



Editorial

Vitamin D and Vitamin D-Binding Protein in Health and Disease

Charlotte Delrue¹ and Marijn M. Speeckaert^{2,*}

¹ Department of Nephrology, Ghent University Hospital, 9000 Ghent, Belgium

² Research Foundation-Flanders (FWO), 1000 Brussels, Belgium

* Correspondence: marijn.speeckaert@ugent.be; Tel.: +32-9-332-4509

Vitamin D is a fat-soluble secosteroid that exists in two forms: vitamin D₂ and vitamin D₃ [1]. While plants and fungi produce vitamin D₂ from ergosterol [2], human skin produces vitamin D₃ from 7-dehydrocholesterol (7-DHC) when exposed to UVB radiation from the sun [3]. The UV photons trigger a photochemical reaction that converts 7-DHC into previtamin D₃, which then becomes vitamin D₃ via a series of thermal isomerizations [4]. Vitamin D₃ is transported to the liver and converted by CYP2R1 to 25-hydroxyvitamin D₃ [25(OH)D₃], the major circulating form of vitamin D₃ [5,6]. Finally, 25(OH)D₃ is converted to its active form, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], in the kidneys via CYP27B1 [7]. The primary function of 1,25(OH)₂D₃ is to maintain normal calcium levels and bone development by regulating phospho-calcium metabolism. Additionally, because vitamin D receptors (VDRs) have been discovered in numerous tissues (prostate, brain, breast, pancreas, colon, and immune cells), vitamin D can also provide non-skeletal actions. 1,25(OH)₂D₃ can play a role in the immune function and regulation of cell proliferation and differentiation in a variety of cell lineages (lymphocytes, endothelial cells, osteoblasts, and keratinocytes). Vitamin D can modify the risk of cardiometabolic outcomes, including hypertension, cardiovascular disease, and diabetes mellitus. Although the regulatory role of vitamin D in many biological processes is well documented, there is insufficient evidence to support the therapeutic use of vitamin D supplementation for the prevention or treatment of immunoinflammatory, infectious, or hyperproliferative diseases. 1,25(OH)₂D₃ exerts most of its functions via nuclear VDR, which forms a heterodimer with the retinoid X receptor (RXR). VDR/RXR in turn binds to vitamin D response elements (VDRE) in target genes and regulates gene transcription. The VDR pathway interacts with other intracellular signaling pathways to exert its biological effects (Figure 1). In some cases, 1,25(OH)₂D₃ exerts its influence without affecting gene expression or protein synthesis [8].

Vitamin D and its metabolites are generally transported from the site of production to target tissues. Mainly responsible for this transport is the vitamin-D-binding protein (DBP) or group-specific component (Gc-globulin), which binds 85% of the circulating 25(OH)D₃ and 1,25(OH)₂D₃. It has a high binding affinity for vitamin D and its metabolites, which contributes to the maintenance of adequate vitamin D levels in the blood. On the other hand, albumin has a low binding affinity for vitamin D but also contributes to vitamin D transport, especially at low DBP levels. The relative proportion of vitamin D bound to DBP and albumin may affect the bioavailability of vitamin D, with vitamin D bound to DBP being more bioavailable than that bound to albumin. Understanding the role of these two carriers in vitamin D transport and regulation is critical for a better understanding of vitamin D metabolism and for developing effective strategies to treat vitamin D deficiency and related diseases. Aside from its sterol-binding capacity, DBP has been shown to possess antioxidant and anti-inflammatory properties, without binding to vitamin D, that likely contribute to its role in disease prevention and treatment. DBP has been found to regulate immune function and play a role in the removal of toxins and pathogens from the bloodstream. DBP is also involved in the regulation of calcium metabolism, which is



Citation: Delrue, C.; Speeckaert, M.M. Vitamin D and Vitamin D-Binding Protein in Health and Disease. *Int. J. Mol. Sci.* **2023**, *24*, 4642. <https://doi.org/10.3390/ijms24054642>

Received: 29 January 2023

Revised: 23 February 2023

Accepted: 27 February 2023

Published: 28 February 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

critical for maintaining healthy bones, and may have anti-cancer properties in the form of the vitamin-D-binding protein macrophage-activating factor (DBP-MAF) (Figure 2) [9].

