

Role of vitamin D in Inflammatory bowel disease in children

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Abstract:

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder with an increasing incidence and prevalence among children worldwide. Micronutrient deficiencies are common in pediatric IBD, particularly deficiencies of iron, calcium, and vitamin D, due to reduced dietary intake, malabsorption, gastrointestinal losses, disease activity, and treatment-related factors. Vitamin D has important functions beyond bone health, including regulation of intestinal epithelial integrity, immune responses, and gut microbiota. In children with IBD, low serum 25-hydroxyvitamin D concentrations have been associated with impaired gut barrier function, increased inflammatory activity, and less favorable disease and treatment outcomes. Vitamin D sufficiency may contribute to reduced disease activity and may enhance response to anti-tumor necrosis factor therapy. Several factors can predispose children with IBD to hypovitaminosis D, including corticosteroid exposure, malnutrition, reduced sunlight exposure, disease activity, gastrointestinal involvement, seasonal variation, and altered body composition. Management includes identification of children at risk, dietary optimization, adequate sunlight exposure, and vitamin D supplementation when needed. However, considerable variation remains regarding definitions of deficiency, supplementation regimens, and optimal monitoring strategies. This review discusses the role of vitamin D in pediatric inflammatory bowel disease, with emphasis on its effects on gut health, disease activity, treatment outcomes, risk factors for deficiency, correction strategies, supplementation, and monitoring.

Keywords: Vitamin D; Inflammatory bowel disease; Children; Crohn's disease; Ulcerative colitis; Hypovitaminosis D; Supplementation.

Introduction:

Inflammatory bowel disease (IBD) is a chronic inflammatory condition, encompassing Crohn's Disease (CD), and Ulcerative Colitis (UC). Individuals may also receive a diagnosis of IBD unclassified (IBD-U), if they do not initially clearly fit in one of the two diagnostic categories. Globally, both the incidence and prevalence of pediatric IBD continues to rise (1).

The pathophysiology of IBD remains multifactorial, with no single underlying etiology. Modernization and shift of environments to having increased industrialization and more 'westernized' diets is thought to be an important contributor to the ongoing rise in IBD by potentially altering the intestinal microbiome, particularly in the developing countries that previously had very low rates of IBD (2).

Micronutrient deficiencies are commonly observed in children with IBD, predominantly attributable to malabsorption and/or decreased intake. Although some micronutrient deficiencies are dependent on disease location, medications or surgery, overall the most common reported deficiencies are of iron, vitamin D and calcium with further deficits in essential fatty acids, and water/fat soluble vitamins. These deficiencies are

particularly problematic when IBD is diagnosed during childhood as it is a critical period of growth and development (3).

Clinical Benefits

Gut Health

Children with IBD commonly have increased permeability of the intestinal barrier, which has been associated with inflammation and dysbiosis due to increased exposure of the immune system to the intestinal microbiota. Vitamin D benefits gut health by targeting three major components of the gastrointestinal tract: the intestinal epithelial barrier, gut immunity, and gut microbiota. Vitamin D signaling is imperative in maintaining the integrity of the epithelial barrier by protecting against infectious and inflammatory insults in a number of ways: by increasing its resistance to irritants in the intestinal mucosa, suppressing epithelial cell apoptosis, enhancing repair, and increasing the expression of specific tight junction proteins (4).

In addition, vitamin D promotes a rich and diverse gut microbiome, with high dose supplementation shown to lead to increased bacterial richness in the gastrointestinal tract. Consequently, sub-optimal concentrations of 25(OH)D may negatively affect the gut barrier and immune function and lead to increased dysbiosis and potential translocation of gut bacteria, thus affecting IBD onset and progression. Much of the research relating to gut integrity is *in vitro*, but low concentrations of 25(OH)D have been shown to inversely correlate with surrogate markers of gut inflammation such as fecal calprotectin, as well as tumor necrosis factor (TNF) and other pro-inflammatory cytokines (5, 6).

