Vitamin D in pediatric gastrointestinal disease

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Purpose of review
The purpose of this review is to examine the prevalence of vitamin D deficiency in pediatric gastrointestinal disease, specifically celiac disease and inflammatory bowel disease (IBD); to discuss the role of vitamin D and its deficiency in gastrointestinal disease pathophysiology; and to present current literature regarding diagnosis and treatment of vitamin D deficiency in these pediatric gastrointestinal diseases.

Recent findings
Vitamin D deficiency is common in children with gastrointestinal symptoms and disease processes. In celiac disease, vitamin D status should be routinely assessed at the time of diagnosis and during subsequent follow up if deficient. There is growing evidence to suggest an inverse association between vitamin D and IBD activity; however, the therapeutic role of vitamin D in IBD patients requires further investigation.

Summary
Suboptimal vitamin D status commonly occurs in children with gastrointestinal disease. It is advisable to check serum 25-hydroxy vitamin D levels in children with newly diagnosed celiac disease and IBD. In celiac disease, vitamin D status should be assessed during subsequent follow up if deficient. In IBD, 25-hydroxy vitamin D levels should be checked at least yearly. Therapy should be provided to maintain a level of greater than 30 ng/ml but less than 100 ng/ml; however, the ideal vitamin D dosing regimen to treat vitamin D deficiency and to maintain this optimum level remains unknown. The role of vitamin D as a therapeutic agent in IBD is still under investigation.

Keywords
celiac disease, Crohn's disease, pediatric inflammatory bowel disease, ulcerative colitis, vitamin D

Vit.D_3 : 1 ng= 40 UI

INTRODUCTION

Nutritional deficiencies are common in gastrointestinal disease. There has been substantial interest regarding the importance of vitamin D in celiac disease and inflammatory bowel disease (IBD) [1–3]. The major idiopathic IBDs are Crohn's disease and ulcerative colitis – commonly labeled IBD. They are chronic, relapsing, and remitting inflammatory diseases mainly affecting the gastrointestinal tract. The pathogenesis of IBD is not fully understood, but it is believed to be related to a dysregulated immune response to intestinal microbiota in a genetically susceptible host. Celiac disease is an autoimmune enteropathy triggered by gluten ingestion in genetically susceptible individuals and resulting from a complex interaction between dietary, immunologic, and environmental factors [4]. Both these conditions may lead to malabsorption of vitamin D.

It is well known that vitamin D plays a central role in bone health, but there is growing evidence to suggest that it also plays an important function in immune regulation [5]. Low bone mineral density (BMD) has been described in children with IBD and celiac disease [6–8]. In this review, the role of vitamin D in the pathogenesis and the consequences of vitamin D deficiency in these gastrointestinal disorders will be discussed. The current literature regarding treatment of vitamin D deficiency and maintenance of optimal levels in these patient populations will be reviewed.

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KEY POINTS

- Vitamin D deficiency is common in children with celiac disease and IBD.
- Vitamin D deficiency is defined as a 25-OH D level below 20 ng/ml (50 nmol/l) and vitamin D insufficiency as a 25-OH D level from 20 to 30 ng/ml (50–75 nmol/l).
- Vitamin D status should be checked in celiac disease at initial diagnosis and corrected if found deficient.
- Vitamin D status should be checked in IBD at initial diagnosis, corrected if found deficient and then checked at least yearly, preferably in the spring. Cholecalciferol, vitamin D_3, is the preferred form of supplementation; however, the ideal dose to treat vitamin D deficiency and the supplementation regimen to maintain optimal 25-OH D levels (>30 ng/ml but less than 100 ng/ml) in pediatric IBD patients is unknown.

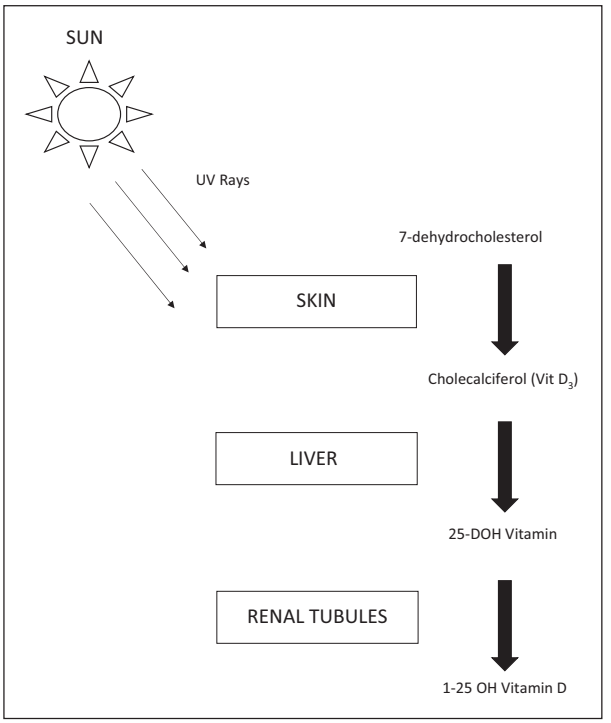

FIGURE 1. Vitamin D metabolism.

