Biomedical & Translational Science

Review Article

Bone Health and the Physiologic Importance of Vitamin D

Phillip J Stokey, Sargampreet Kaur, Cameron Crasto, Nabil Ebraheim

Department of Orthopaedic Surgery, University of Toledo College of Medicine and Life Sciences, Toledo, Ohio, USA

Correspondence

Phillip J Stokey

Department of Orthopaedic Surgery, University of Toledo College of Medicine and Life Sciences, Toledo, Ohio, USA

Abstract

Vitamin D plays a critical role in various physiologic processes throughout the body including metabolism, immune support, and bone formation and mineralization. Vitamin D is chemically modified by enzymatic reactions in the liver and kidney before it can be used by the rest of the body. The process of how Vitamin D is absorbed and metabolically activated is important in understanding how to diagnose and treat patients with low Vitamin D levels. While Vitamin D toxicity can occur, Vitamin D deficiency is more common and can result in increased risk of fractures in the elderly. Vitamin D deficiency can occur because of malabsorption, poor diet, inadequate sun exposure and a variety of other causes. The purpose of this manuscript was to explore the different functions of Vitamin D in the body and significant clinical effects if these levels are below normal limits.

- Received Date: 20 Jul 2022
- Accepted Date: 26 Jul 2022
- Publication Date: 05 Aug 2022

Keywords

Vitamin D, Bone, Basic science, Biochemistry, Metabolism

Introduction

Cholecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2) are fat soluble compounds collectively known as Vitamin D. Their impact on calcium and phosphate metabolism allow them to play a key role in immunity and the maturation and development of bone.

The role of Vitamin D in bone integrity and remodeling makes this hormone pertinent in orthopaedics.

Physiology

Vitamin D stores are accumulated from the diet or by synthesis in the skin epithelium by UV B sunlight. UVB rays from the sun activate 7-dehydrocholesterol in the epithelium to pre-D3 which is then activated to Vitamin D3 also known as cholecalciferol. This compound then enters the blood to the liver where it is hydroxylated to 25 hydroxyvitamin D3 (calcidiol). The compound then travels to the kidney where it is hydroxylated again to its active form of 1,25 dihydroxyvitamin D3, also known as calcitriol. Dietary Vitamin D is absorbed in the small intestine and follows a similar pathway once in the blood stream. The absorption and bioavailability of fat soluble Vitamin D may vary based on overall diet and nutritional status or other factors, but these nuances are not well understood [1]. Once absorbed, the hydroxylation of calcidiol to calcitriol is under the control of parathyroid hormone (PTH). Overall, Vitamin D3 (cholecalciferol) is more potent and distinct from Vitamin D2 (ergocalciferol). Cholecalciferol is typically derived from animal products while ergocalciferol is found in plant-based products. While they both can be used for calcitriol metabolism, cholecalciferol is better absorbed and more effective at increasing serum calcitriol levels than ergocalciferol [2]. Therefore, cholecalciferol is the preferred method of oral Vitamin D supplementation [3].

Once in its active form, calcitriol can now regulate serum calcium and phosphate levels. Calcitriol increases serum calcium levels by promoting intestinal uptake and renal resorption of calcium. It also triggers the release of the RANKL (Receptor Activator of NF-kB Ligand) from osteoblasts to activate osteoclasts by binding the RANK (Receptor Activator of NF-kB) receptor on osteoclast precursors. This cascade promotes bone resorption which releases more calcium and phosphorous into the blood. Overall, calcitriol increases plasma calcium and phosphorous [4-6]. In doing so, calcitriol contributes to improved energy efficiency by promoting fatty acid synthesis, induces glucocorticoid synthesis, and immune modulation [4]. Its role in the immunity is exacted by regulation of the innate and adaptive immune systems, as well as inflammation pathways [7]. There is

Citation: Stokey PJ, Kaur S, Crasto C, Ebraheim N. Bone health and the physiologic importance of vitamin D. Biomed Transl Sci. 2022; 2(3):1-4

also evidence to suggest a protective role of Vitamin D against cardiovascular, endocrine, and neurodegenerative disease, as well as cancer [1]. In all, Vitamin D plays an intimate role in several vital metabolic systems and imbalance of Vitamin D levels manifests in a multitude of signs of symptoms that will be further discussed.

