IJHS

Editorial

Vitamin D at the intersection of health and disease: The immunomodulatory perspective

Aisha Farhana[1]*, Yusuf Saleem Khan[2], Abdullah Alsrhani[1]

[1]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Sakaka, Aljouf Province, Saudi Arabia, [2]Department of Anatomy, College of Medicine, University of Hail, Hail, Hail Province, Saudi Arabia

Address for correspondence:
Aisha Farhana, Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Sakaka, Aljouf Province, Saudi Arabia.
E-mail: afarhana@ju.edu.sa

WEBSITE: ijhs.org.sa
ISSN: 1658-3639
PUBLISHER: Qassim University

Vitamin D is pivotal to the maintenance of human health and preventing diseases.[1] Being a highly studied vitamin, vitamin D is required for the functioning of almost all the cells of the human body. Recognized for its ability to support musculoskeletal health, the function of vitamin D extends to neurological and cognitive junctions, gastrointestinal functions, blood pressure regulation, glucose metabolism, and physiological cellular functions, besides its hormonal actions to maintain calcium and phosphorous homeostasis.[2-4] Recently, scientific interest has riveted toward the immune regulatory functions of vitamin D. Nearly, all the immune cells express vitamin D receptor (VDR), hence pointing to its ability to modulate innate and adaptive immune mechanisms.[5,6] This editorial presents the current knowledge of the functional influence of vitamin D on health and disease, with emphasis on the immunoregulatory mechanisms. It also discusses the possible benefits of vitamin D as therapeutics for degenerative, autoimmune, allergic, and infectious disorders.

Vitamin D, also termed calciferol, is synthesized by thermal-photochemical transformation of cutaneous 7-dehydrocholesterol upon sun (UVB) exposure, and further metabolized by the liver to 25'OH-vitD, the main circulating form, calcidiol. The subsequent step converting 25'OH-D to hormonal form, 1,25(OH)2D (calcitriol), occurs majorly in the kidney but also in paracrine/autocrine tissues such as parathyroid gland, intestinal epithelium, prostate, breast, and immune cells.[7,8] Although calcitriol is the bioactive form, vitamin D concentrations are assessed by measuring calcidiol, generated by first hydroxylation in the liver.[9] Hence, there exist discrepancies in addressing vitamin D deficiencies in the general population. It must therefore be acknowledged that no single standard or methodology defining the normal levels of vitamin D exists thus far. Due to the connection of sun exposure to vitamin D activation, it is conjectured that cutoff serum values reflect seasonal variation, wherein normal values in late winter to early spring are approximately 30 ng/mL (~75 nmol/L).[10] A level ≥20 ng/mL is considered sufficient, 11–20 ng/mL is considered inadequate, and a serum concentration ≤10 ng/mL is considered a deficient state. Although vitamin D intake to achieve optimal serum values remains debatable, the safest amounts are approximated between 800–2000 IU of dietary vitamin D yielding a serum value of 20–50 ng/mL of 25(OH) D. The serum concentration of 25-(OH)D determines the nutritional status of vitamin D in an individual.

The intricate connection between vitamin D and the immune system is yet to be fully uncovered, however, numerous studies have deciphered that vitamin D lies at the key regulatory junctures of innate and adaptive immune responses.[11] The extensive immune effect of vitamin D is facilitated by the strategic expression of the VDR and inducible enzyme 25-hydroxyvitamin D 1a-hydroxylase (CYP27B1) in most immune cells.[12] Furthermore, about 3–4% of the genome-spanning immune effectors are regulated by vitamin D through VDR and subsequent heterodimerization with nuclear retinoid X receptor-α.[13,14]

