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Vitamin D Status in Gastrointestinal and Liver Disease

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Structured Abstract

Purpose of the review—The purpose of this review is to report: a) the prevalence of suboptimal vitamin D status in populations with specific gastrointestinal disorders, b) information regarding the impact of vitamin D deficiency on the bone health of patients with these disorders, c) recommendations regarding optimal vitamin D intake to avoid deficiencies specifically for these disorders, d) the state of knowledge regarding the effect of vitamin D on the disease itself, through its actions on the immune system.

Recent findings—The scientific community has revised upward the serum level of vitamin D considered to reflect optimal vitamin D stores.

Evidence is emerging to support that doses of vitamin D much larger than the currently recommended are needed to maintain optimal vitamin D stores especially in individuals with diseases of the gastrointestinal system and the liver.

The relationship between vitamin D and bone health in individuals with gastrointestinal and liver disease is controversial.

The role of vitamin D in the regulation of the immune system continues being elucidated through findings in animal studies and *in vitro*.

Summary—Suboptimal vitamin D status is prevalent among individuals with gastrointestinal and liver disease, and the etiology of this finding is multifactorial and disease dependent. Although replacement and supplementation guidelines have not been well defined and could be different in different diseases and disease states, practitioners should aim for a serum 25OHD level of at least 32 ng/mL when undertaking these tasks. The contribution of vitamin D status to the bone health of individuals with gastrointestinal and liver disease may be different between active and quiescent phases of the disease. Finally, the role of vitamin D in altering disease course through its actions on the immune system remains to be elucidated.

Keywords

Vitamin D; 25 OH vitamin D; gastrointestinal disease; liver disease; inflammatory bowel disease; cystic fibrosis; celiac disease

Introduction

Adequate skin exposure to solar ultraviolet B (UVB) radiation can satisfy the human requirement for vitamin D. During sunlight exposure, 7-dehydrocholesterol, present in plasma membranes of skin cells is converted to pre-vitamin D₃ (pre-D₃) which then

undergoes thermally induced transformation to vitamin D₃ (1). Season, latitude, time of day, skin pigmentation, aging, and sunscreen influence the cutaneous production of vitamin D₃ (2). No pre-D₃ is produced through skin exposure to sunlight even on cloudless days in Boston (42.2 degrees N) from November through February (3). Thus, patients depend on nutrition and/or oral supplements to satisfy their vitamin D needs during that time. Ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) are the most common forms of oral supplements available. Vitamin D, formed in the skin or ingested, is removed by binding to the plasma transport protein, vitamin D-binding protein (DBP) which delivers vitamin D first to the liver where it undergoes 25-hydroxylation (25OHD), and then to the kidney where it undergoes 1-hydroxylation (4). 1,25-dihydroxyvitamin D (1,25(OH)₂D) is the active metabolite and over 30 tissues have receptors for this steroid (5). The most abundant metabolite in the human body is 25OHD and is indicative of overall vitamin D status (4).

Ingested vitamin D is lipid soluble, and as such, its absorption through the gastrointestinal system is dependent on an intact fat absorption mechanism. Patients with gastrointestinal disease may be particularly prone to deficiencies of this vitamin. Low vitamin D intake, fat malabsorption, bile salt deficiency, loss of absorptive surface, increased intestinal permeability, and loss of liver function are conditions frequently associated with gastrointestinal disease, which may account for the suboptimal vitamin D status encountered in this population.

Vitamin D, via the active form 1,25(OH)₂D, plays a major role in calcium homeostasis, bone metabolism, and immune system regulation. 1,25-hydroxyvitamin D enhances small intestinal calcium absorption by interacting with the Vitamin D receptor-retinoic acid x receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel, (transient receptor potential cation channel, subfamily V, member 6 (TRPV6) and calbindin 9k, a calcium binding protein (CABP), located in the enterocyte (6). Bone is a dynamic tissue which undergoes resorption and formation several times a day. Osteoblasts and osteoclasts, the mature bone cells, are the protagonists in bone formation and resorption respectively.

Activation of osteoclasts is mediated by the receptor activator of NF- κ B (RANK), its ligand (RANKL), and the decoy receptor of this ligand, osteoprotegerin (OPG) (7–11). RANK, which is expressed on the membrane of osteoclastic precursors among other cells (12, 13), is activated by binding to RANKL and leads in turn to activation of osteoclasts (8–10). RANKL is largely expressed by cells of osteoblastic lineage and T-lymphocytes (8). OPG is produced by a number of cells, including osteoblasts (14) and as a decoy receptor for RANKL limits its availability for RANK activation, providing a limiting step in osteoclast activation (7–11).