Disease Outcomes

Vitamin D sufficiency has been linked to a number of clinical benefits for children with IBD, in particular the role vitamin D plays in moderating disease activity. While a small number of studies have observed lower disease activity among children with sufficient, or higher, vitamin D levels, the few studies available on vitamin D supplementation that reported on disease activity also suggest a beneficial effect on these specific clinical indices. A double blind, placebo controlled randomized controlled trial (RCT) to treat hypovitaminosis D showed that supplementation significantly reduced disease activity indices, relapse frequency, disease severity score, and a number of inflammatory markers: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin, TNF- α , and the interleukins (IL) IL-17, 10, 12, and 23 (7).

Treatment Outcomes

In addition to the benefits previously highlighted, vitamin D may play a beneficial role in the response of children with IBD to anti-TNF medications, which are an effective treatment for CD and UC. Anti-TNF primary nonresponse, or loss of response, poses a significant problem but vitamin D sufficiency may ameliorate this. Studies have reported that children and adults with IBD on anti-TNF therapy with vitamin D insufficiency had significantly higher levels of early treatment termination due to loss of response (8).

Another report indicated decreased odds of being in remission following induction in subjects with insufficiency compared to those that were vitamin D sufficient. In addition, when those treated with an anti-TNF therapy were given vitamin D supplementation remission rates were higher for those with greater 25(OH)D concentrations. It is hypothesized that the way in which vitamin D affects disease severity is via the TNF pathway, with genome-wide analysis revealing that 25(OH)D concentrations influence a large number of genes. These data suggest anti-TNF medications and vitamin D may be synergistic in decreasing TNF levels, thereby suggesting an adjunctive role of vitamin D in IBD treatment regimens (9).

Vitamin D Concentrations in the Setting of IBD in Children

Vitamin D deficiency among the general pediatric population has been defined in a number of ways in the literature. In guidelines from Central Europe, Australasia, and the Americas moderate and severe deficiency is defined as serum 25(OH)D concentrations less than 50 nmol/L and 30 nmol/L respectively, and insufficiency as between 51 and 75 nmol/L. Other work in Europe defines the cutoff for deficiency as 50 nmol/L. When studies specific to children with IBD are examined there is considerable variation in terminology, units of measurement,

and concentration cutoffs, even within geographic areas. Inferences on the proportion of children with IBD and hypovitaminosis D is, therefore, complex with prevalence up to 81% of individuals being below the recommended range by definition (10).

A number of systematic reviews that included children with IBD, and additional pediatric studies, report that overall the serum concentrations of 25(OH)D in children with IBD are lower than controls. However, this was not evident in two individual studies. Evidence to determine whether there is a difference in concentrations between the IBD clinical sub-types is lacking, with one study reporting children with UC having significantly lower vitamin D than children with CD some reporting no difference, and many not comparing the groups (11).

Risk Factors for Hypovitaminosis D

A number of disease-related risk factors for hypovitaminosis D have been identified for children with IBD, with additional factors that are also relevant to the general population. The magnitude of exposure to corticosteroids has been shown to negatively affect 25(OH)D concentrations, as well as factors relating to a reduced intake and absorption of vitamin D such as reduced appetite, malnutrition, and gastrointestinal (GI) losses. Disease activity, whether classified by increased inflammatory markers or clinical indices, may be associated with sub-optimal vitamin D (7).

Furthermore, a number of studies have reported increased risk of low 25(OH)D concentrations in children with upper gastrointestinal CD. Poor growth as represented by a low body mass index (BMI) score was shown to be a risk factor in one study, with the opposite found in other research with a high BMI being a risk factor likely due to a greater proportion of the body's vitamin D being stored in adipose tissue (12).