Although both innate and adaptive responses are regulated by vitamin D, it prominently activates the innate responses, while the effect on adaptive immune responses is majorly suppressive.[15] The immune mechanisms that underlie vitamin D-regulated inflammation occur through 25(OH)D and 1,25(OH)2D forms. The 1,25(OH)2D form is multifactorial in regulating immune homeostasis through effectors such as B- and T-lymphocytes, monocytes, macrophages, natural killer cells, and dendritic cells. In macrophages, immune signals mediate the induction of CYP27B1 to subsequently synthesize 1,25(OH)D at the infection site, thereby inducing genes associated with antimicrobial peptides. 1,25(OH)2D induces specific chemical modulators such as cathelicidin, which are effective in exerting antibacterial and antiviral

effects.[14,15] Furthermore, the 1,25(OH)2D form also maintains immune tolerance by modulating the surface expression of MHCII molecules, co-stimulatory signals, and immunogenic cytokines.[16] Thus, the 1,25(OH)D form stimulates the inflammatory immune regulatory axis.[16] Therefore, in healthy individuals, the balance of 25(OH)D to 1,25(OH)2D form shifts toward normal 1,25(OH)2D and low 25(OH)D. Contrarily, individuals with health conditions demonstrate higher serum levels of 1,25(OH)D, wherein pro-inflammatory and inflammatory cytokines are increased to facilitate inflammatory responses to counter disease.

Vitamin D deficiency intensifies the risk of immune-associated diseases; autoimmune diseases, allergies, sepsis, viral and bacterial infections, and neurodegenerative diseases. Epidemiological and clinical studies confirm the association of vitamin D deficiency with autoimmune diseases.[17] In rheumatoid and psoriatic arthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, irritable bowel disease, and idiopathic inflammatory myopathies, vitamin D deficiencies have been observed.[18] Moreover, the deficiency may be linked to the development and exacerbation of disease pathologies. It is interesting to note that during the surge of autoimmune diseases, the worldwide prevalence of vitamin D deficiency was also noted.[19,20] Autoimmune diseases show a peak in winter months, wherein sun exposure is limited and is often linked with vitamin D deficiency. This points to the function of vitamin D in autoimmune disease development and immune tolerance. Adequate dosages of vitamin D are noted to alleviate inflammation and reduce pain and symptoms of autoimmune rheumatic diseases. Autoimmune thyroid diseases, especially Hashimoto's thyroiditis, are linked to vitamin D deficiency.[21] The manifestation of these diseases usually encompasses inflammatory processes, wherein vitamin D harbors the ability to normalize the inflammation process and alleviate pain and other disease symptoms.

The global prevalence of vitamin D deficiency vis-à-vis allergic responses has shown an upward trend within the past 50–70 years.[22] With observational and interventional studies, a plausible contribution of vitamin D deficiency in atopic dermatitis, asthma, sinusitis, and food allergies has become obvious.[23-25] Allergic diseases are manifested through an intersection of genetic traits and environmental factors, wherein vitamin D deficiency can be categorized as an important environmental mediator.[26] Vitamin D significantly modulates the allergen-induced inflammatory mechanisms, through skewing of the Th1/Th2 responses and the activation of mast cells.[27] Clinical studies have demonstrated that vitamin D supplementation reduces allergic symptoms in pollen-induced allergies in children. Increased risk of food and skin allergies are also associated with vitamin D deficiency.[28] The ability of vitamin D to regulate mast cell function is a defining factor in slowing down histamine release and hence subduing the effectors of allergic responses. The current knowledge points that disturbed vitamin D signaling due to deficiency may also arbitrate IgE-mediated allergic responses and the development of type I hypersensitivity.

