

Vitamin D and the Immune System. When? Why? How?

Alida Moise *, Carmen Balescu-Arion

Department of Anaesthesia and Intensive Care, “Prof. Dr. D. Gerota” Hospital, Bucharest 2139, Romania; carmenarionbalescu@yahoo.com

* Corresponding author: alidamoise@gmail.com

Submitted: 2 December 2019, accepted: 3 January 2020, published: 15 January 2020

Abstract: Vitamin D, called “the sunshine vitamin” is essential for the good functioning of the human body. Vitamin D generates its principal effects via the vitamin D receptor (VDR), a specific zinc-finger nuclear receptor, located primarily in the nuclei of target cells. VDR is present in most tissues and cells in the body such as in the: digestive system, cardiovascular system, immune system. This receptor represents the key to the understanding of vitamin D non-skeletal effects. Recently, some data were published on the correlation between vitamin D levels and sepsis, indicating a prevalence of vitamin D deficiency of approximately 61.6% in sepsis patients and of 74% in patients admitted to intensive care units (ICU). Vitamin D deficiency in critically ill patients is associated with infection and sepsis, and this association is based on the relation between vitamin D and inflammatory cytokine. Vitamin D, via VDR influences the secretion of cytokines and antimicrobial peptides. Practically, vitamin D acts as an immunomodulator stimulating the differentiation of cells of the innate immune system and, regulating T and B cell proliferation. The data clearly show predominant effects of vitamin D on the adaptive immune function. Vitamin D modulates the T cell phenotype specially that of CD4⁺ helper T cells (Th₁, Th₂, as well as Th17 sub-grups). The amplitude of the response to vitamin D depends on a cell’s state of activation, as the number of VDR in inactive cells is low, but may increase five times after activation. It was found that the intestinal expression of VDR regulates the host’s microbiome and mediates the anti-inflammatory effects of probiotics. A low level of vitamin D in ICU patients is demonstrated and has many causes. The rapid correction of this deficiency by administering very high doses of vitamin D is possible without causing adverse effects like hypercalcemia or hypercalciuria. Vitamin D is more than just a vitamin. It has clear effects on the immune system, in particular in patients with autoimmune diseases and critically ill. Currently, the majority of data strongly support the association, between low vitamin D levels and sepsis rather than a causal relation. Vitamin D is emerging as a promising and relatively safe nutrient for developing new preventive strategies and adjuvant treatments of diseases, caused by impaired immune-homeostasis. In addition, its supplementation is very easy and safe.

Keywords: vitamin D; sepsis; immunity; interleukin

How to cite: Moise, A.; Balescu-Arion, C. Vitamin D and the Immune System. When? Why? How? *Cent. Eur. Ann. Clin. Res.* **2020**, 2(1), 1; doi:[10.35995/ceacr2010001](https://doi.org/10.35995/ceacr2010001).

Introduction

Vitamin D, called “the sunshine vitamin” is essential for the good functioning of the human body. Vitamin D can be obtained from the diet or from nutritive supplements and is produced by the skin. The most important forms of vitamin D are vitamin D₂ and vitamin D₃, both biologically inactive.

The deficiency of vitamin D has an estimated prevalence of around 20%–100% in the population, higher among the elderly [1], and is a major public healthcare problem.

The Roles of Vitamin D

Vitamin D, after being activated, has multiple roles, including hormonal non-hormonal, genomic and non-genomic functions. In the last years vitamin D non-hormonal and non-skeletal effects have been analyzed. Vitamin D exerts its genomic effects via the vitamin D receptor (VDR), a specific zinc-finger nuclear receptor of the superfamily of steroid/thyroid hormone receptors, located primarily in the nuclei of target cells. VDR is present in most cells and tissues of the body, including: the digestive system, the cardiovascular system, the immune system. This receptor acts as a transcription factor. VDR regulates the expression of many genes (more than 1000 genes), therefore approximately 3% of the human genome is affected by vitamin D, directly or indirectly. The serum level of vitamin D and its function are strongly related to VDR expression and function. Moreover, the correlation between vitamin D and different diseases is proven to be linked to VDR expression and function. For example, type 2 diabetes mellitus and Crohn’s disease are associated with the polymorphism of the VDR gene [1–11].

