Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.50.007886

Vitamin D and its Antioxidant and Anti-Inflammatory Role in Cardiovascular Diseases

Georgiadis Theofylaktos[1], Kourti Areti[1], Georgiou Elisavet[2], Iliadis Stavros[2], Gkeka Ioanna[1], Georgiadis Ioannis[1] and Makedou Kali[1]*

[1]*Laboratory of Biochemistry, AHEPA University Hospital, School of Medicine, Aristotle University of Thessaloniki, Greece*

[2]*Laboratory of Biological Chemistry, School of Medicine, Aristotle University of Thessaloniki, Greece*

***Corresponding author:** Kali Makedou, Laboratory of Biochemistry, AHEPA University Hospital, School of Medicine, Aristotle University of Thessaloniki, Greece

ARTICLE INFO

Received: April 17, 2023

Published: April 26, 2023

Citation: Georgiadis Theofylaktos, Kourti Areti, Georgiou Elisavet, Iliadis Stavros, Gkeka Ioanna, Georgiadis Ioannis and Makedou Kali. Vitamin D and its Antioxidant and Anti-Inflammatory Role in Cardiovascular Diseases. Biomed J Sci & Tech Res 50(1)-2023. BJSTR. MS.ID.007886.

ABSTRACT

Vitamin D, a hormone synthesized in the skin by ultraviolet radiation, is regulating bone metabolism, but has many extra-skeletal actions as well. It has been suggested that vitamin D plays a significant role in the pathophysiology of cardiovascular diseases. Its involvement in anti-inflammatory and antioxidant mechanisms results in an inverse relationship between vitamin D levels and cardiometabolic risk, as shown by observational studies. Randomized controlled studies have shown that vitamin supplementation has decreased inflammatory and oxidative stress biomarkers.

Keywords: Vitamin D; Antioxidant; Cardiovascular

Introduction

Vitamin D is traditionally known as the hormone involved in calcium and phosphorus metabolism, regulating bone homeostasis and health. However, it has been found to participate in several extra-skeletal conditions, like cancer and cardiovascular diseases (CVD). During the last decade, there has been increasing evidence of the consequences of vitamin D deficiency in health, in skeletal and non-skeletal clinical conditions, an issue that is controversial [1]. There are two known forms of vitamin D, vitamin D_3 or cholecalciferol produced in the skin after exposure to ultraviolet radiation, and vitamin D_2 or ergocalciferol found in plants and fungi. These two forms present certain structural similarities [2]. Cardiovascular diseases (CVD), i.e., hypertension, coronary heart disease, stroke, etc., are a major cause of increased mortality worldwide. Inflammation and oxidative stress seem to play a crucial role in the pathophysiology of CVD. Different researchers have suggested that there is an association between vitamin D deficiency and the onset of CVD, not being able to define the threshold that is the most appropriate for the prevention of CVD [3,4]. There are many mechanisms proposed for the involvement of vitamin D in the pathophysiology of CVD, among which are inflammation and oxidative stress [5]. The aim of the present review is to summarize all the existing data on the role of vitamin D in oxidative stress and CVDs.

Vitamin D Levels and Metabolism

Vitamin D existing in the human body is either synthesized within the skin by ultraviolet radiation (about 90%) or is received by food, like fish (salmon, tuna, etc.), veal liver, egg yolk, mushrooms, shrimps, and

cod liver oil. In some counties, the enrichment of certain foods, such as cereals, dairy products, and margarine, with vitamin D is allowed. Vitamin D is absorbed mainly in the duodenum, and in the large intestine [6]. Another source of vitamin D is the dietary supplements received per os, either as multivitamin products containing 400-1000 IU of vitamin D_2 or as pure vitamin D_3 supplements containing 400-50,000 IU [7].

Vitamin D is synthesized by photolysis of 7-dihydro cholesterol by UV radiation (290-315 nm). The first compound synthesized is provitamin D_3, which is then transformed into vitamin D_3 or cholecalciferol [8]. Vitamin D_3 is a pro-hormone, activated by the addition of two hydroxyl groups on the C25 and C1a, producing $1,25(OH)_2D_3$, with the help of the enzymes of the family of cytochrome P450 (CYP) [9]. The first hydroxylation takes place in the liver and 25(OH)vitamin D_3 [25(OH)D], the main circulating form of vitamin D, is produced. Bound to an α-globulin, the vitamin D- binding protein (VDBP), 25(OH)vitamin D_3 is transferred to the kidneys where a second hydroxylation by 1α-hydroxylase takes place and $1,25(OH)_2$ vitamin D_3 [$1,25(OH)_2$ D_3], the most potent vitamin D metabolite, is produced. VDBP binds 25(OH)D with 10-100 higher affinity than that of $1,25(OH)_2D_3$ [10].

