Original Article

An Overview About Vitamin D Role in Human Health

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Abstract

Background: Vitamin D is a micronutrient that plays a critical role in human health; vitamin D has both skeletal and extra skeletal functions. Vitamin D is essential for maintenance of bone and musculoskeletal health. It plays a crucial role in calcium and phosphate homeostasis as well as normal bone growth and mineralization. Although vitamin D, which is an essential fat-soluble nutrient, was first identified as a vitamin, it is now considered a prohormone and is unique to other nutrients because it can be synthesized in the skin through exposure to sunlight. Cutaneous synthesis of vitamin D3 requires the exposure of ultra-violet B rays at wavelength of 290 -315 nm. Once formed, vitamin D3 exits the cutaneous tissue and enters the circulation. Vitamin D is essential for maintenance of bone and musculoskeletal health. It plays a crucial role in calcium and phosphate homeostasis as well as normal bone growth and mineralization. 1,25(OH)2D has been shown to have prodifferentiation and antiproliferation effects on the keratinocyte, anti-tumergenic and anti-metastatic activities on several types of cancer cells, immune-modulatory effects on macrophages and on activated T and B lymphocytes, effects on skeletal muscle function, and protective effects against cardio-metabolic disorders and pregnancy related complications. Vitamin D hormone has important functions including immunomodulant, anti-inflammatory and anti-infective roles. It acts via monocyte and cell-mediated immunity stimulation, suppression of lymphocyte proliferation, antibody production and cytokine synthesis.

Keywords: Vitamin D

INTRODUCTION

Vitamin D is a micronutrient that plays a critical role in human health; vitamin D has both skeletal and extra skeletal functions. Vitamin D is essential for maintenance of bone and musculoskeletal health. It plays a crucial role in calcium and phosphate homeostasis as well as normal bone growth and mineralization **(1).**

Vitamin D sources

Although vitamin D, which is an essential fat-soluble nutrient, was first identified as a vitamin, it is now considered a prohormone and is unique to other nutrients because it can be synthesized in the skin through exposure to sunlight.There are two forms of vitamin D: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is synthesized endogenously in the skin and found naturally in oily fish and cod liver oil. Vitamin D2 is synthesized from ergosterol and found in yeast and mushrooms. So, Vitamin D is obtained through either synthesis in the epidermis upon exposure to ultraviolet sunlight or by the intake of vitamin D-rich foods such as oily fish, egg yolks, veal, beef, liver, and sun-dried mushrooms **(2).**

Cutaneous synthesis of vitamin D3 requires the exposure of ultra-violet B rays at wavelength of 290 -315 nm. Once formed, vitamin D3 exits the cutaneous tissue and enters the circulation. Humans also absorb vitamin D as a fat-soluble vitamin from the diet and supplements primarily in the duodenum. **(3).**

Vitamin D metabolism:

Vitamin D is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation, which occurs in the liver by the enzymes cytochrome P450 2R1 (CYP2R1) and cytochrome P450 27 (CYP27A1) becoming 25(OH) D, also known as “calcidiol.” The second hydroxylation occurs primarily in the kidney by the enzyme CYP27B1, PTH, and FGF-23 forming the physiologically active 1, 25(OH) 2D, also known as “calcitriol” **(4).**

Vitamin D mechanism of action:

It is this active form that binds to receptors (intracellular nuclear VDR) in the intestine, kidney, parathyroid glands, and bone, helping to regulate the plasma levels of calcium and phosphorus, and in turn, bone mineralization and bone quality. Activation of vitamin D receptor (VDR) by 1, 25-dihydroxyvitamin D [1,25(OH)2D] promotes intestinal calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilization from the bone. 1,25(OH) 2D binds to receptors also to regulate its own level via negative feedback mechanism**.** Synthesis of 1,25(OH)2D is strictly regulated in a renal negative feedback loop: high levels of 1,25(OH)2D and Fibroblast growth factor (FGF-23) inhibit CYP27B1 and induce the cytochrome

P45024A1(CYP24A1), which transforms 1,25(OH)2D into the inactive water-soluble metabolite excreted in the bile**.** Furthermore, 1,25(OH)2D directly inhibits parathormone hormone (PTH) production and induces fibroblast growth factor 23 (FGF-23) production in osteocytes as a part of negative feedback loops to maintain serum calcium and phosphate concentration in a physiologic range **(5).**

Functions:

Vitamin D is essential for maintenance of bone and musculoskeletal health. It plays a crucial role in calcium and phosphate homeostasis as well as normal bone growth and mineralization **(1).** In the last two decades, increasing preclinical evidence supports a role for vitamin D in a multitude of extra-skeletal physiological functions **(6).**