Vitamin D maintains a balanced immune response to effectively fight infections besides its functional significance in the pathogenesis, prognosis, clinical symptoms, and treatment of numerous diseases. Vitamin D significantly regulates antibacterial and antiviral inflammatory responses. It is easy to conjecture that viral diseases are more widespread during the winter months, which coincides with an overall observed low level of vitamin D. Interestingly, vitamin D was researched to be a putative immune regulating nutrient against COVID-19.[29] The stimulation of antimicrobials and the immunomodulatory response of vitamin D has been significant in subduing cytokine release. Maintaining normal serum levels is associated with a reduced risk of acute respiratory tract infections and a decrease in illness span. Vitamin D therapy is suggested as a novel therapeutic approach against tuberculosis.[30] Numerous clinical studies and cohorts have identified severely low vitamin D in tuberculosis patients. Some randomized controlled trials showed that adjunct therapy with vitamin D resulted in increased intracellular killing of tuberculosis bacteria within the macrophages.[31] However, the protective and therapeutic efficacy of vitamin D needs more conclusive data to understand accurate modalities and dosage for effective protection and treatment. Studies on vitamin D deficiency and HIV highlight its function in T and B-cell modulation and macrophage chemotaxis.[32] Vitamin D induces antiviral genes, downregulates viral receptors in $CD4^+$ T-cells, and enhances HIV-1-restrictive cellular phenotypes leading to inhibition of HIV infection of T-cells.[33] Although further clinical research is mandated, the current knowledge is excessively promising. In addition, due to inherent antimicrobial effector mechanisms, optimum vitamin D levels may restrict superinfections in HIV patients and help to decrease morbidity.[34]

Notably, the significance of vitamin D deficiency in the manifestation of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, vascular dementia, and macular degeneration has gained prominence.[35] Optimum vitamin D is instrumental in preventing neurodegenerative diseases and delaying onset and disease progression. The biological role of vitamin D in ameliorating neurodegeneration is manifested through its genomic and non-genomic actions that impede inflammation, maintain signaling events and calcium homeostasis, alleviate oxidative stress, and subsequently prevent protein aggregation and plaque development.[36,37] Furthermore, classified as a neurosteroid, vitamin D exerts its transcription regulatory effects on thyroid hormones, androgens, glucocorticoids, and vitamin A, influencing a vast number of genes involved in maintaining healthy neurological reflexes.[38]

Although current data are limited, the effect of vitamin D deficiency on metabolic disease cannot be less emphasized. Clinical evidence potentiates vitamin D deficiency as the risk

factor for insulin resistance and the development of type 2 diabetes.[39,40] Vitamin D regulates normal serum calcium and reactive oxygen and nitrogen species in the β-cells.[41] The increase of serum calcium and reactive species is an incident in diabetes and coincident with low concentrations of vitamin D. In addition, optimal vitamin D serum values encompass reduced colorectal and bladder cancer risk, with sporadic reports from other cancer types.[42] The modulatory action of vitamin D in cellular proliferation and differentiation is central to its response to cancer. Important pathways deranged in cancers such as apoptosis, differentiation, cell signaling, and cell cycle progression are regulated by vitamin D.[43] Recent studies have emphasized the efficacy of vitamin D in preventing and improving cancer management.[44]

Vitamin D deficiency presents an important yet easily modifiable risk factor for developing a plethora of diseases. It is humbling to note that global deficiency prevails with significant health-care costs, despite being correctable through accurate serum estimations, dietary and supplemental methods, and easily through sun exposure.

Conflict of Interest Statement

The author declares no competing interests.