Hypovitaminosis D

Low Vitamin D or hypovitaminosis D is a common finding due to inadequate dietary intake or insufficient exposure to proper sunlight. The calcidiol precursor has a serum half-life of 15 days while the active calcitriol has a serum half-life of approximately 15 hours [8]. While Vitamin D toxicity is possible and would cause hypercalcemia with symptoms such as bone pain, vomiting, nephrolithiasis, and psychiatric symptoms, this condition is rare. Due to the relatively short half-life of calcitriol in the body, toxicity would typically only be seen in patients with surreptitious Vitamin D supplementation. Conversely, hypovitaminosis D is relatively common. Low Vitamin D is most likely due to nutritional or environmental deficiency, but can be caused by malabsorption, liver disease, and medications such as steroids and anticonvulsants [9].

While common, there is debate regarding the definition and prevalence of Vitamin D deficiency. Because of its longer half-life of approximately 15 days, serum calcidiol or 25 Vitamin D3 is the preferred serum measurement to assess Vitamin D levels. While calcitriol is the active form of Vitamin D3, its transient half-life in serum makes it an unattractive biomarker. The threshold for diagnosis of Vitamin D deficiency varies by different sources. Generally, a calcidiol level of 25-75 nmol/L is considered within normal limits [10]. Deficiency of Vitamin D is often categorized as levels under 20 nmol/L while insufficiency is defined as calcidiol levels between 20-30 nmol/L. Levels above 30 are generally accepted as adequate. A 2020 study utilizing a US National Institute of Health program estimating the impact of Vitamin D deficiency estimate 5.9% of the US population to be Vitamin D deficient and 24% Vitamin D insufficient [10]. This is an average total population estimate with prevalence higher in the elderly population and lower in children. However, this is a conservative estimate and other sources suggest approximately 34-37% of US adults are lacking adequate Vitamin D; this estimate is even higher for populations of other countries where food is not fortified with Vitamin D [11]. This phenomenon creates a significant disease burden that manifests as high rates of rickets and osteomalacia in lower income populations.

Patients with Vitamin D deficiency may supplement with oral Vitamin D3 or consciously obtain more sunlight. While UVB (Ultraviolet B) rays from sunlight so activate Vitamin D precursors in the epithelium as discussed in the previous section, the subsequent rise in serum Vitamin D from this method is limited. Fifteen minutes in the sun is estimated to yield approximately 10,000 international units (IU) of Vitamin D [12]. However, this estimate varies greatly based on environmental and individual factors. For example, the angle of UV rays entering the atmosphere varies based on weather, geographic location, or time of year. Maximal UV rays are obtained from direct sunlight in the spring and summer seasons while levels are low between October and March. Individual factors such as age, clothing, and skin pigment or type also affect how much UV (ultraviolet) radiation is absorbed by the skin. In addition, extended exposure to UVB rays also increases the chance of skin cancers, including melanoma, over time. [13, 14] Due to this unreliable variability and increased risks associated with Vitamin D supplementation by sunlight, oral Vitamin D supplementation is often preferred.

Oral supplementation of Vitamin D3 can be achieved by vitamin capsules or dietary sources. Vitamin D3 is found in fish such as salmon, sardines, herring, and mackerel, as well as egg yolks, mushrooms, and fortified dairy products. While patients can be encouraged to get more sunlight or add Vitamin D rich foods to their daily diet, this may not be enough for to rectify the deficiency and vitamin supplements are often needed. For example, an 8oz serving of milk only provides 100 IU of Vitamin D3 [15]. The goal of a Vitamin D3 supplemental regimen is to increase the serum calcidiol above 30 nmol/L; therefore, it is important to obtain a serum calcidiol level prior to any supplementation in order to confirm level of deficiency and track progress. Vitamin D3 supplements are started at 50,000 IU once a week for eight weeks. Serum calcidiol will be tested after this eight week trial with a goal of levels above 30 nmol/L. Of note, it can take much longer for some patients to reach this this goal calcidiol level. Once this is achieved, patients will shift to a maintenance dose of 15,000-20,000 IU per day which can be obtained by diet or supplements. The body must have stable and adequate supply of calcidiol constantly to produce calcitriol as needed and this balance takes time to achieve [16]. It is important to reach this balance and follow up closely to ensure it is maintained.

