Open Access Indonesian Journal of Medical Reviews

Journal Homepage: https://hmpublisher.com/index.php/OAIJMR

Vitamin D and Its Role in Modulating Immune System: A Narrative Literature Review

Chaula Putri Rizkia[1*]

[1]Department of Clinical Nutrition, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

ARTICLE INFO

Keywords:
Calcium
Cholecalciferol
Immune system
Immunology
Vitamin D

***Corresponding author:**
Chaula Putri Rizkia

E-mail address:
chaulaputri@gmail.com

The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/oaijmr.v3i1.282

A B S T R A C T

Vitamin D is recognized for its pivotal role in maintaining calcium-phosphorus homeostasis and regulating bone metabolism. The beneficial effects of vitamin D on the protective function of the immune system are seen in the innate immune system. It increases the production of defensin β2 and cathelicidin by macrophages, monocytes, and keratinocytes in response to infection. Cathelicidin is produced by neutrophils, macrophages, and cells lining epithelial surfaces such as skin, respiratory, and digestive tracts. Recent research showed that vitamin D exerts potent immunomodulatory effects by modulating the innate and adaptive immune systems. This led to the recognition of various disease conditions associated with vitamin D deficiency. This narrative review aimed to describe the molecular mechanisms for the vitamin D immunomodulatory effect.

1. Introduction

Vitamin D is a fat-soluble vitamin and is known as a prohormone due to its active form, 1,25(OH)$_2$D3 or calcitriol, which is classified as a steroid hormone.[1] Two main forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol).[2,3] Ergocalciferol is a derivative of plant sterol ergosterol, while cholecalciferol is synthesized in the skin from 7-dehydrocholesterol by exposure to sunlight.[4] This is a non-enzymatic process where 7-dehydrocholesterol is a breakdown by ultraviolet B (UVB) radiation to form pre-vitamin D3.

Besides its classical function in maintaining calcium homeostasis, vitamin D can also modulate the innate and adaptive immune system.[5-7] Vitamin D deficiency has been reported in several conditions associated with infectious, inflammatory, and dysregulation of the immune system, such as diabetes or asthma.[7,8] It has also been reported in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. The role of vitamin D in immune system regulation is mediated by calcitriol and vitamin D receptor (VDR) as well as a 1α-hydroxylase enzyme (CYP27B1), which are expressed in various tissues of the body, including immune cells such as B lymphocytes, T lymphocytes, monocytes, macrophages, and dendritic cells.[7,9] This narrative review aimed to describe the molecular mechanisms for the vitamin D immunomodulatory effect.

Sources of vitamin D

Vitamin D can be obtained from natural food sources, fortified food, or supplement. However, the main source comes from the synthesis in the skin induced by sun exposure.[10,11] The ideal intensity of UV radiation is between 11:00 am to 1:00 pm or UVB radiation with a wavelength of 290-315 nm.[12] To achieve optimal vitamin D levels, sun exposure should reach the minimal erythemal dose (MED) - The lowest dose on a small skin area with a specific wavelength causes slow reddish-pink erythema on the skin.[12] Exposing the face, hands, arms, and legs to sunlight without sunscreen for 5-30 minutes between 10:00 am to 4:00 pm every day or twice a week is sufficient to increase vitamin D levels.[13] The duration required to achieve the desired level varies depending on skin pigmentation, season, and geographic location.[13,14]

Fish are known as an excellent source of vitamin D, especially oily fish, including salmon, tuna, and mackerel.[11,13] Fish oil contains the highest concentration, with a tablespoon of cod liver oil providing up to 1360 International Units (IU).[13] However, meat, egg yolks, and beef liver contain only small amounts of vitamin D3. Common mushroom species can produce nutritionally significant levels of vitamin D when they are subjected to an ultraviolet (UV) radiation source, such as sunshine or a UV lamp. D2 is the most prevalent kind of vitamin D found in mushrooms.[13] Vitamin D is also added to fortified foods such as milk, infant formula, orange juice, butter, yogurt, cereal, and others.[13,15]