Vitamin D plays an important role in the normal coupling of bone remodeling, promoting both osteoblastic and osteoclastic activity: 1,25(OH)₂D₃-vitamin D receptor defective mice manifested impaired osteoblastogenesis in the presence of normal PTH (15), and vitamin D enhances osteoblast differentiation and mineralization in humans (16). 1,25(OH)₂D₃ also stimulates RANKL expression (17), and inhibits OPG production by osteoblasts (18), thus promoting osteoclastogenesis.

The optimal level of serum 25OHD to maximize bone health in the general population, remains controversial(6) Although Vitamin D deficiency has been classically defined as a serum 25OHD level of less than 20ng/ml (50nmol/Liter) (19) ((20), there is recent evidence to suggest that a level of at least 30ng/ml (75nmol/liter) is required to minimize hyperparathyroidism and maximize intestinal calcium transport (6), (21) (22). Intestinal

calcium transport increased by 45–65% in healthy women when 25OHD levels were increased from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter) (22)

It has been well established that vitamin D₃ (cholecalciferol) is a more potent form of vitamin D than vitamin D₂ (ergocalciferol) (23, 24). There is evidence to support the fact that an intake of 400 IU of vitamin D₂/day may not be adequate to maintain optimal vitamin D stores (25OHD = 32 ng/mL), especially during winter in healthy adults and children in the northern hemisphere (25–29). Several investigators have suggested that daily doses of vitamin D₃ between 1,000 – 4,000 IU/day are needed in order to achieve and maintain serum 25OHD concentrations = 30 ng/mL, starting from a point of vitamin D sufficiency in healthy adults (21, 30–33). Adults and children with gastrointestinal disease could have an even greater requirement for vitamin D intake in order to overcome malabsorption, reduced sunlight exposure, and nutrient loss through an inflamed intestine. The US National Academy of Sciences has indicated that the current “no observed adverse effect level” for vitamin D₃ intake is 2,000 IU/day (34).

The relationship between vitamin D status and the regulation of the immune system is well-established. 1,25(OH)₂D appears to play a pivotal role in the development of self-tolerance (35). It regulates T-helper cell (Th-1) function and dendritic cell function, while inducing regulatory T-cell function (35). The net result is a decrease in the Th1-driven autoimmune response and decreased severity of symptoms. The role of vitamin D in the pathogenesis and course of Th-1 cytokine-mediated immune diseases, such as multiple sclerosis (36) (37) (38) (39) (40), rheumatoid arthritis (41) (42), inflammatory bowel disease (43) (44) and type 1 diabetes mellitus (45) (46) (47, 48) is supported by findings in both animal models and epidemiologic studies in humans. Serum 25OHD levels much higher than what we consider “adequate” for bone health may be needed in order to exert beneficial effects on the immune system.

In this article, we intend to review: a) the prevalence of suboptimal vitamin D status in populations with specific gastrointestinal disorders, b) information regarding the impact of vitamin D deficiency on the bone health of patients with these disorders, c) recommendations regarding optimal vitamin D intake to avoid deficiencies specifically for these disorders, d) the state of knowledge regarding the effect of vitamin D on the disease itself, through its actions on the immune system.

Vitamin D status in inflammatory bowel disease

Reports of vitamin D status in adults with IBD place the prevalence of vitamin D deficiency between 22–70 % for Crohn disease (CD) (49–59), and up to 45% for ulcerative colitis (UC) (59). Data concerning the vitamin D status of children with IBD are limited and conflicting (60–63) and could be explained by different thresholds for vitamin D deficiency. We found this prevalence to be as high as 34.5% among pediatric patients with IBD, and higher than that encountered among healthy New England adolescents studied in our hospital using the same 25OHD assay (24.1%) (63, 64).

In pediatric subjects with IBD, cross-sectional studies have associated lower 25OHD levels with winter season, dark skin complexion, upper gastrointestinal disease, higher lifetime corticosteroid exposure, lower Z-scores for weight and body mass index (BMI), higher erythrocyte sedimentation rate (ESR), not taking vitamin D supplements, and lower serum albumin levels (60, 63). Absorption of vitamin D was normal in reports of adults with IBD and hypovitaminosis D (65, 66).