According to the Endocrine Society, the optimal serum levels are advised to be above 30ng/mL, ideally between 40 and 60 ng/mL. Serum levels between 21 and 29 ng/mL are considered "insufficiency", levels lower than 20 ng/mL are "deficiency", and levels less than 10 ng/mL are "extreme deficiency" [7]. However, the Institute of Medicine has reported the threshold of 20 ng/mL for physiologically optimal levels of vitamin D [11]. Intoxication of vitamin D is rarely reported. Increased exposure to the sun cannot result in intoxication if the excess of vitamin D is neutralized within the skin. The only way of intoxication is the consumption of large quantities of vitamin D for a long period of time, resulting in hypercalcemia and/or hypercalciuria and, possibly, kidney stones. On the other hand, insufficiency and deficiency of vitamin D have a high prevalence worldwide nowadays [12].

Vitamin D Biological Action

Vitamin D, like all steroid hormones, acts in the nucleus and on the surface of the cells, like all peptide hormones. Its nuclear receptor, vitamin D receptor (VDR) is connected to both the DNA and the ligand. It has been found in the gut, the bones, the kidneys, and in other organs not related to calcium metabolism, like immune cells, myocardiocytes, and other muscle cells, liver cells, prostate cells, etc. [13]. Vitamin D action on genes is rapid, enhancing the synthesis of proteins like osteocalcin and calcium-binding protein, and down-regulating the synthesis of parathormone and cytokines, like IL-17 [14].

The extra-DNA action of vitamin D is exerted via cytoplasmic membrane receptors ($1,25$ D_3-MARRS or PDIA3) and secondary messengers (cAMP and kinases) that affect calcium channels and intracellular calcium concentration. This action takes place in tissues like pancreas, smooth muscle cells, the gut and monocytes, and regulates cell differentiation and function [15]. In small intestine, $1,25(OH)_2D_3$ increases calcium absorbance via increased expression of calcium channels, increased production of proteins, such as alkaline phosphatase and calmodulin, that help calcium enter the circulation [16]. The skeletal actions of vitamin D include increased bone absorption by osteoclasts and increased osteoclasts proliferation. Vitamin D also increases calcium reabsorption in distant renal tubules [17]. All these actions are exerted in response to low calcium serum levels [18,19].

Non-classical actions of $1,25(OH)_2D_3$ include:

i) Regulation of cell proliferation and differentiation,

ii) Strengthening of epidermal barrier,

iii) A inflammatory and immune compromising properties,

iv) Role in reproduction, pregnancy, placenta integrity and fetal growth,

v) Role in the development and proper function of central and peripheral nervous system,

vi) Appetite reduction,

vii) Regulation of metabolism and endocrine homeostasis,

viii) Regulation of the cardiovascular system [20] and

ix) Anti-carcinogenic action via genes' activation or suppression in all stages of carcinogenesis [21].

Vitamin D and Cardiovascular Diseases

Seasonal changes in blood pressure and the identification of VDR and 1a-hydroxylase in cardiomyocytes, in endothelial and vascular smooth muscle cells, implicate the involvement of vitamin D in cardiovascular diseases. Animal studies have provided proof that vitamin D signaling is necessary for cardiovascular integrity, especially for the regulation of vascular tone, as well as for anti-fibrotic and anti-hypertrophic signaling in the heart. In specific, researchers have attributed seasonal cardiovascular events to low levels of 25(OH)D that was observed in winter [22]. Although there are many observational studies indicating a correlation between vitamin D deficiency and hypertension, atherosclerosis, and heart failure, they have failed to prove an aetiological relation between vitamin D supplementation and cardiovascular health [23]. Similarly, a study of 25,871 subjects failed to show favorable action of vitamin D on cardiovascular system [24,25].

