroenterologists appears to be closely related to their awareness of this treatment modality during training. Those who did not use EN regularly reported issues related to adherence, cost, and resource requirements. When asked similar questions, North American respondents expressed similar concerns. Again, routine recommendation of enteral nutrition was associated with practitioners' previous experience with enteral nutrition. Furthermore, enteral feeding protocols vary in many respects across units and countries. Differences include the duration of enteral feeding, the type or brand of formula used, and the inclusion of other oral products (e.g., other liquids or boiled lozenges) during enteral feeding. Several studies have found no differences between outcomes using elemental or polymeric enteral formulas. [39] and suggest that polymeric formulas have better palatability and tolerability. However, the impact of any other differences on comparative outcomes has not yet been assessed.

A typical regimen involves the use of a polymer formula administered exclusively for eight weeks [. The formula is introduced gradually over the first three days of therapy until the required daily amount is achieved (specific information on calculating caloric requirements and additional practical aspects of enteral enteral nutrition (EEN) is provided in reference [39]). Although most children can take the required volumes orally, some will require placement of a nasogastric tube to facilitate compliance. During the enteral feeding period, children are encouraged to drink more water orally and chew small amounts of sugar-free gum. After the eight-week enteral feeding period is completed, one small meal every three days is typically resumed, with the daily volume of formula being reduced with each additional meal.

Vitamin D

Vitamin D plays a key role not only in bone and tooth mineralization but also in other metabolic functions, as well as a protective role in immune-mediated diseases and allergies. Vitamin D status is assessed by analyzing its metabolite, 25-hydroxyvitamin D (25-OH-D), in plasma or serum, which reflects the amount of vitamin D converted in the skin by sunlight and from dietary sources. Low vitamin D levels can have detrimental consequences for a child's future health, so achieving optimal vitamin D status is a critical public health goal. Vitamin D levels are classified as severely deficient at <37 nmol/L, insufficient at <50 nmol/L, and optimal at 50–75 nmol/L. Sunlight exposure is generally the most important source of vitamin D3, while dietary and supplemental vitamin D is of fundamental importance for populations living in sunlight-poor latitudes. Obesity is a risk factor for vitamin D deficiency, as most of the body's vitamin D is stored in adipose tissue.

Current national recommendations recommend a daily intake of 7.5 µg of vitamin D. Foods high in vitamin D include fatty fish and eggs. Vitamin D is produced endogenously in the skin by the reduction of 7-dehydrocholesterol in response to ultraviolet light. Human exposure to sunlight is limited over a lifetime, and some foods are fortified with vitamin D (e.g., milk, some juices, bread, and cereals). Children with chronic illnesses are therefore at risk of vitamin D deficiency. The Institute of Medicine recommends a vitamin D intake of 600 IU/day for individuals aged 1 to 70 years, plus 700–1300 mg/day of calcium (depending on age) to promote healthy skeletal growth. Vitamin and mineral deficiencies have been described in patients with congenital bowel diseases and have been attributed to intestinal mucosal inflammation and reduced oral intake. The greatest body of evidence on vitamin D status and bone health has focused on older adults, while few studies have focused on infants, children, and adolescents. There has been inconsistent evidence for an association between circulating 25(OH)D levels and bone mineral content in infants. Compelling evidence has been found that consumption of vitamin D-fortified foods consistently increases serum 25(OH)D levels in both young and older adults. In short, studies have provided fairly strong evidence for an association between circulating 25(OH)D concentrations and some measures of bone health (established rickets, parathyroid hormone). Vitamin D (3) (>700 IU/day) with calcium supplementation has been reported to have a small beneficial effect on bone health and to reduce the risk of fractures and falls, although this benefit may be limited to certain subgroups. A recent retrospective study in the United States examined the prevalence of vitamin and zinc deficiencies in 61 children (aged 1–18 years) with newly diagnosed congenital bowel diseases from 2006 to 2010 (80% with ileal inflammation) compared with a control group of 61 age- and sex-matched individuals. Although none of the patients with congenital bowel disease had folate or vitamin B12 deficiency, 62% of them had vitamin D deficiency (compared to 75% in the control group), 16% had vitamin A deficiency, 5% had vitamin E deficiency (compared to 8% in the control group), and 40% had zinc deficiency (compared to 19% in the control group). The authors concluded that vitamin B12 and folate deficiencies are rare in children with newly diagnosed congenital bowel disease in the United States, so there is no reason to support their routine monitoring. On the other hand, vitamin A and zinc deficiencies were statistically more common in patients with congenital bowel disease than in the control group, so their levels should be assessed at the time of diagnosis to initiate enteral feeding. Vitamin D deficiency was common in the study population, so routine screening for this deficiency and supplementation are warranted.