Hypovitaminosis D has been associated with low BMD in studies of healthy adults (67–70) and adolescents, the latter suggesting that hypovitaminosis D may compromise the

attainment of peak bone mass (71, 72). The relationship between 25OHD levels and BMD is controversial among adults with IBD. Some investigators found a positive association between 25OHD levels and BMD (52, 54). Others reported low BMD, despite the presence of normal 25OHD levels (73–75), and some found no relationship (53, 59).

The contribution of vitamin D status to bone mineral accrual in children with IBD is unknown. A few cross-sectional studies report no relationship between BMD and vitamin D levels (60, 61, 63). Others report a positive relationship between these variables in corticosteroid-treated children, including children with IBD (76). The relationship between vitamin D status and bone quality (as represented by bone biomechanical properties measured by peripheral quantitative computerized tomography) has not been studied. Vitamin D regulates the release of several cytokines (77) (78, 79). There are reports of decreases in the levels of bone-resorption promoting cytokines that parallel increases in 25OHD serum concentration and improvement in BMD in inflammatory conditions (80, 81). These properties of vitamin D could counteract the effects of systemic inflammation on bone health. Clinical trials showed that supplementation with vitamin D and its analogues protected against bone loss in subjects with rheumatoid arthritis and lupus erythematosus (82–85). The capacity of vitamin D to promote both osteoblastic and osteoclastic activity, may be of great importance especially in children, since both osteoblastic and osteoclastic activity seem to be depressed, at least in the initial stages of inflammation in children (86).

Studies in animal models support the hypothesis that the vitamin D endocrine system may play a role in the maintenance of normal immune responses in the gut. A lack of expression of the vitamin D receptor (VDR) aggravates symptoms in murine experimental colitis models (43); 1,25(OH)₂D₃ prevents and ameliorates IBD symptoms in an experimental mouse model (IL-10 ko. mouse) (44), and calcium and 1,25(OH)₂D₃ together target the TNF- pathway to suppress experimental IBD (87). One *in vitro* human study found a synergistic inhibitory effect of cyclosporin A and vitamin D derivatives on T-lymphocyte proliferation in active ulcerative colitis (88). Another found that calcipotriol (a vitamin D analogue) inhibits rectal epithelial cell proliferation in ulcerative proctocolitis (89). A study of the effect of vitamin D supplementation on disease activity is under way at our center.

The optimal vitamin D intake for repletion and maintenance of vitamin D stores in this population has not been identified yet. Studies regarding this are underway in our center, including a controlled clinical trial of two forms of vitamin D replacement.

Vitamin D status in celiac disease

Celiac disease is an immune mediated enteropathy that can occur in response to the ingestion of gluten proteins present in wheat, barley and rye. The disease can affect genetically susceptible individuals and is closely associated with genes that code class II human leukocyte antigens predominantly HLA- DQ2 and less frequently HLA-DQ8 classes (90). Celiac Disease is now considered a common condition affecting a variety of organ systems including the skeleton. The prevalence of celiac disease is estimated at 0.7% to 2.0% of the general population (91). Diagnosis includes screening serologic antibodies for tissue transglutaminase antibody and anti-endomysial antibody and obtaining the gold standard diagnostic duodenal biopsy revealing characteristic inflammation and tissue injury (91, 92). Adherence to a lifelong strict gluten free diet (GFD) leads to symptomatic and histopathologic remission, serologic normalization, and recovery of many of the affected organ systems (93) (94).

Hypovitaminosis D and hypocalcemia are reported in some newly diagnosed patients (95) (96). However, the true prevalence of hypovitaminosis D in patients with celiac disease

remains unknown. Inadequate intake of calcium and vitamin D is often present in undiagnosed patients as a result of general malnutrition and anorexia related to gastrointestinal complaints including abdominal pain, nausea, and diarrhea. The recommended GFD can lead to suboptimal intake of calcium and vitamin D. Kinsey et al noted that 100% of individuals older than 50 years of age with celiac disease on a GFD reported a vitamin D intake below reference nutrient intake values (97). Similarly, in children complying with a strict GFD, nutritional imbalances were reported (98) although vitamin D status was not examined.