Vitamin D metabolism

Vitamin D2 and D3 are subjected to two stages of enzymatic hydroxylation to become active. The first stage involves the conversion of vitamin D to 25-hydroxyvitamin D (25(OH)D) in the liver by 25-hydroxylase (CYP2R1).[3,4] Once 25(OH)D reaches the circulation, it's transported to the kidney to be further metabolized by the enzyme 1α-hydroxylase (CYP27B1) into the biologically active metabolite, 1,25-dihydroxy-vitamin D ($1,25(OH)_2D3$). The $1,25(OH)_2D3$, also known as calcitriol, is the active form of vitamin D and a steroid hormone. Even though the kidney is the main source of calcitriol in circulation, the CYP27B1 enzyme is also expressed by extra-renal tissues, including the skin, lungs, intestines, prostate, and endocrine glands such as the parathyroid, pancreatic cells, thyroid, testes, ovaries, placenta, and immune system cells.[16] Both 25(OH)D and $1,25(OH)_2D3$ in circulation are bound to a specific plasma protein called vitamin D binding protein (DBP).[4] $1,25(OH)_2D3$ increases calcium absorption in the gut and the reabsorption in the kidney when blood calcium levels decrease. Meanwhile, the thyroid gland releases the hormone calcitonin, which converts 25(OH)D into 24,25-dihydroxy-vitamin D3 with the help of the enzyme 24-hydroxylase (CYP24A1) when blood calcium levels increase. The metabolite 24,25-dihydroxy-vitamin D3 is an inactive form of vitamin D that increases calcium absorption from the gut but lowers serum calcium and phosphorus to increase bone mineralization.[3,10] Due to its lipid-soluble nature, adipose tissue is identified as the major site of vitamin D storage.[10] This is related to the VDR and its metabolic enzymes expressed by adipocytes.[11] The vitamin D metabolism products are excreted through bile and feces. Meanwhile, in urine, the metabolites are found only in small amounts because the kidneys undergo a reuptake process of the metabolites bound to DBP and mediated by the cubilin-megalin receptor system.[4,10]

Vitamin D intake

According to the Indonesian Recommended Dietary Allowances (RDA), the vitamin D requirement for children and adults is 15 mcg or 600 IU, while individuals over 65 are expected to consume 20 mcg or 800 IU.[17] The American Association of Clinical Endocrinologist recommends daily vitamin D3 supplementation of 1000-2000 IU to maintain optimal serum 25(OH)D levels. Higher doses may be needed for conditions such as obesity, malabsorption, and certain ethnicities.[14] The intoxication is rare and usually caused by excessively high doses.[16] A dose of more than 50,000 IU per day can increase 25-hydroxyvitamin D levels to more than 150 ng per

milliliter (374 nmol per liter) and is associated with hypercalcemia and hyperphosphatemia.[16]

Vitamin D status

Serum 25(OH)D levels reflect the overall vitamin D from the synthesis in the skin, food, or supplements.[18] Therefore, it indicates an individual's vitamin D status[10,18], with a half-life of 2-3 weeks. $1,25(OH)_2D3$ is not an ideal marker for determining an individual's vitamin D status because it is regulated homeostatically and has a short half-life of 4-8 hours.[19] The Endocrine Society Guideline's Reference Values for Vitamin D Status include 25(OH)D levels of ≤20 ng/ML, 21-29 ng/ML, and ≥30 ng/mL in the deficient, insufficient, and sufficient categories.[14,19] Various research indicated that vitamin D deficiency and insufficiency remain high worldwide, including in tropical countries.[20-22]

The South East Asian Nutrition Surveys (SEANUTS) conducted in 2010-2011 identified factors contributing to high deficiency rates among ASEAN populations, including obesity, skin pigmentation, sun avoidance habits, and more covered clothing.[22] The use of clothing that covers more skin, specifically among women from certain ethnic or religious groups, can reduce the amount of skin exposed to sunlight, resulting in lower levels of 25(OH)D.[21-23] Furthermore, the use of sunscreen with a sun protection factor (SPF) 30 reduces vitamin D synthesis in the skin by more than 95%.[21] Aside from these factors, genetic variations in certain populations can affect 25(OH)D levels.[24,25] These genetic variations, called polymorphisms, occur in at least 1% of the population.[25] An intervention research conducted by Tomei et al. showed that polymorphisms in the rs731236 (VDR) and rs7116978 (CYP2R1) genes were significantly associated with vitamin D status.[24] Meanwhile, various research showed that polymorphisms in genes such as VDR, and the CYP24A1 enzyme, CYP27B1, and others could have clinical implications for individuals.[25]

Vitamin D – Mechanism of action

The vitamin D genomic action begins when $1,25(OH)_2D3$ binds to VDR, which then interacts with the retinoid X receptor (RXR) to form a VDR/RXR heterodimer binding to vitamin D-responsive elements (VDRE).[6,26,27] This process initiates several gene expressions in various types of cells and synthesizes proteins in different cellular processes.[2,4,26] VDR is found in the nucleus of cells involved in calcium and phosphate metabolism.[26] These cells include keratinocytes, hepatocytes, pancreatic and immune system cells such as macrophages, and monocytes.[10,26] Vitamin D activity is also determined by VDREs found in several human genes involved in cell proliferation, differentiation, and apoptosis.