References

1. Murdaca G, Gangemi S. Vitamin D in health and disease. Biomedicines 2022;11:10.
2. Di Mauro G, Musarra M, Similia SD, Puzzolo D, Minutoli L, Morace C, *et al*. The multiple effects of Vitamin D on chronic diseases. World Cancer Res J 2024;11:e2739.
3. Akimbekov NS, Digel I, Sherelkhan DK, Lutfor AB, Razzaque MS. Vitamin D and the host-gut microbiome: A brief overview. Acta Histochem Cytochem 2020;53:33-42.
4. Gu JC, Wu YG, Huang WG, Fan XJ, Chen XH, Zhou B, *et al*. Effect of vitamin D on oxidative stress and serum inflammatory factors in the patients with type 2 diabetes. J Clin Lab Anal 2022;36:e24430.
5. Bikle DD. Vitamin D regulation of immune function. Curr Osteoporos Rep 2022;20:186-93.
6. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: Antibacterial, antiviral, anti-inflammatory. JBMR Plus 2021;5:e10405.
7. Herrmann M. Assessing vitamin D metabolism-four decades of experience. Clin Chem Lab Med 2023;61:880-94.
8. Saponaro F, Saba A, Zucchi R. An update on vitamin D metabolism. Int J Mol Sci 2020;21:6573.
9. Makris K, Sempos C, Cavalier E. The measurement of vitamin D metabolites: Part I-metabolism of vitamin D and the measurement of 25-hydroxyvitamin D. Hormones (Athens) 2020;19:81-96.
10. Hribar M, Hristov H, Gregorič M, Blaznik U, Zaletel K, Oblak A, *et al*. Nutrihealth study: Seasonal variation in vitamin D status among the Slovenian adult and elderly population. Nutrients 2020;12:1838.
11. Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. Nutrients 2020;12:2097.
12. Lin R. Crosstalk between vitamin D metabolism, VDR signalling, and innate immunity. Biomed Res Int 2016;1375858.
13. Pike JW, Meyer MB. Fundamentals of vitamin D hormone-regulated gene expression. J Steroid Biochem Mol Biol 2014;144:5-11.
14. Koivisto O, Hanel A, Carlberg C. Key vitamin D target genes with functions in the immune system. Nutrients 2020;12:1140.
15. Ismailova A, White JH. Vitamin D, infections and immunity. Rev Endocr Metab Disord 2022;23:265-77.
16. Fabbri A, Infante M, Ricordi C. Editorial-vitamin D status: A key modulator of innate immunity and natural defense from acute viral respiratory infections. Eur Rev Med Pharmacol Sci 2020;24:4048-52.
17. Sîrbe C, Rednic S, Grama A, Pop TL. An update on the effects of vitamin D on the immune system and autoimmune diseases. Int J Mol Sci 2022;23:9784.
18. Athanassiou L, Kostoglou-Athanassiou I, Koutsilieris M, Shoenfeld Y. Vitamin D and autoimmune rheumatic diseases. Biomolecules 2023;13:709.
19. Cui A, Xiao P, Ma Y, Fan Z, Zhou F, Zheng J, *et al*. Prevalence, trend, and predictor analyses of vitamin D deficiency in the US population, 2001-2018. Front Nutr 2022;9:965376.
20. Abo-Zaid MA, Hamdi HA, Elashmawy NF. Vitamin D and immunity: A comprehensive review of its impact on autoimmunity, allergy suppression, antimicrobial defense, and cancer inhibition. Egypt J Immunol 2023;30:47-66.
21. Durá-Travé T, Gallinas-Victoriano F. Autoimmune thyroiditis and vitamin D. Int J Mol Sci 2024;25:3154.
22. Alswailmi FK, Sikandar MZ, Shah SI. Biological roles of vitamin D and immunoglobulin E: Implications in allergic disorders. Pak J Med Health Sci 2020;14:495-8.
23. Psaroulaki E, Katsaras GN, Samartzi P, Chatziravdeli V, Psaroulaki D, Oikonomou E, *et al*. Association of food allergy in children with vitamin D insufficiency: A systematic review and meta-analysis. Eur J Pediatr 2023;182:1533-54.
24. Yao TC, Tu YL, Chang SW, Tsai HJ, Gu PW, Ning HC, *et al*. Suboptimal vitamin D status in a population-based study of Asian children: Prevalence and relation to allergic diseases and atopy. PLoS one 2014;9:e99105.
25. Sikorska-Szaflik H, Sozańska B. The role of vitamin D in respiratory allergies prevention. Why the effect is so difficult to disentangle? Nutrients 2020;12:1801.
26. Kojima R, Shinohara R, Kushima M, Horiuchi S, Otawa S, Miyake K, *et al*. Effect of birth season on allergic rhinitis and cedar pollinosis considering allergen and vitamin D exposure: The Japan environment and children's study (JECS). Allergol Int 2023;72:411-7.
27. Lipińska-Opałka A, Tomaszewska A, Kubiak JZ, Kalicki B. Vitamin D and immunological patterns of allergic diseases in children. Nutrients 2021;13:177.
28. Jerzyńska J, Stelmach W, Rychlik B, Majak P, Podlecka D, Woicka-Kolejwa K, *et al*. Clinical and immunological effects of vitamin D supplementation during the pollen season in children with allergic rhinitis. Arch Med Sci 2018;14:122-31.
29. Kumar R, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. Virus Res 2021;292:198235.
30. Ganmaa D, Uyanga B, Zhou X, Gantsetseg G, Delgerekh B, Enkhmaa D, *et al*. Vitamin D supplements for prevention of tuberculosis infection and disease. N Engl J Med 2020;383:359-68.
31. Chandra H, Rahman A, Yadav P, Maurya G, Shukla SK. Effect of adjunct vitamin D treatment in vitamin D deficient pulmonary tuberculosis patients: A randomized, double blind, active controlled clinical trial. Indian J Tuberc 2024;71:170-8.
32. Wang Y, Huang X, Wu Y, Li A, Tian Y, Ren M, *et al*. Increased risk of vitamin D deficiency among HIV-infected individuals: A systematic review and meta-analysis. Front Nutr 2021;8:722032.