Vitamin D status in newly diagnosed celiac disease appears to be primarily a function of the degree of sunlight exposure and vitamin D ingestion and not intestinal absorption. The intestinal vitamin D receptors in patients with newly diagnosed celiac disease and intestinal villous atrophy have been shown to be equally abundant in the crypts of the duodenal mucosa of patients with active disease as with control subjects(99).

At the time of diagnosis of celiac disease, bone mineral density is decreased in approximately 3–39% of children and adolescents and 22–80% of adults. (100). Osteoporosis has been estimated in approximately one quarter of adult patients. (101). Newly diagnosed patients with celiac disease were reported to have elevated RANKL/OPG ratios compared with controls and patients on a gluten free diet (102). Fiore demonstrated that some patients on a strict GFD and normal follow up duodenal histology continue to display evidence of elevated RANKL/OPG ratio and persistently low spine and femoral bone mineral density compared with controls (103).

The age of the patient at time of diagnosis and initiation of GFD has a marked impact on the long term skeletal health. Children on a GFD for one year often display complete recovery of the bone disease with normalization of the bone mineral density and often achieve peak bone mass similar to controls (104), (105). Following institution of a GFD, adults with newly diagnosed celiac disease will show improvement of bone mineral density but often do not normalize to the levels seen in matched control groups ((106), (96) (103). The etiology of the lack of full normalization of bone health, despite normal follow up intestinal histology reported in some studies (103) remains unknown, but it could be related to ongoing hypovitaminosis D and sub clinical hyperparathyroidism. The relationship between vitamin D status and bone health has not been systematically studied with cross-sectional or longitudinal studies in this population.

New insights into vitamin D requirements and an understanding of the underlying immunologic pathways involved in skeletal mineralization will pave the way for optimizing bone health in all patients with celiac disease. Until specific recommendations for the pediatric population are developed, vitamin D supplementation, whether with ergocalciferol or cholecalciferol, must be sufficient to produce a serum 25OHD value > 32 ng/mL. All adult patients regardless of age with treated celiac disease with or without bone disease should follow the recommendations of the National Osteoporosis Foundation for those over 50 years of age to ingest 800 IU-1000 IU vitamin D₃ and 1200 mg calcium daily (www.nof.org). Serum levels of 25OHD must be maintained > 32ng/mL(6).

Vitamin D status in cystic fibrosis

Bone health in patients with cystic fibrosis is becoming a topic of great interest as the mechanisms that control bone accrual and loss become amenable to detailed investigation (107). At present, the term “CF bone disease” is used to describe a variety of abnormalities in bone found in approximately 50% of adult patients (108). CF bone disease increases in frequency with advancing age, worsening pulmonary status and malnutrition. Among the factors that influence bone composition in CF are pancreatic insufficiency leading to

decreased absorption of vitamin D and calcium; reduced exposure to sunlight; sub-optimal nutrition producing poor growth, loss of body fat stores and pubertal delay; diabetes; pulmonary inflammation associated with elevated circulating and tissue cytokines; glucocorticoid use; decreased weight-bearing exercise; and vitamin K deficiency with reduced γ -carboxylation of osteocalcin (107, 109).

While a complete understanding of the causes of low vitamin D stores in CF remains to be delineated, low serum 25OHD levels are commonly found. Five to 10% of CF patients have severe vitamin D deficiency with 25OHD levels <10 ng/mL (25 nmol/L) (107), and the mean level of 25OHD in CF adults is approximately 21.5 ng/mL (median 20.3) (110). Vitamin D deficiency occurs in 25–33% of patients with late-stage CF (107).

The target 25OHD levels that avoid hyperparathyroidism have changed over the years; thus the literature describing supplementation with vitamin D for CF patients must be read in the context of the target level considered optimal at the time of the study (107) (6), (21) (22). For example, it is clear that 800 IU of cholecalciferol (vitamin D₃) per day is inadequate as only 30% of patients studied by Hanly et al (111) attained levels of 25OHD >20 ng/mL. If current levels of >32 ng/mL had been used, the number of patients adequately treated would have been much lower. Kelly et al (112) found that 1,800 IU of ergocalciferol (vitamin D₂) per day were required to bring the 25OHD levels of CF patients to >25 ng/mL. When a target value of 30 ng/mL was used, Boyle et al found that only 8% of patients receiving 50,000 IU ergocalciferol per week for 8 weeks achieved 25OHD levels >30 ng/mL. A number of those who failed to increase their levels were then given 50,000 IU twice weekly for 8 weeks. Surprisingly, none of them increased their 25OHD levels significantly (110). In contrast, a more recent study of 215 patients (113) demonstrated that 40 patients with baseline 25OHD values <10 ng/mL (<25 nmol/L) achieved mean levels of 53 nmol/L after at least 3 months of therapy (median intake 1800 IU per day). However, only 17% of the 215 patients had follow-up 25OHD values of >75 nmol/L ($>$ approximately 30 ng/mL).