VITAMIN D METABOLISM, SOURCE, AND ACTIONS

Vitamin D is a hormone manufactured in the skin upon exposure to the ultraviolet radiation of the sun (Fig. 1). Vitamin D is also obtained from vitamin supplementation as well as dietary intake of naturally occurring and vitamin D fortified foods. The two forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2 is found in plants. The majority of vitamin D_3 is synthesized in the skin with the rest derived from consuming oily fish, beef liver, egg yolk, cod liver oil, and vitamin D_3 fortified foods. Ultraviolet solar radiation converts 7-dehydrocholesterol in the skin to vitamin D_3. Endogenous vitamin D_3 as well as ingested D_2 and D_3 are converted in the liver to 25-hydroxy vitamin D (25-OH D). 25-OH D is the major circulating and storage form of vitamin D. 25-OH D is converted to its biologically active form 1,25-dihydroxyvitamin D [1-25(OH) D] in the proximal renal tubules. 1-25(OH) D functions principally to increase the absorption of calcium and phosphorus from the small intestine, a step which is essential for bone mineralization [9,10].

Vitamin D has long been known for its classic role in bone health and calcium homeostasis. Severe vitamin D deficiency in young children whose bones are growing and less mineralized results in the classical skeletal deformities known as rickets. Infants that are exclusively breastfed should receive vitamin D supplementation due to the low content of vitamin D in breast milk. Children with limited sun exposure due to sunscreen use, dark skin pigmentation, or extensive clothing coverage as well as obese children should be screened for vitamin D deficiency [9,11]. There is no recommendation to routinely screen healthy children for vitamin D deficiency.

In more recent years, with the discovery of 1-25(OH) D receptors in a wide variety of tissues, vitamin D has been postulated to play a role in various disorders including diabetes, cardiovascular disease, cancer, psychiatric illness, and infection as well as allergic, immunologic, and inflammatory disorders [3,5]. Vitamin D appears to affect the production of inflammatory cytokines as well as the proliferation of proinflammatory cells. In this capacity, it plays an important role in the regulation of both the immune and inflammatory response, both of which are of fundamental importance in the pathogenesis of inflammatory diseases [2].

Vitamin D is a fat-soluble vitamin whose absorption requires intact small intestinal, biliary, and pancreatic systems. Vitamin D status can be significantly affected by gastrointestinal disorders such as IBD and celiac disease. These disorders may lead to malabsorption of vitamin D directly through small bowel damage and decreased functioning absorptive surface area as well as exert indirect effects on pancreatic exocrine and hepatobiliary function. Other factors which may contribute to low vitamin D levels include poor vitamin D intake, inadequate sunlight exposure, and use of medications such as

steroids. 25-OH D is the major circulating form of vitamin D and is measured to determine its nutritional status in an individual [9]. There is controversy regarding the most desirable level of serum 25-OH D, but vitamin D deficiency is generally defined as a 25-OH D level below 20 ng/ml (50 nmol/l) and vitamin D insufficiency as a 25-OH D level from 20 to 30 ng/ml (50–75 nmol/l) [11,12▪▪,13].

VITAMIN D STATUS IN CELIAC DISEASE

The childhood prevalence of celiac disease in the United States and many European countries is up to 1% [14]. Vitamin and mineral deficiencies have been noted to be common in a population of children with newly diagnosed celiac disease [15]. Tanpowpong and Camargo [16] postulated that early life vitamin D deficiency may play a significant role in childhood onset (<15 years) celiac disease. In genetically predisposed individuals, vitamin D deficiency may result in a dysregulated intestinal immune response that can further lead to a disrupted epithelial barrier with increased permeability to gluten and microbes. This impaired immune response can result in increased susceptibility to acute gastrointestinal infection. These mechanisms may predispose to the development of childhood-onset celiac disease.

Current literature suggests that patients with untreated celiac disease are at increased risk for developing low BMD, osteoporosis, and bone fractures. Children with celiac disease have low BMD at diagnosis in both symptomatic [17] and asymptomatic patients [8]. There are two main mechanisms potentially involved in developing bone disease in these patients. First, small intestinal mucosal damage may lead to impaired intestinal absorption of nutrients including calcium and vitamin D. The second mechanism is that chronic intestinal inflammation may lead to release of proinflammatory cytokines associated with increased bone loss [18]. Treatment with a strict gluten free diet promotes significant improvement and even complete recovery of bone mineralization in children with celiac disease [19].