33. Qurban R, Saeed S, Kanwal W, Junaid K, Rehman A. Potential immune modulatory effect of vitamin D in HIV infection: A review. Clin Nutr ESPEN 2022;47:1-8.
34. Lee S, Lee JE, Lee SO, Sim YK, Lee SH. Influence of vitamin D Deficiency on the development of opportunistic infection in people living with HIV/AIDS (PWHAs). J Am Coll Nutr 2021;40:545-50.
35. Wang W, Li Y, Meng X. Vitamin D and neurodegenerative diseases. Heliyon 2023;9:e12877.
36. Holick MF, Mazzei L, García Menéndez S, Martín Giménez VM, Al Anouti F, Manucha W. Genomic or non-genomic? A question about the pleiotropic roles of vitamin D in inflammatory-based diseases. Nutrients 2023;15:767.
37. Anwar MJ, Alenezi SK, Alhowail AH. Molecular insights into the pathogenic impact of vitamin D deficiency in neurological disorders. Biomed Pharmacother 2023;162:114718.
38. Wassif GA, Alrehely MS, Alharbi DM, Aljohani AA. The impact of vitamin D on neuropsychiatric disorders. Cureus 2023;15:e47716.
39. He LP, Song YX, Zhu T, Gu W, Liu CW. Progress in the relationship between vitamin D deficiency and the incidence of type 1 diabetes mellitus in children. J Diabetes Res 2022;2022:5953562.
40. Maddaloni E, Cavallari I, Napoli N, Conte C. Vitamin D and diabetes mellitus. Front Horm Res 2018;50:161-76.
41. Yaribeygi H, Maleki M, Sathyapalan T, Iranpanah H, Orafai HM, Jamialahmadi T, *et al*. The molecular mechanisms by which vitamin D improve glucose homeostasis: A mechanistic review. Life Sci 2020;244:117305.
42. Muñoz A, Grant WB. Vitamin D and cancer: An historical overview of the epidemiology and mechanisms. Nutrients 2022;14:1448.
43. Sobhi P, Bahrami M, Mahdizadeh F, Fazaeli A, Babaei G, Rezagholizadeh L. Vitamin D and potential effects on cancers: A review. Mol Biol Rep 2024;51:190.
44. Chandler PD, Chen WY, Ajala ON, Hazra A, Cook N, Bubes V, *et al*. Effect of vitamin D3 supplements on development of advanced cancer: A secondary analysis of the VITAL randomized clinical trial. JAMA Netw Open 2020;3:e2025850.