On the basis of available data, it is fair to state that vitamin D supplementation, whether with ergocalciferol or cholecalciferol, must be sufficient to produce a serum 25OHD value of >32 ng/mL (approximately >75 nmol/L). If this cannot be accomplished using oral therapy, parenteral vitamin D must be provided. The ultimate challenge will be to monitor outcomes of such therapy, considering that vitamin D has a number of potentially beneficial effects in addition to those on bone metabolism.

Vitamin D status in liver disease

Both cholestatic and non-cholestatic liver disease is associated with suboptimal vitamin D stores. Cholestasis reduces the intestinal availability of bile salts which are needed for the absorption of fat-soluble vitamins such as vitamin D. Among 6 subjects (mean age 12.1 years) with cholestasis since infancy, most displayed a significantly blunted absorption response to enteral vitamin D₂ as compared to healthy children, and baseline serum 25OHD values were undetectable in five out of the six subjects (114). Cholestatic children may also have defective hepatic conversion of vitamin D₂ or D₃ to the hydroxylated molecule. In five cholestatic children admitted to a research unit with controlled exposures to ultraviolet light, circulating levels of 25OHD₃ were low or undetectable on admission and continued to be so after 8 days of therapy (115).

Non-cholestatic diseases may also result in abnormalities of vitamin D physiology, with the burden on patients with cirrhosis. Impaired conversion of vitamin D to the 25 hydroxylated form in the liver is the major mechanism for the resulting vitamin D insufficiency, since photo conversion in the skin is normal in patients with liver disease (116). In 100 adult subjects (1/3 women; mean age 49 years) with non-cholestatic chronic liver disease, Fisher

et al reported serum levels of 25OHD <50nmol/L (20ng/mL) in 86% of the cirrhotic versus 49% of the non-cirrhotic patients (P=0.001), and this level correlated inversely with the international normalized ratio (INR), suggesting that Vitamin D status may be determined in part by chronic liver disease severity (117).

Vitamin D insufficiency is present in up to 96 percent of patients before liver transplantation (118). In contrast, vitamin D deficiency post-transplantation is uncommon. Some investigators found that serum 25OHD levels were low in only 5 of the 87 pediatric liver transplant recipients, with a cut off value set relatively low at 15ng/ml (119), and others found that vitamin D stores normalize within 1 year following liver transplantation in children (120).

Metabolic bone disease such as osteomalacia and osteopenia is relatively common in patients with liver disease, particularly cholestatic liver diseases. Potential mechanisms for this include inadequate calcium intake, and suboptimal vitamin D status. Other non-vitamin D related factors may be important, such as hypogonadism (121), vitamin K deficiency (122), medications (123), and alcohol intake (124) in adults.

The relationship between bone health and vitamin D status in liver disease is unclear. Investigators did not find any relationship between bone mineral content and serum 25OHD levels in subjects with cholestatic disease(125)(126). There is evidence that osteoblastic dysfunction may play a major role in the pathogenesis of metabolic bone disease in patients with chronic liver disease, and this dysfunction may not be explained by abnormalities in vitamin D metabolites alone (127).

The most robust relationship between bone health and vitamin D status is found in patients post liver transplantation. Low serum 25OHD levels were highly associated with the risk for osteoporosis post-transplantation (128), and spinal bone mass gains in adults post liver transplantation were related to higher serum 25OHD levels(129). It is known that both bone mineral density and vitamin D stores normalize within 1 year following liver transplantation in children (120).

Vitamin D is known to have non-skeletal functions, including serving as a modulator of immune responses via paracrine mechanisms (6). Although the effect of vitamin D or vitamin D analogues on the course of liver disease has not been studied in humans, polymorphisms in the vitamin D receptor have been associated with autoimmune hepatitis and primary biliary cirrhosis (130).

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