VDR, first identified in cardiovascular tissues in 1986 [26], is a member of the transcription factor superfamily of nuclear receptors and translocate to the nucleus regulating the transcription of target genes, after the stimuli of vitamin D [27]. Experimental models have shown that vitamin D has many cardiovascular actions, such as inhibiting hypertrophy, decreasing cardiomyocytes' proliferation, increasing vascular smooth muscle cells' proliferation, increasing the expression of vascular endothelial growth factor (VEGF) and inhibiting of the renin-angiotensin-aldosterone system (RAAS) and the release of natriuretic peptides [28]. VDR activation by calcitriol or its analogues may directly inhibit the expression of angiotensin I and local production of angiotensin II in cardiomyocytes, in renal arteries and in kidneys [29]. It seems that vitamin D is also involved in the pathophysiology of heart failure by regulating the expression of certain metalloproteinases and metalloproteinases inhibitors [30]. Moreover, vitamin D can also affect the cardiovascular system indirectly, by being involved in the pathophysiology of hypertension, dyslipidemia, and diabetes. Finally, there is increasing evidence implicating an anti-inflammatory role by inhibiting TNF-α and nuclear factor k-B and promoting IL-10 expression in cardiovascular disease [31].

Vitamin D is an Antioxidant and Anti-inflammatory Factor

Epidemiological data have shown a significant contribution of vitamin D to the maintenance of cardiovascular health [32]. The pathophysiology of cardiovascular events includes endothelial dysfunction, vascular injury, inflammation, oxidative stress, thrombosis and, finally, plaque rupture [33] a process enhanced by several modifiable and non-modifiable risk factors, such as obesity, hypertension, and insulin resistance [34,35]. Nitric oxide (NO), apart from being a vasodilation factor and acting as a neurotransmitter, it is a potent antioxidant factor as well. Several studies have shown that vitamin D can stimulate NO production by increasing endothelial NO synthase (eNOS) gene expression [36,37]. Moreover, vitamin D seems to increase the expression of antioxidant enzymes and to up-regulate the intracellular antioxidant pathway of the nuclear factor erythroid 2-related factor 2 [38-40].

Vitamin D seems to reduce chronic inflammation, pathophysiologically involved in endothelial dysfunction, atherosclerosis, and CVD. Its anti-inflammatory actions include down-regulation of NF-kB and STAT1/5-mediated signaling, with subsequent down-regulation of the production of anti-inflammatory cytokines, such as TNF-α, IL-1, IL-2β, etc. [41]. Moreover, binding of vitamin D to VDR results in the decrease of prostaglandin and cyclooxygenase 2 production, reduction of metalloproteinase-9 (MMP-9) and increase in anti-inflammatory IL-10 production [42]. The threshold for vitamin D deficiency is set to favor bone metabolism and health [43]. It is, however, still unknown which levels of vitamin D are the optimal for maintaining cardiovascular health [44]. Randomized controlled trials have shown that vitamin D supplementation improves oxidative and inflammatory biomarkers, such as total antioxidant capacity, C-reactive protein, and glutathione, but has no effect to others like malondialdehyde and carbonyl group levels [43-47]. More studies are needed to address the certain vitamin D status necessary for CVD prevention and for the best cardiovascular benefit.

Conclusion

The involvement of vitamin D in the pathophysiology of CVD has been demonstrated by both observational and epidemiological studies. It seems to be significantly related to its anti-inflammatory and antioxidant properties. Vitamin D deficiency has been shown to be associated with greater CVD risk, but any possible etiological relation must be clarified. Vitamin D supplementation is considered beneficial for the reduction of oxidative and inflammatory parameters and for the prevention of CVD, but the optimal vitamin D status for the maximum cardiovascular benefit needs further investigation.