Risk factors common to children with IBD as well as the general population are well reported. Low exposure to UV light is a significant cause of hypovitaminosis D that could be consequent to reduced outdoor activities as a consequence of IBD symptomatology. Other factors such as darker skin pigmentation, age, and use of sunscreen may reduce the effective exposure to UV light of the vitamin D precursor. Seasonal variations in 25(OH)D concentrations during winter months are well reported as there is insufficient UV light exposure to allow cutaneous synthesis (13).

In addition, the latitude at which people reside exerts an influence as the skin synthesizes lower levels of vitamin D from sun exposure at latitudes 37° north or south of the equator. Further evidence of this link is seen in the emerging global gradient of IBD with higher incidence rates in more northern or southern countries, as well as within-country gradients (14).

While work has been carried out confirming that genetic polymorphisms and alterations are related to vitamin D status, the underlying genetic determinants remain poorly understood. Additional research is needed in order to clarify these genetic determinants, and to examine the mechanisms of action responsible for the association with vitamin D status that may identify susceptible individuals who may benefit from supplementation (15).

The main prevention strategy for vitamin D insufficiency within the population of children with IBD should be to identify those at risk according to the criteria outlined above, and to correct and optimize their 25(OH)D concentrations, as below.

Correction of Hypovitaminosis D

In order to correct and optimize 25(OH)D concentrations for children with IBD a number of strategies may be applied relating to environmental factors, dietary intake, and clinical treatment. Vitamin D may be obtained from two sources: UV mediated synthesis and oral intake. UV exposure accounts for 80% to 90% of vitamin D in the human body, but if there is inadequate exposure to sunlight then support from diet and/or supplements is fundamental to achieve optimal concentrations. Education on the importance of including vitamin D rich foods in the diet is beneficial, with recommendations from the European Food Safety Authority being for a daily intake of 1000 IU/day for infants 0 to 12 months, 2000 IU/day for children ages 1 to 10 years, and 4000 IU/day for children ages 11 to 17 years of vitamin D (16).

While few foods contain substantial amounts, sources with high levels include: oily fish, eggs, beef liver, as well as fortified products such as milk, juices, breads, and cereals. However, with only 20% of daily vitamin D needs being met through diet, and children with IBD experiencing risk factors that may contribute to further reduced intake or absorption, oral supplementation may provide a method for restoring optimal concentrations (17).

Supplementation

Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are the most frequently used forms of oral supplement, with evidence recommending preferential use of cholecalciferol due to superior efficacy. A number of regimens for supplementation of vitamin D2/D3 may be used, such as daily, weekly, or oneoff high dose vitamin D3 (Stoss therapy). Varying levels of efficacy were reported in a systematic review. When studies looking specifically at restoration of hypovitaminosis D were examined it was seen that while many regimens are effective at increasing serum concentrations, few report on longitudinal benefit or comment on the proportion who sustain sufficient levels. No definitive dosing recommendations for daily, weekly, or Stoss therapy can be extrapolated from these studies, or identified in reviews (18, 19).

Attention should be paid to the research presented comparing different supplements and doses as are available in individual centers, and to evaluate which are effective for restoration and maintenance. Patient preference should also be considered, with Stoss therapy reported as the patient's preferred method, with this one-off dose reducing associated problems of ongoing treatment adherence and increased medication burden (20).

Vitamin D supplementation may result in hypervitaminosis D, leading on to adverse effects related to high concentrations of calcium, phosphate, and parathyroid hormone, and consequent complications such as renal calculi. However, these adverse effects were not seen in the identified literature among children with IBD using a range of supplementation regimens (21).

Testing Frequency

Screening for hypovitaminosis D should be carried out on children with CD or UC as both are at risk of deficiency. While concentrations are lower at the time of diagnosis, many children remain deficient following treatment and follow up, and should be monitored accordingly. Few papers provide recommendations relating to testing frequency, but screening is recommended at diagnosis and then at least yearly, with particular attention to seasonality, as well as during active and asymptomatic periods (22).

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