Therefore VDR represents the key to the understanding of vitamin D non-skeletal effects.

The correlation between sepsis and vitamin D levels, as well as the correlation between cognitive impairment and vitamin D levels, especially Alzheimer’s disease or delirium during hospitalization, are very interesting [1].

Vitamin D and Sepsis

In the past 3–5 years, some data were published in regards to the correlation between vitamin D levels and sepsis, indicating decreased serum level of vitamin D in septic patients, although some data are contradictory, probably due to the fact that this correlation has been documented only recently, and thus more data are required to confirm it.

A recent study reported that, the prevalence of vitamin D deficiency was approximately 61.6% in sepsis patients [6]. Moreover, 74% of the patients admitted to intensive care units ICU presented a decrease of the vitamin D serum level [8], and a higher percentage of critically ill patients, corresponding to 81.5%–99% had vitamin D deficiency or insufficiency. These studies revealed many other consequences of vitamin D deficiency. The most significant and indirect correlation were found between the serum level of vitamin D₃ and prolonged time of stay in ICU or hospital, infection, acute kidney injury and mortality, especially in older patients. Moreover, the plasmatic level of vitamin D was significantly lower in non-survivor sepsis patients when compared to survivor sepsis patients. It seems that the consumption of vitamin D supplements might be helpful in decreasing the prevalence of infection, sepsis, and mortality caused by vitamin D deficiency, especially in older age. The correlation between vitamin D deficiency and severe infections and sepsis is based on the fact that vitamin D is an important mediator in the immune system [6]. Zhou W and his team have proven that a lower level of vitamin D can be a biomarker of sepsis risk in Caucasians, and Africans patients, but it does not appear to be associated with sepsis death ($p > 0.05$) [9].

Zapatero found an association between severe vitamin D deficiency and mortality as well as renal acute dysfunction in critically ill patients. In addition, he identified the cut-off point of the serum level of vitamin D that predicts mortality in critically ill patients, which corresponds to a concentration lower than 10.9 ng/mL [8]. In another study, 90-day mortality did not differ among critically ill patients with or without vitamin D deficiency [12].

Vitamin D deficiency in critically ill patients is associated with infection and sepsis, and this association is based on the interaction between vitamin D and the immune system [13].

Vitamin D and the Immune System

The immune system's response to infections is a very complex process in which multiple cell types and multiple soluble factors, such as cytokines, chemokines and hormones participate [14–29]. Vitamin D is involved both in the innate and in the adaptive immune responses to viral and bacterial infections [14]. Moreover, (VDR) is present in several cells of the immune system, for example macrophages, dendritic cells, and T and B cells, and it influences their functions [15]. The medical literature has shown a long time ago a connection between the serum level of vitamin D and the serum concentrations of different pro-inflammatory cytokines. A study on an infant population found a negative correlation between the levels of vitamin D and those of pro-inflammatory cytokines, so that, the treatment of vitamin D deficiency in premature babies, resulted in a decrease of the serum concentrations of the pro-inflammatory cytokines: interleukin-6 (IL-6) and tumor necrosis factor α (TNF- α), regardless of the doses of vitamin D used [15].

Vitamin D has immunosuppressive effects by reducing the prolonged inflammatory response of the host [17]. These effects, considered non-genomic, explain the link between a low vitamin D level and many autoimmune diseases [15]. Practically, vitamin D acts as an immunomodulator stimulating cell differentiation within the innate immune system, such as the differentiation of monocytes [18,19]. Therefore, vitamin D, via VDR influences the secretion of cytokines or antimicrobial peptides (AMPs) such as cathelicidins and interleukins [18,20,21].

Cathelicidins are antimicrobial substances that act by disrupting foreign-cells membranes. The only identified human cathelicidin is the antimicrobial protein-18 (hCAP18) present in the granules of neutrophils, and produced and secreted by monocytes, macrophages, epithelial cells, and other cell types. There is a direct relation between the serum level of vitamin D and the levels of cathelicidin in fact, low vitamin D levels are associated with reduced production of hCAP18 by macrophages in critically ill patients. Low hCAP18 levels in patients admitted to ICU, especially in the first day of admission are associated with an increased risk of 90-day mortality [18].