In summary, regarding vitamin D, it should be noted that the literature does not yet provide convincing evidence of a link between circulating 25(OH)D concentrations and bone health indicators. Only partial benefits of vitamin D(3) (>700 IU/day) and calcium supplementation have been observed in studies and in reducing the risk of fractures and falls, and only in certain subgroups . Nevertheless, vitamin D supplementation in children is generally recommended when its levels are found to be depleted, given its effects not only on bone metabolism but also in terms of immunomodulation.

Bone Health And Crohn's Disease In Children

Although current treatment strategies for celiac disease, including anti-TNF-α therapy, promote growth, linear growth deficits persist even with optimized therapy. Children with celiac disease continue to suffer from short stature and poor growth, and several studies have shown that children with IBD may not achieve optimal bone mass. Children with celiac disease have multiple risk factors for impaired bone growth. The skeleton is a highly dynamic tissue regulated by local, systemic, and environmental factors that alter osteoblast (bone formation) and/or osteoclast (bone reabsorption) activity. Congenital bowel diseases affect bone regulation at all levels: environmental—through disruption of the intestinal barrier and/or altered gut microbial composition; Systemically, through the circulation of intestinal immune cells and cytokines throughout the body; and locally, by causing inflammation of extraintestinal organs (e.g., bone marrow). Bone formation and reabsorption play an important role in bone health and growth. In children with celiac disease, both of these processes are impaired, so bone growth is ultimately suboptimal [49]. Factors that contribute to this impairment include inflammation, delayed growth and puberty, muscle mass deficiency, and glucocorticoid use. A recent study by Irvine et al. examined

the impact of an experimental congenital intestinal disease on bone health. Interleukin-10-deficient animals infected with Helicobacter hepaticus (H. hepaticus) were used as a mouse model of colitis, and the molecular and histological properties of their bones and intestines were examined to identify the immunopathological consequences of colitis in mice. Six weeks after infection, male mice (but not females) exhibited significant trabecular bone loss in the distal femur and vertebrae. The authors concluded that the severity of H. hepaticus-induced colitis and associated bone loss are sex-dependent, possibly due to gender differences in H. hepaticus colonization of the mouse gastrointestinal tract and subsequent immunopathological responses.

Another study by Schmidt et al. involving 144 patients with congenital bowel diseases (including 83 with ulcerative colitis and 45 with Crohn's disease) concluded that children with congenital bowel diseases have the potential to improve their condition by early adulthood. In children with ulcerative colitis and Crohn's disease, mean lumbar spine Z-scores were significantly lower both at baseline and after 2 years. Additional analysis of different age groups at baseline revealed the lowest values in patients aged 17 to 19 years, in both boys and girls; however, these patients improved significantly at follow-up.

Puberty Problems In Children With Crohn's Disease

Many nutritional, inflammatory, immunological, and endocrine factors affecting growth in patients with congenital bowel diseases also have a significant impact on the onset and progression of puberty. The onset of bowel disease before puberty is often associated with delayed growth and weight gain, as well as significantly slower growth and lower final height than parental goals. This is more pronounced in children with Crohn's disease than in cases of ulcerative colitis. Other correlations include delayed puberty and menarche, prolonged pubertal phase, and secondary amenorrhea. Potential causes of late puberty in patients with congenital bowel diseases in the prepubertal and pubertal stages include : (1) malnutrition: this correlates primarily with delayed menarche and puberty. A link has been hypothesized between late puberty and decreased fat mass, which is normally rich in aromatase, which induces the conversion of androgens to estrogens and subsequent active production of female hormones; and (2) the interaction of proinflammatory cytokines with the endocrine system: patients with bowel diseases appear to have impaired endocrine function, including due to the direct effects of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β on hormonal feedback mechanisms.

A recent retrospective study by Mason et al. aimed to clarify the influence of celiac disease and ulcerative colitis on the pubertal growth spurt. Growth at puberty was assessed by calculating the peak growth velocity index, growth velocity index at diagnosis, and age-adjusted growth velocity index in patients with Crohn's disease (30 boys, 11 girls) and ulcerative colitis (14 boys and 12 girls). Systemic markers of disease activity were also recorded. In cases of Crohn's disease, changes in growth parameters at puberty were observed compared with the normal population, especially in boys. In the overall group, age (AGVI) showed a correlation with ESR ($r = 0.4$; $P = 0.005$) and an inverse correlation with BMI ($r = 0.4$; $P = 0.001$).