Nrf2 and the anti-aging-gene Klotho are two important genes activated by vitamin D. After this activation, the work of various cellular components is initiated.[27] These components include antioxidant enzymes such as catalase, detoxification enzymes involving alcohol dehydrogenase, and cytochrome p450. Furthermore, Klotho also influences the Na+K+ATPase enzyme involved in calcium homeostasis. Besides enzymes, these genes activate various signal transduction components. One example is peroxisome proliferator-activated receptor gamma (PPAR-γ), which plays a role in glucose homeostasis, lipid metabolism, and adipokine regulation, affecting insulin sensitivity.[26] The number of cellular components is influenced by VDRE, which underlies vitamin D involvement in various disease pathogenesis, including cancer, autoimmune diseases, cardiovascular disease, and infections.[4,26] Vitamin D also controls the oxidative stress level in the body, which affects the aging process and degenerative diseases such as diabetes mellitus, heart disease, and dementia.[2,26]

Immunomodulatory effects of vitamin D

The immunomodulatory effects of a vitamin D-mediated by 1,25(OH)D (calcitriol) - are based on genomic response and its ability to modify gene transcription.[6] The 1,25(OH)D activity enhances and

triggers natural immune responses to pathogens. This response can occur directly or as a continuation of instructions from natural immune responses.[5,28] VDR is expressed by various immune cells such as T cells, B cells, and antigen-presenting cells (APCs). Since these cells can synthesize active vitamin D metabolites, the autocrine function in immune cells remains unaffected by renal control.[29]

Vitamin D's beneficial effects on the protective function of the immune system are seen in the innate immune system. It increases the production of defensin β2 and cathelicidin by macrophages, monocytes, and keratinocytes in response to infection. Cathelicidin is produced by neutrophils, macrophages, and cells lining epithelial surfaces such as skin, respiratory, and digestive tracts. Additionally, it has broad-spectrum antimicrobial activity against certain gram-positive and gram-negative bacteria, viruses, and fungi.[5] Macrophages recognize the lipopolysaccharide component of bacteria through toll-like receptors (TLR).[29] TLR binding triggers an increase in the expression of 1-α-hydroxylase and VDR, which then forms a complex between the vitamin D-VDR-RXR with VDRE on the cathelicidin and beta-defensin 4 genes, leading to the transcription of these proteins.

Vitamin D inhibits the proliferation and differentiation of B cells and immunoglobulin secretion. Furthermore, it suppresses T cells' proliferation and shifts the Th1 phenotype to Th2. Vitamin D affects the T cells' maturation and facilitates the induction of regulatory T cells (Treg). This results in a decrease in pro-inflammatory cytokines (IL-17, IL-21) production with an increase in anti-inflammatory cytokines, such as IL-10.[29] Prietl et al. conducted a clinical trial on 57 healthy subjects who were given high-dose vitamin D supplementation.[30] The results showed that sufficient levels affected the number of Treg cells. A decrease in the number or function of T_{reg} cells can increase the autoimmune diseases risk.[30,31]

Vitamin D can also inhibit monocytes from producing pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and TNFα (Table 1). In addition, it inhibits the differentiation and maturation of dendritic cells by maintaining an immature phenotype as indicated by the decreased expression of major histocompatibility class (MHC) class II molecules, the cluster of differentiation (CD) 86 (co-stimulatory molecule), IL-12, CD54 (adhesion molecule), increased expression of CCR5 (chemokine receptor), DEC205 (antigen uptake receptor), F4/80 (macrophage marker), and CD40.[29,31]

Table 1. Vitamin D regulation of the immune system.

1,25(OH)D (Calcitriol) effects on immune system[11,29,31]	**Innate immune system**
	↑ Antimicrobial peptide e.g. Cathelicidin, β-defensin
	↑ Monocyte and macrophage response
	↓ Differentiation, maturation, and activation of dendritic cells
	↑ T-reg
	Adaptive immune system
	Th1 → Th2 shift: ↓ IFN **γ**, TNF **α**, IL-2 ↑ IL-4 ↑ IL-5, ↑ IL-10 ↓ IL-12
	↓ Th17: ↓ IL-17, IL-23
	↓ B cells proliferation and differentiation into plasma cells

2. Conclusion

Vitamin D can lower the risk of developing several diseases associated with infection, inflammation, and autoimmunity when its level is within the normal range.