Extra-skeletal functions of vitamin D

1,25(OH)2D has been shown to have prodifferentiation and antiproliferation effects on the keratinocyte, anti-tumergenic and anti-metastatic activities on several types of cancer cells, immune-modulatory effects on macrophages and on activated T and B lymphocytes, effects on skeletal muscle function, and protective effects against cardio-metabolic disorders and pregnancy related complications **(5).**

Vitamin D hormone has important functions including immunomodulant, anti-inflammatory and anti-infective roles. It acts via monocyte and cell-mediated immunity stimulation, suppression of lymphocyte proliferation, antibody production and cytokine synthesis**.** Human lung cells are able to intra-cellularly convert the inactive 25-hydroxy vitamin D [25(OH) D] to its active form 1,25(OH)2D which reduces proinflammatory cytokines and increases peptides (e.g., the innate antimicrobial peptide cathelicidin). Cathelicidin has direct antiviral activity against enveloped respiratory viruses such as influenza, respiratory syncytial virus and possibly the COVID-19 as well **(7).**

It has been hypothesized that vitamin D has anti-inflammatory properties that contribute to relieving pain. In vitro studies have found that the vitamin can reduce prostaglandin E2 synthesis to down-regulate proinflammatory pathways. Moreover, vitamin D has also anti-fibrotic effects. The renin-inhibiting activity and down-regulation of the renin-angiotensin system activity seem to be the beneficial effects of vitamin D. In addition to, vitamin D has been shown to suppress angiotensinogen and regulate its expression**.**The potential extra-skeletal effects of the vitamin D endocrine system (which refers to vitamin D in its active form, its precursors and metabolites, and vitamin D receptor) are based on several arguments. For example, the VDR and CYP27B1 (the enzyme primarily responsible for producing the active form of vitamin D) are widely expressed, including in tissues that are not involved in calcium or phosphate transport **(8).**

Assessment of vitamin D status:

Measurement of 25(OH)D

Serum concentration of 25(OH)D is considered the best indicator of vitamin D status, as it reflects both vitamin D produced in the skin and that acquired from the diet, furthermore, 25(OH)D has a fairly long circulating half-life of 15 days. Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL) **(9).**

Assessing vitamin D status by measuring serum 25(OH)D concentrations is complicated by the considerable variability of the available assays (the two most common ones involve antibodies or chromatography). As a result, a finding can be falsely low or falsely high, depending on the assay used and the laboratory. The international Vitamin D Standardization Program has developed procedures for standardizing the laboratory measurement of 25(OH)D to improve clinical and public health practice **(10).**

Measurement of 1,25(OH)2D

Measurement of 1,25(OH)2D is not included in the identification of vitamin D deficient patients. 1,25 (OH)2D has a short half-life measured in hours, and serum levels are tightly regulated by PTH, calcium, and phosphate. Calcitriol levels are maintained in the normal range even in the presence of severe calcidiol deficiency and will not reflect many patients' vitamin D balance **(6).**

Vitamin D deficiency

Definition:

There has been considerable debate on its suggested thresholds (cut-offs) to define low vitamin D status. Some of the variability in threshold concentration relate to differences in the associated severity of low vitamin D status, ranging from vitamin D deficiency, inadequacy to insufficiency, while some of it just relate to difference of opinion among expert groups on the threshold applied to even the same degree of low status. This is despite the fact that in nearly all cases, the thresholds relate primarily to musculoskeletal health outcomes **(11).**

The institute of medicine, had established four cut-off levels for vitamin D status where serum 25(OH)D level less than 12 ng/ml (<30 nmol/L) is considered deficient, level between 12-20 ng/ml (30-50 nmol/l) is insufficient, level between 20-50 ng/ml (50-125 nmol/l) is sufficient, and level greater than 50 ng/ml (125 nmol/l) is high **(11).**

The Endocrine Society's practice guidelines detail three categories where vitamin D sufficiency at 25(OH)D level of > 30 ng/mL (75 nmol/L), vitamin D insufficiency at 25(OH)D level between 21-29 ng/mL (51-74 nmol/L) and vitamin D deficiency level at 25(OH)D of < 20 ng/mL (<50 nmol/L).While universal agreement on the definition of vitamin D deficiency is yet to be reached, overall it is generally agreed that we do not wish to have individuals in the populations (patient or otherwise) with circulating concentrations < 25/30 nmol/L that are indicative of increased risk, and that prevention of such vitamin D deficiency is a public health priority **(2).**