The signs and symptoms of hypovitaminosis D are subtle and often missed or mistaken for other causes. Patients may experience non-specific symptoms such as fatigue, hair loss, or disturbance in sleeping patterns. Patients may also complain of muscle weakness and loss of muscle mass [17]. While low Vitamin D may contribute to may disease processes, its most profound effect is that on bone integrity. Without proper calcium and phosphate balance in the body, poor bone health leads to rickets and osteomalacia, as well as osteoporosis, fractures, and delayed bone healing. The effect of severe Vitamin D deficiency on bone is clear in the case of improper bone development—rickets in children and osteomalacia in adults. If not supplemented, nutritional deficiency results in inadequate calcium and phosphorous stores to synthesize bone. Children with rickets develop “soft” bones that can become deformed as the child grows. This may result in bowing of the legs, abnormal spinal curvature, weakness, delayed growth, and bone pain in the axial skeleton [18]. Adults with osteomalacia have similarly inadequate mineralization of the bone and may suffer from chronic pain and fractures.

Clinical considerations

Vitamin D supplementation has an obvious role in bone development pathologies such as rickets and osteomalacia, as well as bone density problems such as osteoporosis. Vitamin D and calcium supplementation is an established treatment for rickets [19]. This is shown to prevent long-term deformity and improve symptoms. Osteomalacia in adults with closed epiphyseal plates may not have gross deformity of the bones but will experience pain and fractures of the pelvis, sacrum, proximal tibia, and ribs [20]. If osteomalacia is suspected, serum levels Vitamin D, calcium, and phosphorous as well as radiographs and a bone density test can aid in diagnosis.

Bone density tests are conducted with dual energy X-ray absorptiometry, also known as DEXA (Dual-energy x-ray absorptiometry) scan. This test uses radiation to measures the percentage of bone mineral density present in bone. While it can determine low bone density, a DEXA scan cannot differentiate between osteomalacia and osteoporosis. This dinstinction must be made by the unique fragility fracture pattern of each pathology and clinical findings. Ultimately, the gold standard for diagnosis of osteomalacia is by bone biopsy but this is rarely done. Osteoporosis is a condition of "porous" bone caused by abnormal bone homeostasis. Bone formation by osteoblasts is uncoupled from osteoclast bone resorption, leading to low bone density [21]. Estrogen has a protective effect on cancellous and cortical bone, thus osteoporosis is most prevalent in post-menopausal women. While Vitamin D and calcium supplementation are supported to reduce risk of fracture in these patients, their effects are not sufficient alone. Bisphosphonate therapy to inhibit osteoclastic activity and weight bearing exercise are the standard treatment [22].

Fractures due to mechanical falls in elderly patients is an important topic for medical institutions. While institutional standards of care and ambulation protocols are vital for prevention of these incidents, these patients are given Vitamin D supplementation to prevent fractures. However, there is little consensus on how such protocols should be designed. A 2019 Oxford meta-analysis found that while daily or bolus dosing of Vitamin D3 alone was not sufficient to reduce the risk of fractures in elderly patients, daily supplementation of 400-800 IU of Vitamin D with 1000-1200 mg calcium reduced fracture risk by 6% [23].

This is further corroborated by a 2005 Harvard study showing that 700-800 IU/day Vitamin D3 supplementation significantly reduced he risk of non-vertebral fractures in institutionalized elderly patients [24]. However, dosing of Vitamin D3 and calcium supplementation is important as this regimen comes with side effects such as risk of nephrolithiasis [25].

A 2017 randomized clinical trial found that doses below 800 IU/d and over 4000 IU/d did not significantly reduce risk of fractures. Instead, they concluded medium doses between 1600-3200 UI/d to fit the ideal therapeutic window [26]. A 2021 randomized clinical trial assessed dosage of supplementation for fall risk patients over 70 with calcidiol level between 25 and 72.5 nmol/L. Groups of patients were given either 200, 1000, 2000, or 4000 IU Vitamin D3 per day and followed for 2 years. Their results suggest that there is no benefit to Vitamin D3 supplementation over 1000 IU/d [27]. Overall, there is a definite role of Vitamin D3 supplementation in improving bone health and, therefore, fragility fractures. However, lack of consensus for the parameters of hypovitaminosis D, variability between the composition and bioavailability of Vitamin D3 manufacturers, and exact dosage makes the logistics of this treatment unclear [28,29].

Conclusion

The role of Vitamin D in bone health, metabolism, chronic disease and the immune system makes it an attractive therapeutic target. Vitamin D supplements are linked to improvement in chronic pain, obesity, diabetes, autoimmune disease, and even COVID-19 [30-32]. While Vitamin D3 supplements are effective at raising serum calcidiol levels and improving symptoms, more research is needed to understand the exact mechanisms and formulate a comprehensive protocol for supplementation.

Disclosures

There are no conflicts of interest present with the authors of this manuscript.