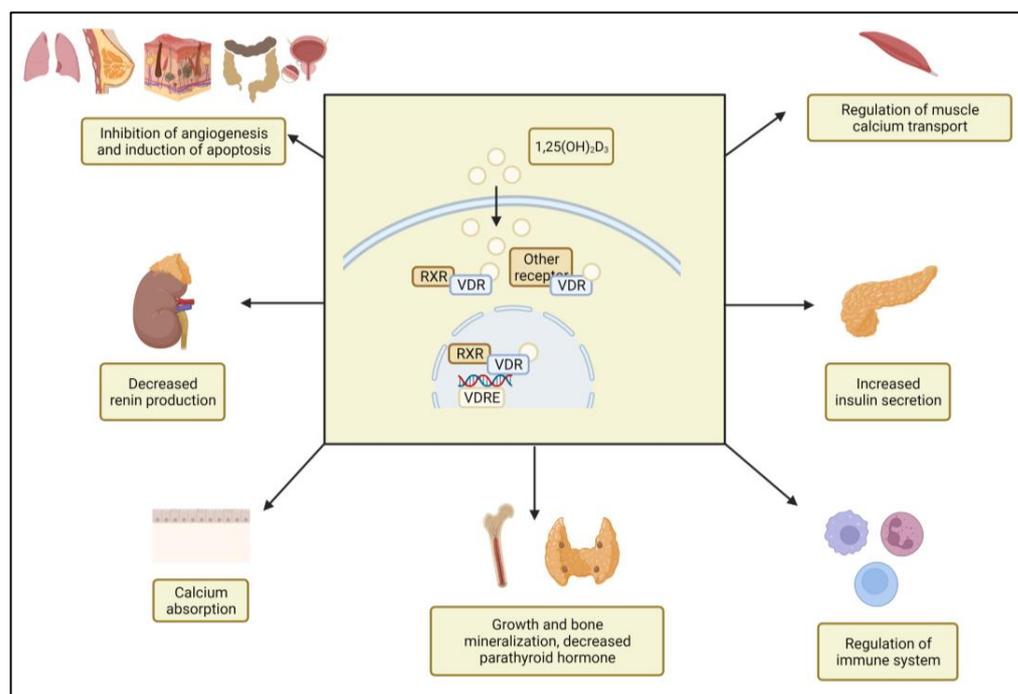


Figure 1. Vitamin D exerts its biological effects through the vitamin D receptor (VDR). 1,25(OH)₂D₃ can quickly diffuse through cell membranes and bind to VDR. VDR forms heterodimers with the retinoid X receptor (RXR) after binding to the ligand, moving into the nucleus where it binds to vitamin D response elements (VDREs) to regulate gene transcription. The VDR also controls the transcription of genes by interacting with other nuclear receptors. The functions of vitamin D include growth and bone mineralization, immune function regulation, insulin secretion regulation, cell proliferation control, cell differentiation stimulation, apoptosis induction, phosphor–calcium homeostasis regulation, and muscle calcium transport regulation.

Seven interesting manuscripts (three original articles and four review articles) were included in the Special Issue titled “Vitamin D and Vitamin D-Binding Protein in Health and Disease”. In the first paper, Xu et al. [10] investigated how 1,25(OH)₂D₃ can affect the regenerative ability of intestinal stem cells. A novel approach was used to deliver regionally high concentrations of 1,25(OH)₂D₃ only to the inflamed intestine. Throughout the epithelial regeneration process, a pulse-and-chase method using 5-bromo-2'-deoxyuridine (BrdU) labeling was used to track Lgr5⁺ stem cells. Macrophages engineered to synthesize high levels of 1,25(OH)₂D₃ de novo specifically migrated into the inflamed intestine and supported the regenerative capacity of intestinal stem cells by hosting CD11b⁺Grl⁺ macrophages. The results of this study may contribute to the development of a promising therapy to accelerate the repair of the intestinal epithelium in patients with inflammatory bowel disease (IBD). The second paper [11] addressed the free-hormone hypothesis for vitamin D in psoriasis patients. In a retrospective cross-sectional study involving 40 bionative patients with mild-to-severe plaque psoriasis, total 25(OH)D₃ serum levels appeared to be a reliable indicator of vitamin D status, as they correlated well with free 25(OH)D₃ serum levels. No associations were found between any of the vitamin D metabolites and psoriatic disease severity. Despite potential confounding variables, such as age, sex, and body weight, DBP serum levels were higher in patients who self-reported having arthropathy than in those who did not. DBP may be a brand-new indicator of inflammation in psoriasis, particularly psoriatic arthritis.