The associated laboratory studies with reduced 25 (OH) D include a, normal or low normal calcium levels, elevated PTH levels,

elevated alkaline phosphatase levels and a reduced 24-hour urinary calcium excretion rate **(6).**
Vitamin D levels demonstrate seasonal variation because environmental exposure to ultra-violet B irradiation is required for the endogenous synthesis of vitamin D **(12).**

- **Epidemiology:**

Vitamin D deficiency is a global public health issue. About one billion people worldwide have vitamin D deficiency, while 50% of the population has vitamin D insufficiency**.** Vitamin D deficiency and insufficiency are highly prevalent, as is shown by the fact that more than half of the population worldwide has levels lower than 30 ng/ml.Vitamin D deficiency in Egypt has reached epidemic proportions. Females are the most affected members of society. Urbanization and social factors are thought to cause that phenomenon**.** It was reported that 77% of healthy Egyptian adults aged 20-60 years had 25 (OH) D level < 20 ng/ml and 20% had level of 25(OH)D between 20-29 ng/ml**.** Moreover, the prevalence of vitamin D deficiency was 78.9 % Egyptian adolescent aged 10-19 **(13).**
Interestingly, vitamin D deficiency is more common in the subtropical and mid-latitude countries than the tropical and high-latitude countries. Contrary to the expectation, the most commonly affected countries with severe vitamin D deficiency are from the subtropical (Saudi Arabia 46 %; Qatar 46 %; Iran 33·4 %; Chile 26·4 %) and mid-latitude (France 27·3 %; Portugal 21·2 %; Austria 19·3%) regions. On the other hand, severe vitamin D deficiency was found to be nearly 0 % in some high-latitude countries (e.g.Norway, Finland, Sweden, Denmark and Netherlands). The low prevalence of severe vitamin D deficiencies in high-latitude countries (except for the United Kingdom; 23·7 %) can possibly be attributed to the high awareness of vitamin D deficiency, high amount of vitamin D supplementation, food fortification and health policies as well **(7).**

Health consequences of vitamin D deficiency

Vitamin D deficiency is a serious public health problem worldwide that affects not only skeletal health, but also a wide range of acute and chronic diseases. However, the majority of patients with vitamin D deficiency have few, if any signs or symptoms related to the condition**.** Vitamin D status significantly affects skeletal health during growth and in adult age, it can lead to chronic hypocalcemia and hyperparathyroidism. its deficiency during growth leads to rickets, whereas during adult age it results in osteopenia and osteomalacia, and to worsen osteoporosis. **(4).**
Vitamin D deficiency also leads to muscle weakness, resulting in an increased fall risk, and corresponding risk of fractures. Furthermore, the vitamin D status of adult patients with a long bone fracture affects the healing of fractures **(14).**
Patients with a prolonged and severe vitamin D deficiency can experience symptoms associated with secondary hyperparathyroidism including bone pain, arthralgia, myalgia, fatigue, muscle twitching and weakness **(6).**
Low vitamin D levels have been linked in observational studies to immune dysfunction, infections, malignancies (e.g. breast, colon, prostate), decreaswd skeletal muscle strength, cardiovascular diseases and glycemic dysregulation **(6).**

Prevention of vitamin D deficiency

Twenty minutes of sunshine daily with over 40% of skin exposed is required to prevent vitamin D deficiency. Sufficient sun exposure to produce a light-pink skin hue (one minimal erythema dose) is equivalent to 20,000 international units (IU) of oral vitamin D. Adults less than 65 years of age who do not have year-round effective sun exposure shall consume 600 to 800 IU of vitamin D3 daily to prevent deficiency. Older adults 65 years of age or more shall consume 800 to 1000 IU of vitamin D3 daily to prevent deficiency and to reduce the risk of fractures and falls. The American academy of pediatrics recommended that infants who are breastfed and children who consume less than one liter of vitamin D-fortified milk need 400 IU of vitamin D supplementation **(15).**

- **Screening for vitamin D deficiency**

U.S. Preventive Services Task Force (USPSTF) concluded that no studies evaluated the direct benefit or harms of screening for vitamin D deficiency.
American family physician strongly recommend that physicians should not measure 25(OH) D levels or prescribe vitamin D supplementation in the treatment of depression, fatigue, osteoarthritis, or chronic pain **(16).**
Over the last decade, there has been exceptional interest from all quarters in relation to the role of vitamin D in human health and disease, and in the possibility that improving vitamin D status would bring benefits in relation to not only skeletal, but also a myriad of non-skeletal health outcomes **(11).**
Among asymptomatic, community-dwelling populations with low vitamin D levels, the evidence suggests that treatment with vitamin D (with or without calcium) has no effect on mortality or incidence of fractures, falls, depression, diabetes, cardiovascular disease, cancer, or adverse events. The evidence is inconclusive about the effect of treatment on physical functioning and infection **(17).**