For many years, it has been known that vitamin D is a suppressor of the proliferation of mitogen-activated lymphocytes [20]. Initial studies (Bhalla, 1983), showed the role of vitamin D as a regulator of T and B cell proliferation, with predominant effects on the adaptive immune function, involving the modulation of T cell phenotype, specially that of CD4⁺ helper T cells (T helper1-Th₁ and T helper 2-Th₂ sub-grups) [22,23]. VDR can act as a selective inhibitor of the Th1 pathway, so vitamin D decreases the expression of Th₁ cytokines: IL-1, IL-6, IL-2, interferon γ (IFN γ), TNF α [23,28]. Data regarding the Th2 pathway are controversial: in general, vitamin D promotes the expression of Th₂ cytokines, with increases of IL-3, IL-4, IL-5, IL-10) [23,28]. The CD4⁺ T cell line includes also cell secreting IL-17 (Th17). Similar to Th1 and Th2, Th17 cells carry out specific immune functions, important for the response to extracellular bacteria, such as *Klebsiella* spp. [25,26]. The inhibition of IL-17 production by Th17 cells occurs through a direct mechanism, but vitamin D can indirectly inhibit the proliferation and maturation of Th17 [23]; this interaction between vitamin D and

Th17 cells should be thoroughly investigated in future studies because the immune response to *Klebsiella* is very important in critically ill patients. In addition to its effects on Th cells, vitamin D may also act on CD8⁺ cytotoxic T cells (which express relatively high levels of VDR). In conclusion, vitamin D can influence the adaptive immunity by promoting the suppression T cells [24].

Different studies, analyzed the effect of vitamin D on some pro-inflammatory cytokines were showing in general a decrease in the expression of these molecules under the influence of vitamin D. The amplitude of the response depends on the cell's state of activation, as the number of VDR in inactive cells is low, but it may increase five times after cell activation [28]. This activation produces direct and indirect effects, on the evolution of diseases involving immunological mechanism such as; diabetes mellitus, Crohn's disease, multiple sclerosis, psoriasis, cardiovascular diseases, cancer, various eye diseases, cognitive impairment and very interestingly, on the evolution of critically ill septic patients [29–34].

An important category of patients comprises ICU patients with trauma. An increased inflammatory response can be observed in patients with traumas [30]. The role of vitamin D as an immunomodulator suggests the administration of vitamin D, alone or along with other substances, such as vitamin C, may influence the evolution of polytrauma patients. Large doses of Vitamin D possibly with vitamin C could be beneficial for ICU patients, although, more research should be conducted on this topic.

Vitamin D and the Microbiome

The gut microbiome has metabolic functions; there are complex interactions between immune and microbial factors on one hand and the host genetic factors on the other. This strongly suggests the essential role of the microbiome in the development and evolution of metabolic conditions. The interaction between the gut microbiome and VDR signals affects the host's responses and inflammation. It was found that intestinal expression of VDR regulates the host's microbiome and mediates the anti-inflammatory effects of probiotics [11,31–38].

In the gut, there are the Paneth cells, which are specialized intestinal epithelial cells, located at the bottom of the ileal crypts. These cells are characterized by granules that contain AMPs— α -defensins, lysozyme, and secretory phospholipase A2. Paneth cells produce the cytokine IL-17. A recent study demonstrated that Paneth cells are a site of origin of intestinal inflammation via IL-17, because IL-17 has a role in acute inflammation and can participate in fast amplifying responses to systemic inflammatory changes. Because of the above, Paneth cells play a key role in innate immune responses [11,31–38].

VDR regulation of Paneth cells' function is not clearly known, but several studies have identified vitamin D as a potent stimulator of autophagy, the link between VDR, autophagy, and Paneth cell being important for intestinal inflammation. Cathelicidin is a mediator of autophagy, and has direct antimicrobial activity. The serum level of vitamin D is related to the composition and function of the intestinal microbiome, because intestinal epithelial VDR induces dysbiosis through its actions on the autophagy [35].