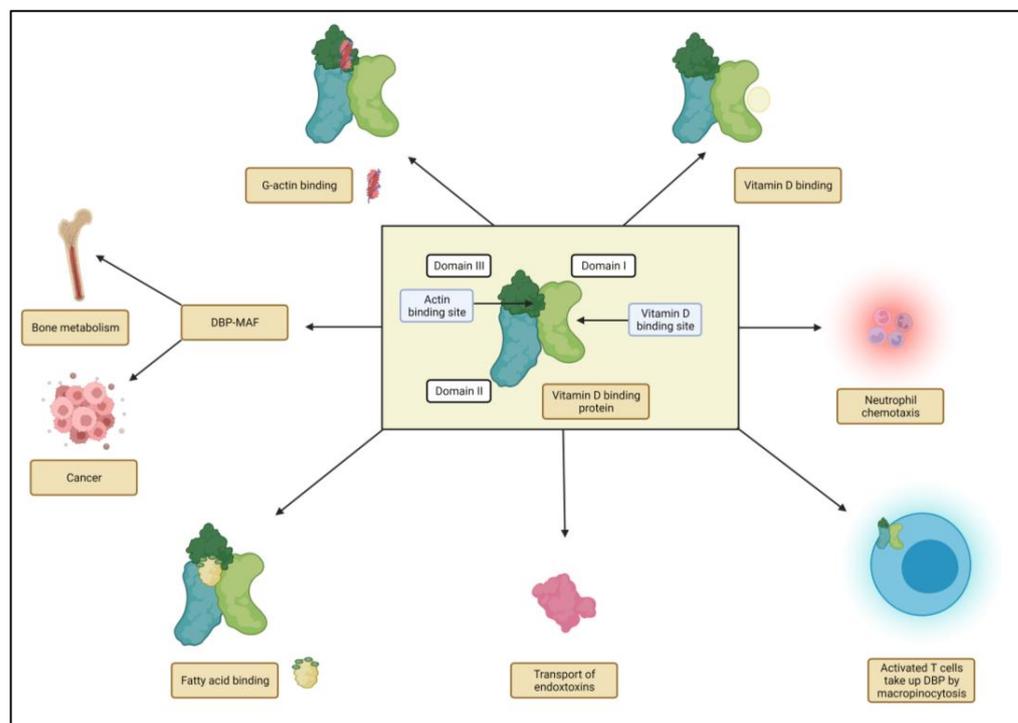


Figure 2. An overview of vitamin-D-binding protein's various physiological roles, including the binding of vitamin D metabolites, the binding of fatty acids, the transport of endotoxins, neutrophil chemotaxis, the influence on T cell response, actin scavenging, and the influence of vitamin-D-binding protein-macrophage activating factor (DBP-MAF) on bone metabolism and cancer.

As mentioned in the introduction, DBP performs a number of other roles in addition to binding to vitamin D, including therapeutic properties against tumors after conversion to DBP-MAF. Dolgova et al. [12] evaluated the benefit of the DBP-MAF-related factor (DBP-MAF-RF) in a Lewis carcinoma model under two clinical conditions: untreated tumor lesions and tumor resorption after “Karanahan” (derived from Sanskrit “killing the source”) therapy. The results of the study suggest that the primary requirement for the manifestation of the antitumor effect of DBP-MAF-RF is the inhibition of the suppressor effect of tumor-associated stroma (myeloid-derived suppressor cells, regulatory T lymphocytes). The anti-inflammatory effect of DBP-MAF-RF supports tumor progression and immune surveillance defense when the tumor has an active protective humoral background. The pro-inflammatory tumor reactive effects of DBP-MAF-RF become more pronounced when the tumor loses the suppressive humoral background. The results of this study demonstrate that DBP-MAF-RF, when used properly in conjunction with the “Karanahan” strategy, may enhance the antitumor immune response elicited by “Karanahan” therapy.