There are several studies demonstrating low levels of various vitamins and minerals in celiac disease [5,15,20,21]. Both the American College of Gastroenterology [22] and the British Society of Gastroenterology [23] recommend testing of vitamin D and other micronutrients including vitamin B_{12}, folic acid, and iron in adults at the time of initial diagnosis. The presentation of celiac disease in childhood has been changing in more recent years to include not only the classic symptoms of malabsorption with diarrhea and failure to thrive but also nongastrointestinal and asymptomatic conditions. This raises more questions regarding associated deficiencies, including vitamin D. Recent evidence-informed expert opinion recommends screening for vitamin D status in children at the time of initial evaluation for celiac disease but note there is little evidence for this position and recommend further studies [24▪▪]. This is the only pediatric article stating general recommendations for follow-up of celiac disease including vitamin D monitoring based upon expert opinion.

There are few pediatric studies, which assess vitamin D status in newly diagnosed celiac disease patients. Pediatric retrospective studies [15,25,26] report vitamin D deficiency in 9–52% of celiac disease patients. The small retrospective study by Villanueva *et al.* [25] showed no difference in the average 25-OH D level in children with newly diagnosed celiac disease versus controls, although both groups demonstrated insufficient levels of 25-OH D. In the cross-sectional study by Lerner *et al.* [27], insufficient but comparable 25-OH D levels were noted in Israeli children with celiac disease as well as those with nonspecific abdominal pain. Because there is no recommendation to screen all children for vitamin D status, these studies may be pointing to a more widespread state of vitamin D insufficiency in the general pediatric population. In a recent case control study by Wessels *et al.* [21], 27% (8/30) of children were found to be vitamin D deficient [<20 ng/ml (50 nmol/L)] at diagnosis and 25% (7/28) remained vitamin D deficient at 5-year follow up. Because only a minority of children presented with vitamin D deficiency, the study authors concluded that vitamin D deficiency may not be directly linked to celiac disease. Until more studies that include the different presentations of childhood celiac disease along with study designs that include controls, measurement of vitamin D intake, and season of the year are performed, the role of vitamin D in the pathogenesis of celiac disease will remain unclear. However, from a practical point of view given the known association of celiac disease with malabsorption and low BMD, we screen all celiac disease patients for vitamin D deficiency at initial presentation and treat those found to be deficient and insufficient to maintain a vitamin D level greater than 30 ng/ml but less than 100 ng/ml.

VITAMIN D STATUS IN PEDIATRIC INFLAMMATORY BOWEL DISEASE

Nutritional deficiencies are common in pediatric IBD patients and depend on disease activity, severity, location, and associated complications

[28]. The prevalence of vitamin D deficiency in children with IBD varies from 14.3 to 62% [29,30]. Risk factors for vitamin D deficiency are similar to those found in healthy populations: poor dietary intake, skin pigmentation, seasonal sun exposure, and obesity. An elevated erythrocyte sedimentation rate that reflects intestinal inflammation is an additional risk factor and is negatively correlated with 25-OH D levels [29,31,32]. Studies comparing vitamin D status in children with IBD and healthy controls have shown variable results. Some studies [32,33] found that 25-OH D levels were lower in IBD compared with controls whereas others found no difference between the two groups [30,31]. In addition, children with ulcerative colitis are reported to have lower 25-OH D levels in comparison to those with Crohn's disease [29,32,33]. When low levels of vitamin D are noted, treatment to obtain a level greater than 30 ng/ml but less than 100 ng/ml should be initiated.

Adult studies have explored the relationship between vitamin D status and different markers of disease activity including disease activity indices, inflammatory markers C-reactive protein (CRP), and fecal calprotectin, with conflicting results. A cross-sectional study by Raftery *et al.* [34] involving Crohn's disease patients ($n = 119$) showed a significant inverse association between serum 25-OH D levels and fecal calprotectin. Vitamin D level was not associated with disease activity score (CDAI) or CRP level. In contrast, another study revealed that Crohn's disease patients ($n = 182$) on vitamin D supplementation with higher 25-OH D levels had lower CDAI scores [35]. In a double-blind randomized controlled trial (RCT) in Crohn's disease patients in clinical remission, patients on vitamin D supplementation with 25-OH D levels at least 30 ng/ml (75 nmol/l) demonstrated significantly higher quality of life scores, lower CRP levels, and a trend toward lower CDAI scores compared with those with 25-OH D levels less than 30 ng/ml (75 nmol/l). No difference in fecal calprotectin was noted [36]. Similarly, a longitudinal study with 5-year follow up demonstrated that low vitamin D is related to more severe disease activity and poor quality of life with significantly increased use of steroids, biologics, narcotics, emergency visits, hospitalization, and surgery [37].