Recent studies demonstrated that probiotic treatment could increase VDR expression and VDR activity in the host and the secretion of *cathelicidin*. VDR decrease can diminish the protective role of probiotics [36]. Vitamin D, activation of VDR plays a fundamental role in intestinal homeostasis, through its effects on autophagy, Paneth cells, and the intestinal microbiota itself. This mechanism may also be involved in other autoimmune diseases [36,39], and is important for critically ill patients. According to recent data the role of vitamin D in the evolution of critically ill patients, can be explained by its effect on cathelicidin, which is extremely sensitive to vitamin D supplements [40]. There is evidences for critically ill patients, including those with mechanical ventilation suggesting that supplementation with vitamin D

may decrease susceptibility or enhance recovery to infections such as influenza, recurrent pneumonia and tuberculosis [41].

In the end, a low level of vitamin D in ICU patients is a proven fact with many causes, such as preexisting deficiency (before ICU admission), pathophysiological mechanisms of sepsis (decrease of the activity of 1 α hydroxylase via cytokines), as well as patient's care procedures (dialysis and plasma exchange). The rapid correction of this deficiency by administering very high doses of vitamin D is possible without causing adverse effects like hypercalcemia or hypercalciuria [42–44].

Two ongoing studies, performed by the same team analyze the effects of a loading dose of 540,000 IU cholecalciferol, followed by 4000 IU or a placebo, daily; they are specifically;

- VITdAL-ICU a randomized, double-blind, placebo-controlled, single-center trial including 492 critically ill patients with vitamin D deficiency (25(OH)D \leq 20 ng/mL) and
- VITDALIZE a randomized, placebo-controlled, double-blind, multicenter, international trial, including 2400 adult patients with severe vitamin D deficiency.

The second study uses an improved method is being conducted on a higher number of patients therefore the results will be more detailed and accurate. First reports show that the huge loading dose is not toxic, further results will be published in the near future [43,44].

Conclusion

Vitamin D is more than just a vitamin. It clearly influences the function of the immune system, in particular in critically ill patients. Currently, the majority of data strongly support association of low Vitamin D levels and sepsis, rather than a causal relation. Vitamin D is emerging as a promising and relatively safe nutrient for the development of new preventive strategies and adjuvant treatments of diseases, caused by impaired immune-homeostasis. In addition, vitamin D supplementation is very easy and safe.

Author Contributions: Conceptualization, A.M. and C.B.-A.; Writing—A.M. and C.B.-A.

Funding: This research received no external funding.

Acknowledgments: We all declare that, this work did not receive any kind of funding.

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

References

1. Moise, A. Vitamin D in Critically Ill Patients—From Molecular Damage Interactions to Clinical Outcomes Benefits. When, Why, How? *Cent. Eur. J. Clin. Res.* **2018**, *1*, 59–66. [[CrossRef](#)]
2. Haussler, M.R.; Whitfield, G.K.; Kaneko, I.; Haussler, C.A.; Hsieh, D.; Hsieh, J.C.; Jurutka, P.W. Molecular mechanisms of vitamin D action. *Calcif. Tissue Int.* **2013**, *92*, 77–98. [[CrossRef](#)] [[PubMed](#)]
3. Wacker, M.; Holick, M.F. Vitamin D—Effects on Skeletal and Extraskelatal Health and the Need for Supplementation. *Nutrients* **2013**, *5*, 111–148. [[CrossRef](#)] [[PubMed](#)]
4. Jamali, N.; Sorenson, C.M.; Sheibani, N. Vitamin D and regulation of vascular cell function. *Am. J. Physiol. Circ. Physiol.* **2018**, *314*, H753–H765. [[CrossRef](#)] [[PubMed](#)]