As discussed in two reviews [13,14] in this Special Issue, diabetes mellitus, renal dysfunction, and heart failure act synergistically. Diabetes mellitus and its complications have been associated with vitamin D deficiency, although the major question remains whether vitamin D deficiency is a cause or merely a consequence of diabetic kidney disease (DKD). The possible renal protective role of vitamin D in the development of DKD and the reversal of pre-existing renal damage is not known, although vitamin D has been shown to play a critical role in the development of DKD in numerous animal and human studies. More extensive, protracted, randomized, controlled human studies are needed to determine how vitamin D and its analogues may affect mortality, end-stage kidney disease (ESKD) progression, the development of DKD, and the decline in estimated glomerular filtration rate (eGFR) [14].

In another article, Chan et al. [15] provided a systematic review of the association between vitamin D and various ocular diseases. In addition to the association with diabetic

retinopathy, vitamin D was also associated with myopia, age-related macular degeneration, and dry eye syndrome. Evidence for an association with other ocular diseases such as glaucoma, thyroid disease, and retinoblastoma is still sparse. Although vitamin D has been associated with several disease-related processes, the causes of these diseases are complex, and knowledge of their underlying mechanisms remains limited. Vitamin D not only has an impact on the homeostasis of mineral metabolism, but also has anti-inflammatory and antioxidant properties. It influences the process of anti-angiogenesis by modulating various aspects of the cell cycle, such as cell division, proliferation, and apoptosis. Ocular tissues contain the vitamin D receptor (VDR) and vitamin-D-regulating enzymes, and research has shown that these tissues can activate and regulate vitamin D, indicating the importance of vitamin D in maintaining eye health.

Finally, Papagni et al. [16] studied the antifungal effect of vitamin D. Due to its relationship with oxidative balance, vitamin D inhibits the replication of *Mycobacterium tuberculosis* in vitro and has shown promise for the treatment of tuberculosis. Further clinical studies are needed to evaluate the efficacy of the drug in vivo, rule out confounding factors, and ultimately determine the dosages and delivery systems best suited for the treatment and prophylaxis of tuberculosis. It is important to investigate the potential benefits of combining vitamin D with other vitamins, such as vitamin A, which has antifungal activity in vitro. On the other hand, it would be advisable to measure vitamin D levels in both patients with active tuberculosis and those at risk, and to administer vitamin D, at least to achieve adequate levels, based on evidence of its efficacy in vitro and taking into account its low incidence of side effects, even at high doses, and its low cost.

In summary, this Special Issue on vitamin D and its binding proteins showcases a promising role in monitoring, preventing, and treating a variety of human diseases, including IBD, psoriasis, tuberculosis, diabetic nephropathy and retinopathy, and cancer. However, more research is needed to fully understand the mechanisms by which vitamin D affects these diseases and to determine the optimal vitamin D levels needed to prevent and treat disease. Future studies will also explore the potential use of DBP as a biomarker for disease and as a therapeutic target. The discovery of the unique role of vitamin D and its binding protein in human health has the potential to lead to new and innovative treatments for a variety of diseases, making it an exciting and rapidly evolving area of research.

Author Contributions: Conceptualization, C.D. and M.M.S.; writing—original draft preparation, C.D. and M.M.S.; writing—review and editing, C.D. and M.M.S. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bikle, D.D. Vitamin D and the Skin: Physiology and Pathophysiology. *Rev. Endocr. Metab. Disord.* **2012**, *13*, 3–19. [[CrossRef](#)] [[PubMed](#)]
2. Jäpelt, R.B.; Jakobsen, J. Vitamin D in Plants: A Review of Occurrence, Analysis, and Biosynthesis. *Front. Plant Sci.* **2013**, *4*, 136. [[CrossRef](#)] [[PubMed](#)]
3. Bikle, D.; Christakos, S. New Aspects of Vitamin D Metabolism and Action—Addressing the Skin as Source and Target. *Nat. Rev. Endocrinol.* **2020**, *16*, 234–252. [[CrossRef](#)] [[PubMed](#)]
4. Tian, X.Q.; Holick, M.F. Catalyzed Thermal Isomerization between Previtamin D₃ and Vitamin D₃ via Beta-Cyclodextrin Complexation. *J. Biol. Chem.* **1995**, *270*, 8706–8711. [[CrossRef](#)] [[PubMed](#)]
5. Bhattacharyya, M.H.; DeLuca, H.F. Subcellular Location of Rat Liver Calciferol-25-Hydroxylase. *Arch. Biochem. Biophys.* **1974**, *160*, 58–62. [[CrossRef](#)] [[PubMed](#)]
6. Zhu, J.G.; Ochalek, J.T.; Kaufmann, M.; Jones, G.; Deluca, H.F. CYP2R1 Is a Major, but Not Exclusive, Contributor to 25-Hydroxyvitamin D Production in Vivo. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 15650–15655. [[CrossRef](#)] [[PubMed](#)]
7. Bikle, D.D.; Patzek, S.; Wang, Y. Physiologic and Pathophysiologic Roles of Extra Renal CYP27b1: Case Report and Review. *Bone Rep.* **2018**, *8*, 255–267. [[CrossRef](#)] [[PubMed](#)]