A recent prospective study by Meckel *et al.* [38] assessed the relationship between vitamin D status and mucosal inflammation. An inverse correlation between serum 25-OH D levels and mucosal inflammation was noted based on Mayo endoscopic score and histological activity in ulcerative colitis patients. 25-OH D concentrations were negatively correlated with proinflammatory cytokines and positively correlated with the mucosal expression of vitamin D receptor and epithelial junction proteins. These findings suggest vitamin D plays a protective role in colitis by maintaining epithelial barrier function and decreasing mucosal inflammation.

The role of vitamin D as a potential therapeutic agent for IBD remains under investigation. In a double-blind randomized placebo-controlled trial, Jorgensen *et al.* [39] assessed the effectiveness of vitamin D_3 as maintenance treatment in 118 Crohn's disease patients in clinical remission. The treatment group that received 1200 IU of vitamin D_3 with 1200 mg of calcium daily for 1 year was noted to have a lower clinical relapse rate when compared with placebo (13 vs. 29%; $P = 0.06$). In another small retrospective study [40], the effect of vitamin D status on the durability of anti-tumor necrosis factor therapy in IBD patients was assessed. Individuals with insufficient 25-OH D levels (<30 ng/ml) had earlier cessation of therapy from loss of response ($P = 0.04$). Although these studies have shown promising results, the current data are insufficient to support the use of vitamin D as an anti-inflammatory agent in IBD. There is a need for large, well-designed randomized clinical trials, especially in children.

Vitamin D status in children with IBD should be assessed at the time of diagnosis and during subsequent follow up. It is recommended that levels are checked at least yearly, optimally in the spring when it is presumed that levels are at their lowest [28]. This is the only article with official recommendations regarding screening for vitamin D deficiency in pediatric IBD. To maintain optimal bone health and extra-skeletal benefits, it has been suggested that the 25-OH D level should be at least 30 ng/ml [41]. There is no consensus on the vitamin D treatment regimen dose required to maintain this level. Few pediatric studies have attempted to investigate the most effective vitamin D repletion regimen. Cholecalciferol is the preferred form of oral supplementation of vitamin D. In a RCT, Pappa *et al.* [42] compared three oral treatment regimens in 61 children with IBD and 25-OH D levels less than 20 ng/ml. Children received calcium supplementation for a 6-week period together with either 2000 IU vitamin D_2 daily, 2000 IU vitamin D_3 daily, or 50 000 IU vitamin D_2 weekly. The mean change in serum 25-OH D level from baseline to follow up was assessed with significant improvement in the serum 25-OH D concentration noted in the latter two groups. In another RCT in 83 pediatric Crohn's disease patients followed for 6 months by Wingate *et al.* [43], vitamin D supplementation with 2000 IU/day was more effective in normalizing 25-OH D levels when compared

with 400 IU/day. A retrospective study by Shepherd *et al.* [44] in 76 IBD children with 25-OH D levels less than 20 ng/ml (50 nmol/l) assessed the use of a single high dose vitamin D_3 regimen. Children received doses ranging from 200 000 to 800 000 IU based on their age. A significant increase in the mean 25-OH D levels was noted at 1, 3, and 6 months compared with pretreatment levels. No level obtained was in the toxic range; however, only 63% of children had normalized their 25-OH D levels to more than 30 ng/ml (>75 nmol/l) at 3 months.

Most recently a small, randomized pilot study was performed to attempt to determine appropriate dosing for repletion of hypovitaminosis D in children [45]. 32 children with IBD and 25-OH D levels less than 30 ng/ml received 6 weeks of vitamin D_3 dosed at 10 000 IU or 5000 IU per 10 kg body weight per week. They were noted to have significantly increased 25-OH D levels at 8 weeks but the effect was lost by 12 weeks with 25-OH D levels of 35.1 ± 8.4 ng/ml in the higher dose arm and 30.8 ± 4.2 ng/ml in the lower dose arm.

These findings suggest the importance of maintenance vitamin D therapy following initial treatment of low vitamin D levels to sustain normal vitamin D status.

CONCLUSION

The exact role of vitamin D in the pathogenesis and exacerbation of both celiac disease and IBD is not fully known. Nevertheless, the known role of vitamin D in bone health and its potential role in immune regulation mandate that vitamin D be examined and maintained in these diseases. This is especially relevant given the low vitamin D levels commonly found in these disorders. For celiac disease, our practice is to screen for low 25-OH levels at initial presentation and if needed treat to a level greater than 30 ng/ml but less than 100 ng/ml. Long-term treatment consists of a strict gluten free diet with routine multivitamin supplementation. For IBD, screening occurs at initial diagnosis and then at least yearly, if possible, in the spring. Those with levels below 30 ng/ml are treated generally with 2000 IU per day of vitamin D and then levels followed and adjusted accordingly about every 3 months. Large RCTs are needed to further investigate the role of vitamin D in disease remission and the optimal 25-OH vitamin D levels to be maintained.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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