5. Ezhilarasi, K.; Dhamodharan, U.; Vijay, V.; Krishnamoorthy, E.; Umapathy, D.; Viswanathan, V. BSM1 single nucleotide polymorphism in vitamin D receptor gene is associated with decreased circulatory levels of serum 25-hydroxyvitamin D among micro and macrovascular complications of type 2 diabetes mellitus. *Int. J. Biol. Macromol.* **2018**, *116*, 346–353. [[CrossRef](#)] [[PubMed](#)]
6. Shojaei, M.; Sabzegahabaei, A.; Barhagh, H.V.; Soltani, S. The Correlation between Serum Level of Vitamin D and Outcome of Sepsis Patients; a Cross-Sectional Study. *Arch. Acad. Emerg. Med.* **2019**, *7*, e1. [[PubMed](#)]
7. Trochoutsou, A.; Kloukina, V.; Samitas, K.; Xanthou, G. Vitamin-D in the Immune System: Genomic and Non-Genomic Actions. *Mini-Rev. Med. Chem.* **2015**, *15*, 953–963. [[CrossRef](#)] [[PubMed](#)]
8. Zapatero, A.; Dot, I.; Díaz, Y.; Gracia, M.; Pérez-Terán, P.; Climent, C.; Masclans, J.; Nolla, J. Severe vitamin D deficiency upon admission in critically ill patients is related to acute kidney injury and a poor prognosis. *Med. Intensiv.* **2018**, *42*, 216–224. [[CrossRef](#)]
9. Zhou, W.; Mao, S.; Wu, L.; Yu, J. Association Between Vitamin D Status and Sepsis. *Clin. Lab.* **2018**, *64*, 451–460. [[CrossRef](#)]
10. Gisbert-Ferrándiz, L.; Salvador, P.; Ortiz-Masiá, D.; Macías-Ceja, D.C.; Orden, S.; Esplugues, J.V.; Calatayud, S.; Hinojosa, J.; Barrachina, M.D.; Hernandez, C. A Single Nucleotide Polymorphism in the Vitamin D Receptor Gene Is Associated With Decreased Levels of the Protein and a Penetrating Pattern in Crohn's Disease. *Inflamm. Bowel Dis.* **2018**, *24*, 1462–1470. [[CrossRef](#)] [[PubMed](#)]
11. Wu, S.; Zhang, Y.G.; Lu, R. Intestinal epithelial vitamin D receptor deletion leads to defective autophagy in colitis. *Gut* **2015**, *64*, 1082–1094. [[CrossRef](#)]
12. Ala-Kokko, T.I.; Mutt, S.J.; Nisula, S.; Koskenkari, J.; Liisanantti, J.; Ohtonen, P.; Poukkanen, M.; Laurila, J.J.; Pettilä, V.; Herzig, K.H.; et al. Vitamin D deficiency at admission is not associated with 90-day mortality in patients with severe sepsis or septic shock: Observational FINNAKI cohort study. *Ann. Med.* **2016**, *48*, 67–75. [[CrossRef](#)]
13. De Haan, K.; Groeneveld, A.B.J.; De Geus, H.R.H.; Egal, M.; Struijs, A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: Systematic review and meta-analysis. *Crit. Care* **2014**, *18*, 660. [[CrossRef](#)]
14. Hewison, M. An update on vitamin D and human immunity. *Clin. Endocrinol.* **2012**, *76*, 315–325. [[CrossRef](#)]
15. Jeffery, L.E.; Burke, F.; Mura, M.; Zheng, Y.; Qureshi, O.S.; Hewison, M.; Walker, L.S.K.; Lammas, D.A.; Raza, K.; Sansom, D.M. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J. Immunol.* **2009**, *183*, 5458–5467. [[CrossRef](#)]
16. Abdel-Hady, H.; Yahia, S.; Megahed, A.; Mosbah, A.; Seif, B.; Nageh, E.; Bhattacharjee, I.; Aly, H. Vitamin D and Inflammatory Mediators in Preterm Infants with Late-Onset Sepsis: A Randomized Controlled Trial. *J. Pediatr. Gastroenterol. Nutr.* **2019**, *4*. [[CrossRef](#)]
17. Bikle, D.D. Vitamin D and the immune system: Role in protection against bacterial infection. *Curr. Opin. Nephrol. Hypertens.* **2008**, *17*, 348–352. [[CrossRef](#)]
18. Leaf, D.E.; Croy, H.E.; Abrahams, S.J.; Raed, A.; Waikar, S.S. Cathelicidin antimicrobial protein, vitamin D, and risk of death in critically ill patients. *Crit. Care* **2015**, *19*, 80. [[CrossRef](#)]
19. Gois, P.H.F.; Ferreira, D.; Olenski, S.; Seguro, A.C. Vitamin D and Infectious Diseases: Simple Bystander or Contributing Factor? *Nutrients* **2017**, *9*, 651. [[CrossRef](#)]
20. Tsoukas, C.; Provvedini, D.; Manolagas, S. 1,25-dihydroxyvitamin D3: A novel immunoregulatory hormone. *Science* **1984**, *224*, 1438–1440. [[CrossRef](#)]