- **Treatment of Vitamin D deficiency**

Supplementation of vitamin D-replete individuals does not generate overall health benefits; however, correction of vitamin D deficiency remains essential and is described as a modifiable risk factor **(8).**
A number of controversies exist regarding appropriate treatment strategy for Vitamin D deficiency: vitamin D3 versus Vitamin D2, oral versus intramuscular (IM) administration, fixed or titrated dosing strategy, lower daily dose or higher intermittent dose **(18).**

Preparations:

Several preparations of vitamin D are available: Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 when compared with vitamin D2, has been shown to be more efficacious in achieving optimal 25 (OH) D levels, thus favoring vitamin

D3 as a treatment of choice **(19).**

Calcitriol is generally not suitable for treatment of vitamin D deficiency as it has a narrow therapeutic window resulting in an increased risk of hypercalcemia or hypercalciuria**.** We do not utilize calcitriol in most instances unless in the following circumstances: **(6).;** In renal failure where there is inability to convert 25(OH) D to 1,25(OH)2D.

- The patient manifests clinical signs of hypocalcemia
- Hypoparathyroidism (and the associated deficit in renal 1-hydroxylation)
- When the patient would be more likely to absorb calcitriol (e.g. following bariatric surgery)

Serum calcium concentrations and renal function must be monitored closely under these circumstances **(20).**

Calcidiol can be considered in patients with severe liver disease or fat malabsorption **(19).**

Supplementation with vitamin D increases serum 25(OH)D levels, but the increment depends upon both body weight and the baseline serum 25(OH)D concentration. Body weight affects the serum 25(OH)D response to both loading and maintenance doses of vitamin D, with larger doses being required. Lower baseline serum 25(OH)D levels are associated with larger increases in serum 25(OH) D for a given dose of vitamin D **(20).**

Levels are again repeated in 2-3 months. We feel the majority of these patients are at a relatively high risk of repeat vitamin D deficiency in the future, and they are counseled that this is life-long therapy. Of note, in obese individuals, steady state levels may take a longer time to reach and hence we often delay repeat measurement for an additional 1-3 months **(6).**

A higher-dose initial supplementation with vitamin D3 at 10,000 IU daily may be needed in high-risk adults who are vitamin D deficient (obese, African Americans, Hispanics, taking certain medications, malabsorption syndrome). Once serum 25-hydroxyvitamin D level exceeds 30ng/mL, 3000 to 6000 IU/day maintenance dose is recommended **(19).**

- **Routes of administration:**

Both oral and IM routes are effective for the treatment of vitamin D deficiency. In comparing oral versus IM treatment of vitamin D deficiency or insufficiency results showed that the vitamin D level after treatment in oral method was significantly higher than in injection one. In addition, oral method had better effect on serum 25(OH)D level, three months after therapy than injection route. Furthermore, oral therapy had better effect on serum 25(OH) D level in overweight persons **(21)**

For loading purposes, the IM route is less effective due to lag time in matching the 25(OH) D increment seen with oral administration. For maintenance purposes, more long-term information is needed in order to determine the appropriate dosing frequency. **(20).** 25(OH) D levels in the IM cholecalciferol group showed a sustained increase from baseline **(22).**

- **Toxicity:**

Vitamin D is a fat-soluble vitamin; hence, toxicity is possible, although rarely noted. Hypervitaminosis D results from excess oral intake and not due to excessive sunlight exposure **(19).** The recommended daily allowance (RDA) for vitamin D is 600 IU/day for adults 70 years or younger and 800 IU/day for those older than 70 years. The tolerable upper limit is 4000 IU/day; beyond this level risk of toxic effects increases **(23).**

The institute of Medicine considers a 25(OH)D level of 50 ng/mL (125 nmol /L) as reflective of the safe upper tolerable intake. Hypercalcemia and hypercalciuria are the hallmarks of excess vitamin D exposure and can eventually lead to nephrolithiasis, soft tissue calcification, and renal and cardiovascular damage. Vitamin D intoxication produces nonspecific symptoms that may include anorexia, weight loss, polyuria, and heart arrhythmias **(16).**