3. References

1. Cutolo M, Paolino S, Sulli A, Vanessa S, Carmen P, et al. Vitamin D, steroid hormones, and autoimmunity. Ann. NY Acad Sci. 2014; 1317(1): 39-46.
2. Wimalawansa SJ. Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. Biology. 2019; 8(2): 30.
3. Combs GF, McClung JP. The vitamins: Fundamental aspects in nutrition and health. 5th ed. United Kingdom: Elsevier. 2017.
4. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical application. Chem Biol. 2014; 21(3): 319–29.
5. Athanassiou L, Mavragani CP, Koutsilieris M. The immunomodulatory properties of vitamin D. Mediterranean Journal of Rheumatology. 2022: 33(1): 7-13.
6. Rak K, Bronkowska M. Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of type 1 diabetes mellitus—A narrative review. Molecules. 2019; 24(1).
7. Sassi F, Tamone C. Vitamin D: Nutrient, hormone, and immunomodulator. Nutrients. 2018; 10(11).
8. Ao T, Kikuta J, Ishii M. The effects of vitamin D on immune system and inflammatory diseases. Biomolecules. 2021; 11(11).
9. Skrobot A, Demkow U, Wachowska M. Immunomodulatory role of vitamin D: A review. Adv Exp Med Biol – Clinical and Experimental Biomedicine. 2018; 2: 13–23.
10. Overview of vitamin D. Institute of Medicine (US) Committee to review dietary reference intakes for vitamin D and calcium; Ross AC, Taylor CL, Yaktine AL, et al., editors. Washington (DC): National Academies Press (US); 2011.
11. Dominguez LJ, Farruggia M, Veronese N, Barbagallo, M. Vitamin D sources, metabolism, and deficiency: available compounds and guidelines for its treatment. Metabolites. 2021; 11(4).
12. Setiati S, Oemardi M, Sutrisna B. The role of ultraviolet-B from sun exposure on vitamin D3 and parathyroid hormone level in elderly women in Indonesia. Asian J Gerontol Geriatr. 2007; 2(3): 126-32.
13. National Institutes of Health Office of Dietary Supplements. Vitamin D – fact sheets for health professional. National Institute of Health; 2022.
14. Holick MF, Binkley NC, Bichoff-Ferrari HA, Gordon CM, Hanley DA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice. J Clin Endocrinol Metab. 2011; 96(7): 1911–30.
15. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-81.
16. Toha SS, Fiqri A, Nurrachmat M. Role of vitamin D3 analogues in dermatology. CDK. 2019; 46(8): 530-4.
17. Indonesian Health Ministry. Regulation of The Minister of Health of Republic Indonesia Number 28 2019: Recommended Dietary Allowances. 2019.
18. Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect. 2019; 8: R27-R43.
19. Martens PJ, et al. High serum vitamin D concentrations, induced via diet, trigger immune and intestinal microbiota alterations leading to type 1 diabetes protection in NOD mice. Fontier in Immunology. 2022.
20. Vranić L, Mikolašević I, Milić S. Vitamin D deficiency: Consequence or cause of obesity?. Medicina (Kaunas). 2019; 55(9): 541.

21. Nair R, Maseeh A. Vitamin D: The "sunshine" vitamin. J Pharmacol Pharmacother. 2012; 3(2): 118-26.
22. Poh BK, Rojroongwasinkul N, Nguyen BKL, Sandjaja, TalibRuzita A, et al. 25-hydroxy-vitamin D demography and the risk of vitamin D insufficiency in the South East Asian Nutrition Surveys (SEANUTS). Asia Pac J Clin Nutr. 2016; 25(3): 538-48.
23. Lin E, Armstrong-Moore D, Liang Z, et al. Contribution of adipose tissue to plasma 25-OH D concentrations during weight loss following gastric bypass surgery. Obesity. 2011; 19(3): 588-94.
24. Sidiropoulou P, Docea AO, Nikolaou V, Katsarou M, Spandidos DA, et al. Unraveling the roles of vitamin D status and melanin during Covid 19 (Review). Int J Mol Med. 2021: 47: 92-100
25. Tomei S, Singh P, Mathew R, Mattei V, Garand M, et al. The role of polymorphism in vitamin D-Related genes in response to vitamin D supplementation. Nutrients. 2020; 12: 2608.
26. Sattar N, Hussain F, Shaheen S, Aleem S, Aslam S. Role of vitamin D receptor (VDR) genetic polymorphism in onset of type 2 diabetes mellitus. Lett Health Biol Sci. 2019; 4(1): 7-15.
27. Berridge MJ. Vitamin D, reactive oxygen species and calcium signalling in ageing and disease. Philos Trans R Soc Lond B Biol Sci. 2016; 371(1700): 20150434.
28. Yani FY. The role of vitamin D in children's respiratory diseases. Jurnal Kesehatan Andalas. 2019; 8(1).
29. Aranow C. Vitamin D and the immune system. J Investig Med. 2011; 59(6): 881-6.
30. Prietl B, Treiber G, Mader JK, Hoeller E, Wolf M, et al. High-dose cholecalciferol supplementation significantly increases peripheral CD4+ Tregs in healthy adults without negatively affecting the frequency of other immune cells. Eur J Nutr. 2014; 53: 751-9.
31. Martens PJ, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's effect on immune function. Nutrients. 2020; 12: 1248.