21. Chun, R.F.; Liu, P.T.; Modlin, R.L.; Adams, J.S.; Hewison, M. Impact of vitamin D on immune function: Lessons learned from genome-wide analysis. *Front. Physiol.* **2014**, *5*, 151. [[CrossRef](#)]
22. Bhalla, A.K.; Amento, E.P.; Clemens, T.L.; Holick, M.F.; Krane, S.M. Specific high-affinity receptors for 1,25-dihydroxyvitamin D₃ in human peripheral blood mononuclear cells: Presence in monocytes and induction in T lymphocytes following activation. *J. Clin. Endocrinol. Metab.* **1983**, *57*, 1308–1310. [[CrossRef](#)]
23. Tang, J.; Zhou, R.; Luger, O.; Zhu, W.; Silver, P.B.; Grajewski, R.S.; Su, S.-B.; Chan, C.-C.; Adorini, L.; Caspi, R.R. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. *J. Immunol.* **2009**, *182*, 4624–4632. [[CrossRef](#)]
24. Yegorov, S.; Bromage, S.; Boldbaatar, N.; Ganmaa, D. Effects of Vitamin D Supplementation and Seasonality on Circulating Cytokines in Adolescents: Analysis of Data From a Feasibility Trial in Mongolia. *Front. Nutr.* **2019**, *6*, 166. [[CrossRef](#)]
25. Happel, K.I.; Dubin, P.J.; Zheng, M.; Ghilardi, N.; Lockhart, C.; Quinton, L.J.; Odden, A.R.; Shellito, J.E.; Bagby, G.J.; Nelson, S.; et al. Divergent roles of IL-23 and IL-12 in host defense against *Klebsiella pneumoniae*. *J. Exp. Med.* **2005**, *202*, 761–769. [[CrossRef](#)]
26. Zhou, L.; Wang, J.; Li, J.; Li, T.; Chen, Y.; June, R.R.; Zheng, S.G. 1,25-Dihydroxyvitamin D₃ Ameliorates Collagen-Induced Arthritis via Suppression of Th17 Cells Through miR-124 Mediated Inhibition of IL-6 Signaling. *Front. Immunol.* **2019**, *10*, 178. [[CrossRef](#)]
27. Lacroix, M.; Lizotte, F.; Hivert, M.-F.; Gerales, P.; Perron, P. Calcifediol Decreases Interleukin-6 Secretion by Cultured Human Trophoblasts From GDM Pregnancies. *J. Endocr. Soc.* **2019**, *3*, 2165–2178. [[CrossRef](#)]
28. Mahon, B.D.; Wittke, A.; Weaver, V.; Cantorna, M.T. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J. Cell. Biochem.* **2003**, *89*, 922–932. [[CrossRef](#)]
29. Zahran, A.M.; Zharan, K.M.; Hetta, H.F. Significant correlation between regulatory T cells and vitamin D status in term and preterm labor. *J. Reprod. Immunol.* **2018**, *129*, 15–22. [[CrossRef](#)]
30. Sandesc, M.; Rogobete, A.F.; Bedreag, O.H.; Dinu, A.; Papurica, M.; Cradigati, C.A.; Sarandan, M.; Popovici, S.E.; Bratu, L.M.; Bratu, T.; et al. Analysis of oxidative stress-related markers in critically ill polytrauma patients: An observational prospective single-center study. *Bosn. J. Basic Med. Sci.* **2018**, *18*, 191–197. [[CrossRef](#)]
31. Bakke, D.; Chatterjee, I.; Agrawal, A.; Dai, Y.; Sun, J. Regulation of Microbiota by Vitamin D Receptor: A Nuclear Weapon in Metabolic Diseases. *Nucl. Recept. Res.* **2018**, *5*, 10137. [[CrossRef](#)]
32. Cipollini, V.; Anrather, J.; Orzi, F.; Iadecola, C. Th17 and Cognitive Impairment: Possible Mechanisms of Action. *Front. Neuroanat.* **2019**, *13*, 95. [[CrossRef](#)]
33. Ma, Y.; Khalifa, B.; Yee, Y.K.; Lu, J.; Memezawa, A.; Savkur, R.S.; Yamamoto, Y.; Chintalacharuvu, S.R.; Yamaoka, K.; Stayrook, K.R.; et al. Identification and characterization of noncalcemic, tissue-selective, nonsecosteroidal vitamin D receptor modulators. *J. Clin. Investig.* **2006**, *116*, 892–904. [[CrossRef](#)]
34. Prietl, B.; Treiber, G.; Pieber, T.R.; Amrein, K. Vitamin D and Immune Function. *Nutrients* **2013**, *5*, 2502–2521. [[CrossRef](#)]
35. Jo, E.-K. Innate immunity to mycobacteria: Vitamin D and autophagy. *Cell. Microbiol.* **2010**, *12*, 1026–1035. [[CrossRef](#)]
36. Shang, M.; Sun, J. Vitamin D/VDR, Probiotics, and Gastrointestinal Diseases. *Curr. Med. Chem.* **2017**, *24*, 876–887. [[CrossRef](#)]