Acknowledgements

Each author contributed in a significant way to the making of this article. Dr. Phillip Stokey was the corresponding author and helped write and oversee the writing of this article. Sargampreet Kaur and Cameron Crasto both helped write and gather research for this article. Finaly, Dr. Nabil Ebraheim provided guidance and supervision for the writing of this article.

References

1. Borel P, Caillaud D, Cano NJ. Vitamin D bioavailability: state of the art. Crit Rev Food Sci Nutr. 2015;55(9):1193-1205.
2. Tripkovic L, Lambert H, Hart K, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr. 2012;95(6):1357-1364.
3. Martineau AR, Thummel KE, Wang Z, et al. Differential Effects of Oral Boluses of Vitamin D2 vs Vitamin D3 on Vitamin D Metabolism: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2019;104(12):5831-5839.
4. Zemel MB, Sun X. Calcitriol and energy metabolism. Nutr Rev. 2008;66(10 Suppl 2):S139-S146.
5. Kulda V. Vitamin D metabolism. Vnitr Lek. 2012;58(5):400-404.
6. Ozono K. Regulatory mechanism of calcium metabolism. Clin Calcium. 2017;27(4): 483-490.
7. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients. 2013;5(7):2502-2521.
8. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008;88(2):582S-586S.
9. Francis RM, Selby PL. Osteomalacia. Baillieres Clin Endocrinol Metab. 1997;11(1):145-163.
10. Cashman KD. Vitamin D Deficiency: Defining, Prevalence, Causes, and Strategies of Addressing. Calcif Tissue Int. 2020;106(1):14-29.
11. Roth DE, Abrams SA, Aloia J, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018;1430(1):44-79.
12. Aguilar Shea AL, Muñoz Moreno-Arrones O, Palacios Martínez D, Vaño-Galván S. Vitamin D for daily practice. Semergen. 2020;46(6):406-410.
13. Piotrowska A, Wierzbicka J, Żmijewski MA. Vitamin D in the skin physiology and pathology. Acta Biochim Pol. 2016;63(1):17-29.
14. Chang SW, Lee HC. Vitamin D and health - The missing vitamin in humans. Pediatr Neonatol. 2019;60(3):237-244.
15. Torres-Gonzalez M, Cifelli CJ, Agarwal S, Fulgoni VL 3rd. Association of Milk Consumption and Vitamin D Status in the US Population by Ethnicity: NHANES 2001-2010 Analysis. Nutrients. 2020;12(12):3720.
16. Hollis BW, Wagner CL. Clinical review: The role of the parent compound vitamin D with respect to metabolism and function: Why clinical dose intervals can affect clinical outcomes. J Clin Endocrinol Metab. 2013;98(12):4619-4628.
17. Halfon M, Phan O, Teta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. Biomed Res Int. 2015;2015:953241.
18. Creo AL, Thacher TD, Pettifor JM, Strand MA, Fischer PR. Nutritional rickets around the world: an update. Paediatr Int Child Health. 2017;37(2):84-98.

19. Thacher TD, Fischer PR, Pettifor JM. Vitamin D treatment in calcium-deficiency rickets: a randomised controlled trial. Arch Dis Child. 2014;99(9):807-811.

20. Tiefenbach M, Scheel M, Maier A, et al. Osteomalacia-Clinical aspects, diagnostics and treatment. Z Rheumatol. 2018;77(8):703-718.

21. Chen X, Wang Z, Duan N, Zhu G, Schwarz EM, Xie C. Osteoblast-osteoclast interactions. Connect Tissue Res. 2018;59(2):99-107.

22. Weaver CM, Alexander DD, Boushey CJ, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int. 2016;27(1):367-376.

23. Yao P, Bennett D, Mafham M, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(12):e1917789.

24. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293(18):2257-2264.

25. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014;(1):CD007470.

26. Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. J Steroid Biochem Mol Biol. 2017;173:317-322.

27. Appel LJ, Michos ED, Mitchell CM, et al. The Effects of Four Doses of Vitamin D Supplements on Falls in Older Adults : A Response-Adaptive, Randomized Clinical Trial. Ann Intern Med. 2021;174(2):145-156.

28. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess (Full Rep). 2007;(158):1-235.

29. Fosnight SM, Zafirau WJ, Hazelett SE. Vitamin D supplementation to prevent falls in the elderly: evidence and practical considerations. Pharmacotherapy. 2008;28(2):225-234.

30. Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database Syst Rev. 2015;2015(5):CD007771.

31. Vranić L, Mikolašević I, Milić S. Vitamin D Deficiency: Consequence or Cause of Obesity?. Medicina (Kaunas). 2019;55(9):541.