8. Khammissa, R.A.G.; Fourie, J.; Motswaledi, M.H.; Ballyram, R.; Lemmer, J.; Feller, L. The Biological Activities of Vitamin D and Its Receptor in Relation to Calcium and Bone Homeostasis, Cancer, Immune and Cardiovascular Systems, Skin Biology, and Oral Health. *Biomed. Res. Int.* **2018**, *2018*, 9276380. [[CrossRef](#)] [[PubMed](#)]
9. Delanghe, J.R.; Speeckaert, R.; Speeckaert, M.M. Behind the Scenes of Vitamin D Binding Protein: More than Vitamin D Binding. *Best Pract. Res. Clin. Endocrinol. Metab.* **2015**, *29*, 773–786. [[CrossRef](#)] [[PubMed](#)]
10. Xu, Y.; Baylink, D.J.; Cao, H.; Xiao, J.; Abdalla, M.I.; Wasnik, S.; Tang, X. Inflammation- and Gut-Homing Macrophages, Engineered to De Novo Overexpress Active Vitamin D, Promoted the Regenerative Function of Intestinal Stem Cells. *Int. J. Mol. Sci.* **2021**, *22*, 9516. [[CrossRef](#)] [[PubMed](#)]
11. Vandikas, M.S.; Landin-Wilhelmsen, K.; Gillstedt, M.; Osmancevic, A. Vitamin D-Binding Protein and the Free Hormone Hypothesis for Vitamin D in Bio-Naïve Patients with Psoriasis. *Int. J. Mol. Sci.* **2022**, *23*, 1302. [[CrossRef](#)] [[PubMed](#)]
12. Dolgova, E.V.; Kirikovich, S.S.; Levites, E.V.; Ruzanova, V.S.; Proskurina, A.S.; Ritter, G.S.; Taranov, O.S.; Varaksin, N.A.; Ryabicheva, T.G.; Leplina, O.Y.; et al. Analysis of the Biological Properties of Blood Plasma Protein with GcMAF Functional Activity. *Int. J. Mol. Sci.* **2022**, *23*, 8075. [[CrossRef](#)] [[PubMed](#)]
13. D’Elia, J.A.; Bayliss, G.P.; Weinrauch, L.A. The Diabetic Cardiorenal Nexus. *IJMS* **2022**, *23*, 7351. [[CrossRef](#)] [[PubMed](#)]
14. Delrue, C.; Speeckaert, R.; Delanghe, J.R.; Speeckaert, M.M. The Role of Vitamin D in Diabetic Nephropathy: A Translational Approach. *Int. J. Mol. Sci.* **2022**, *23*, 807. [[CrossRef](#)] [[PubMed](#)]
15. Chan, H.-N.; Zhang, X.-J.; Ling, X.-T.; Bui, C.H.-T.; Wang, Y.-M.; Ip, P.; Chu, W.-K.; Chen, L.-J.; Tham, C.C.; Yam, J.C.; et al. Vitamin D and Ocular Diseases: A Systematic Review. *IJMS* **2022**, *23*, 4226. [[CrossRef](#)] [[PubMed](#)]
16. Papagni, R.; Pellegrino, C.; Di Gennaro, F.; Patti, G.; Ricciardi, A.; Novara, R.; Cotugno, S.; Musso, M.; Guido, G.; Ronga, L.; et al. Impact of Vitamin D in Prophylaxis and Treatment in Tuberculosis Patients. *IJMS* **2022**, *23*, 3860. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.