37. Yuk, J.-M.; Shin, N.-M.; Lee, H.-M.; Yang, C.-S.; Jin, H.S.; Kim, K.-K.; Lee, Z.-W.; Lee, S.-H.; Kim, J.-M.; Jo, E.-K. Vitamin D3 Induces Autophagy in Human Monocytes/Macrophages via Cathelicidin. *Cell Host Microbe* **2009**, *6*, 231–243. [[CrossRef](#)]
38. Takahashi, N.; Vanlaere, I.; de Rycke, R.; Cauwels, A.; Joosten, L.A.; Lubberts, E.; van den Berg, W.B.; Libert, C. IL-17 produced by Paneth cells drives TNF-induced shock. *J. Exp. Med.* **2008**, *205*, 1755–1761. [[CrossRef](#)]
39. Lim, H.-S.; Kim, T.-H.; Lee, H.-H.; Kim, S.-K.; Lee, B.; Park, Y.-H. Relationship between Serum 25-hydroxy-vitamin D Concentration and Risk of Metabolic Syndrome in Patients with Fatty Liver. *J. Bone Metab.* **2017**, *24*, 223–228. [[CrossRef](#)]
40. Li, C.H.; Tang, X.; Wasnik, S.; Wang, X.; Zhang, J.; Xu, Y.; Lau, K.W.; Nguyen, H.B.; Baylink, D.J. Mechanistic study of the cause of decreased blood 1,25-Dihydroxyvitamin D in sepsis. *BMC Infect. Dis.* **2019**, *19*, 1020. [[CrossRef](#)]
41. Han, J.E.; Alvarez, J.A.; Jones, J.L.; Tangpricha, V.; Brown, M.A.; Hao, L.; Brown, L.A.S.; Martin, G.S.; Ziegler, T.R. Impact of high-dose vitamin D3 on plasma free 25-hydroxyvitamin D concentrations and antimicrobial peptides in critically ill mechanically ventilated adults. *Nutrition* **2017**, *38*, 102–108. [[CrossRef](#)]
42. Amrein, K.; Sourij, H.; Wagner, G.; Holl, A.; Pieber, T.R.; Smolle, K.H.; Stojakovic, T.; Schnedl, C.; Dobnig, H. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: A randomized, double-blind, placebo-controlled pilot study. *Crit. Care* **2011**, *15*, R104. [[CrossRef](#)]
43. Amrein, K.; Schnedl, C.; Holl, A.; Riedl, R.; Christopher, K.B.; Pachler, C.; Urbanic, P.T.; Waltensdorfer, A.; Münch, A.; Warnkross, H.; et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: The VITdAL-ICU randomized clinical trial. *JAMA* **2014**, *312*, 1520–1530. [[CrossRef](#)]
44. Amrein, K.; Parekh, D.; Westphal, S.; Preiser, J.C.; Berghold, A.; Riedl, R.; Eller, P.; Schellongowski, P.; Thickett, D.; Meybohm, P.; et al. Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: A study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). *BMJ Open* **2019**, *9*, e031083. [[CrossRef](#)]