Managing Growth and Puberty Problems in Children with Crohn's Disease

Healthy children grow at a rate of 4–6 cm per year until puberty, after which their growth rate doubles within a year. A trend toward decreasing height and weight percentiles on growth charts raises suspicion of growth deficiency compared to the child's age- and sex-specific growth targets. Early diagnosis of bowel disease is crucial, but early signs of congenital bowel disease are not always evident. Bowel disease varies and can easily go undetected, meaning that growth deficiency and associated late puberty often precede the intestinal manifestations of the disease. It is crucial to monitor patients' growth, using their initial height (measured before the onset of congenital bowel disease) as a baseline, and to regularly reassess patients as the disease progresses to fully assess its impact on their growth. Monitoring patient growth is also important to assess their response to therapy over time. Careful periodic examinations should always include an assessment of patients' pubertal development, which should correlate with their body height. If any discrepancies are detected, action can be taken immediately: radiographic examination is used to establish the skeletal age of patients and thus identify their residual growth potential. On average, it takes approximately 12 months to see any response to treatment in terms of linear growth or pubertal development, so intervals between follow-up assessments should never be less than six months.

To prevent and treat growth deficiency in children with congenital bowel diseases, it is necessary to first determine the most appropriate nutritional, pharmacological, and surgical treatment for the underlying disease: control of chronic inflammation and ensuring adequate nutrition are two synergistically interacting aspects of the same approach. Ensuring long-term control of active inflammation and adequate nutritional intake are fundamental to promoting normal puberty. Controlled clinical trials have documented a significant correlation between enteral nutrition, reduced mucosal cytokine production, and endoscopic healing. Enteral nutrition has the potential to induce remission and achieve nutritional restoration. Trials have also established that the effect of enteral nutrition alone on the inflammatory pattern depends on factors such as disease location in the small intestine or recent onset, while age appears to have less of an impact. Immunomodulators, in addition to corticosteroids, used in the treatment of congenital bowel diseases in children include thiopurines (azathioprine and 6-mercaptopurine), which are used to maintain remission and have no proven adverse effects on growth, and biologic agents (infliximab and adalimumab), which potentially improve growth velocity by inducing and maintaining remission of the disease. Artificial stimulation of puberty with estrogens and testosterone carries the risk of early calcification of cartilage tissue, leading to growth deficiency.

Diagnostic Information

Endoscopy is the gold standard for diagnosing and monitoring inflammatory bowel disease in children. However, it is less desirable in children than in adults due to its invasiveness, the need for sedation and bowel preparation, and additional procedural complications. Furthermore, although radiation exposure should be limited in children during the monitoring of a chronic condition such as Crohn's disease, suspected acute sickle cell anemia remains an indication for abdominopelvic computed tomography. Intestinal ultrasound (US) is an imaging modality that has recently been shown to have comparable accuracy to magnetic resonance enterography in assessing transmural inflammation throughout the intestine. The advantages of US include good tolerability, the absence of radiation exposure, and lower cost. Furthermore, US has demonstrated high sensitivity in detecting small bowel inflammation, particularly active ileal inflammation. The Pediatric Committee of the International Group on Intestinal Ultrasound proposed the first monitoring algorithm in children to more accurately assess and characterize such complications in intestinal diseases. Following endoscopy and transabdominal intervention, magnetic resonance enterography should be considered to determine the extent and activity of the disease, reserving small bowel capsule endoscopy for selected cases where clinical suspicion remains high. Recently, Ungaro et al. identified panels of blood biomarkers, including C-C motif chemokine ligand 3 and C-C motif chemokine ligand 4 proteins, that appear to predict the development of complications. These biomarkers may aid in risk stratification at the time of diagnosis of celiac disease in children. Further research is needed to more accurately evaluate the ability of these biomarkers to predict congenital intestinal pathologies.

Crohn's Disease Treatment

- Aminosalicylic acid medications
- Immunosuppressants
- Symptomatic treatment
- Surgical treatment

The goal of therapy is to achieve clinical remission, improve the patient's quality of life, and minimize complications and indications for surgical treatment.

In the standard treatment of Crohn's disease, first-line medications are aminosalicylic acid medications in various dosage forms (tablets, rectal suppositories, microclysters). They contain two main components: the active ingredient, mesalazine (provides an anti-inflammatory effect), and chemical compounds that ensure the release of the active ingredient in the affected areas of the intestine. The average duration of treatment is 8-16 weeks, followed by a transition to a maintenance dose (usually 50 percent of the initial dose) for at least one year. Second-line medications include prednisolone and glucocorticoids with low bioavailability. In minor cases, they are administered orally, while in more complex cases, they are administered intravenously or intramuscularly. Treatment duration is 2-3 weeks. These medications are available in capsule form, each containing budesonide microgranules encased in an acid-resistant shell. The capsule dissolves in the stomach and reaches the terminal portions of the small intestine unchanged. Third-line (or reserve) medications include non-selective (e.g., methotrexate) or selective (cyclosporine A) immunosuppressants. They are used for refractory and steroid-dependent forms of the disease. Symptomatic therapy: pain relief, enterosorption, digestive enzymes, correction of metabolic and dysbiotic disorders. Surgical treatment: indicated in the presence of complications (perforations, abscesses, stenosis, fistulas) and the ineffectiveness of conservative therapy.

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