REFERENCES

1. Laird, E., J. Rhodes, and Rose Anne Kenny. "Vitamin D and inflammation: potential implications for severity of Covid-19." Ir Med J 113, no. 5 (2020): 81.
2. Zareef, T.A., Jackson, R.T. Knowledge and attitudes about vitamin D and sunlight exposure in premenopausal women living in Jeddah, and their relationship with serum vitamin D levels. J Health Popul Nutr 40, 38 (2021).
3. Buckley, A. J., Hannoun, Z., Lessan, N., Holick, M. F., & Barakat, M. T. (2017). Environmental determinants of previtamin D synthesis in the United Arab Emirates. Dermato-endocrinology, 9(1), e1267079.
4. Sassi F, Tamone C, D'Amelio P. (2018). Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrient; 10(11):1656.
5. Charoenngam, Nipith; Shirvani, Arash; Holick, Michael F. (2019). Vitamin D for skeletal and non-skeletal health: What we should know. Journal of Clinical Orthopaedics and Trauma, (), S0976566219303960.
6. Patel, R. M., Bazydlo, L., Brown, S. A., & Dalkin, A. C. (2021). Vitamin D Replacement in Adults: Current Strategies in Clinical Management. PRACTICAL GASTROENTEROLOGY, 17.
7. Kara, M., Ekiz, T., Ricci, V., Kara, Ö., Chang, K. V., & Özçakar, L. (2020). 'Scientific Strabismus' or two related pandemics: coronavirus disease and vitamin D deficiency. British Journal of Nutrition, 124(7), 736-741.
8. Bouillon, R., Manousaki, D., Rosen, C. et al. The health effects of vitamin D supplementation: evidence from human studies. Nature Reviews Endocrinology (2021).
9. Institute of Medicine (2011) Dietary reference intakes for calcium and vitamin D. The National Academies Press, Washington, D.C.
10. Sempos CT, Heijboer AC, Bikle DD, Bollerslev J, Bouillon R, Brannon PM, et al. Vitamin D assays and the definition of hypovitaminosis D. Results from the First International Conference on Controversies in Vitamin D. Br J Clin Pharmacol 2018;84:2194-207.
11. Cashman, K. D., van den Heuvel, E. G., Schoemaker, R. J., Prévéraud, D. P., Macdonald, H. M., & Arcot, J. (2017). 25-Hydroxyvitamin D as a biomarker of vitamin D status and its modeling to inform strategies for prevention of vitamin D deficiency within the population. Advances in Nutrition, 8(6), 947-957.
12. Yu H-J, Kwon M-J, Woo H-Y, et al: Analysis of 25-hydroxyvitamin D status according to age, gender, and seasonal variation. J Clin Lab Anal 30:905-911, 2016.
13. Hendawy, L. M., Botros, R. M., Sabry, I. M., Abromia, M. M., Marzouk, H. A., & Radwan, R. A. (2020). Vitamin D and Linear Growth in a Sample of Egyptian Adolescents. The Egyptian Journal of Hospital Medicine, 81(3), 1666-1671.
14. Lee, J.S., Kim, J.W. Prevalence of vitamin D deficiency in postmenopausal high- and low-energy fracture patient. Arch Osteoporos 13, 109 (2018).

15. Casey CF, Slawson DC, Neal LR. VItamin D supplementation in infants, children, and adolescents. Am Fam Physician. 2010 Mar 15;81(6):745-8. PMID: 20229973.
16. LeFevre, L. M., & LeFevre, N. M. (2018). Vitamin D screening and supplementation in community-dwelling adults: common questions and answers. American family physician, 97(4), 254-260.
17. Kahwati, L. C., LeBlanc, E., Weber, R. P., Giger, K., Clark, R., Suvada, K., ... & Viswanathan, M. (2021). Screening for vitamin D deficiency in adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA, 325(14), 1443-1463.
18. Francis, R. M., Aspray, T. J., Bowring, C. E., Fraser, W. D., Gittoes, N. J., Javaid, M. K., ... & Tanna, N. (2015). National Osteoporosis Society practical clinical guideline on vitamin D and bone health. Maturitas, 80(2), 119-121.
19. Sizar O, Khare S, Goyal A, et al. (2021) Vitamin D Deficiency. In: StatPearls [Internet]. Accessed 28 December 2021.
20. Ebeling P.R., R A Adler, G Jones et al. (2018). Therapeutics of vitamin D. European Journal of Endocrinology:179, R239–R259.
21. Shahrivari, M. (2011). Comparison of oral versus intramuscular treatment of vitamin D deficiency or insufficiency. In Endocrine Abstracts (Vol. 26). BioScientifica.
22. Gupta, N., Farooqui, K. J., Batra, C. M., Marwaha, R. K., & Mithal, A. (2017). Effect of oral versus intramuscular Vitamin D replacement in apparently healthy adults with Vitamin D deficiency. Indian journal of endocrinology and metabolism, 21(1), 131.
23. Ross AC, Taylor CL, Yaktine AL, Del Valle HB; Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine. Dietary .Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Press; 2011.