References

1. Silva ICJ, Lazaretti Castro M (2022) Vitamin D Metabolism and Extra skeletal Outcomes: An Update. Arch Endocrinol Metab 66(5): 748-755.
2. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357(3): 266-281.
3. Spedding S, Vanlint S, Morris H, Scragg R (2013) Does Vitamin D Sufficiency Equate to a Single Serum 25- 696 Hydroxyvitamin D Level or Are Different Levels Required for Non-Skeletal Diseases? Nutrients 5(12): 5127-5139.
4. Cianferotti L, Marcocci C (2012) Subclinical Vitamin D Deficiency. Best Pract Res Clin Endocrinol Metab 26(4): 523-537.
5. Peek SF, Buczinski S (2018) Cardiovascular Diseases. Rebhun's Diseases of Dairy Cattle: (3rd Edn.)., p. 46-93.
6. Reyes Fernandez PC, Fleet JC (2016) Compensatory Changes in Calcium Metabolism Accompany the Loss of Vitamin D Receptor (VDR) From the Distal Intestine and Kidney of Mice. J Bone Miner Res 31(1):143-151.
7. Holick MF, Binkley NC, Bischoff Ferrari HA, Catherine M Gordon, David A Hanley, et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96(7): 1911-1930.
8. Deluca HF (1988) The vitamin D story: A collaborative effort of basic science and clinical medicine. The FASEB Journal 2(3): 224-236.
9. Cheng JB, Levine MA, Bell NH, Mangelsdorf DJ, Russell DW (2004) Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proc Natl Acad Sci USA 101(20): 7711-7715.
10. Tuckey RC, Cheng CYS, Slominski AT (2019) The serum vitamin D metabolome: What we know and what is still to discover. J Steroid Biochem Mol Biol 186: 4-21.
11. Graham L (2011) IOM Releases Report on Dietary Reference Intakes for Calcium and Vitamin D. Am Fam Physician 83(11): 1352.
12. Holick MF (2017) The Vitamin D Deficiency Pandemic: Approaches for Diagnosis, Treatment and Prevention. Rev. Endocr Metab Disord 18(2): 153-165.
13. Wacker M, Holick MF (2013) Sunlight and Vitamin D: A global perspective

for health. Dermatoendocrinol 5(1): 51-108.

14. Joshi S, Pantalena LC, Liu XK, Sarah L Gaffen, Hong Liu, et al. (2011) 1,25-dihydroxyvitamin $D_{(3)}$ ameliorates Th_{17} autoimmunity via transcriptional modulation of interleukin-17A. Mol Cell Biol 31(17): 3653-3669.
15. Khanal RC, Nemere I (2007) Membrane receptors for vitamin D metabolites. Crit Rev Eukaryot Gene Expr 17(1): 31-48.
16. Hoenderop JGJ, Nilius B, Bindels RJM (2005) Calcium absorption across epithelia. Physiol Rev 85(1): 373-422.
17. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G (2016) Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev 96(1): 365-408.
18. Kim S, Yamazaki M, Zella LA, Shevde NK, Pike JW (2006) Activation of receptor activator of NF-kappaB ligand gene expression by 1,25-dihydroxyvitamin D_3 is mediated through multiple long-range enhancers. Mol Cell Biol 26(17): 6469-6486.
19. Lieben L, Masuyama R, Torrekens S, Riet Van Looveren, Jan Schrooten, et al. (2012) Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. J Clin Invest 122(5): 1803-1815.
20. Merke J, P Milde, S Lewicka, U Hügel, G Klaus, et al. (1989) Identification and regulation of 1,25-dihydroxyvitamin D_3 receptor activity and biosynthesis of 1,25-dihydroxyvitamin D_3. Studies in cultured bovine aortic endothelial cells and human dermal capillaries. J Clin Invest 83(6): 1903-1915.
21. Maier S, Daroqui MC, Scherer S, Stefan Scherer, Stefan Roepcke, Anna Velcich, et al. (2009) Butyrate and vitamin D_3 induce transcriptional attenuation at the cyclin D_1 locus in colonic carcinoma cells. J Cell Physiol 218(3): 638-642.
22. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R (1990) Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D_3 levels: A community-based study. Int J Epidemiol 19(3): 559-563.
23. Skaaby T, Thuesen BH, Linneberg A (2017) Vitamin D, Cardiovascular Disease and Risk Factors. Adv Exp Med Biol 996: 221-230.
24. Djoussé L, Cook NR, Kim E, Vijaykumar Bodar, Joseph Walter et al. (2020) Supplementation with Vitamin D and Omega-3 Fatty Acids and Incidence of Heart Failure Hospitalization: Vital Heart Failure. Circulation 141(9): 784-786.
25. Scragg R, Stewart AW, Waayer D, Carlene MM Lawes, Les Toop, et al. (2017) Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study: A Randomized Clinical Trial. JAMA Cardiol 2(6): 608-616.
26. Walters MR, Wicker DC, Riggle PC (1986) 1,25-Dihydroxyvitamin D_3 receptors identified in the rat heart. J Mol Cell Cardiol 18(1): 67-72.
27. Modarresi Ghazani F, Hejazi ME, Gharekhani A, Entezari Maleki T (2016) Role of Vitamin D in 938 cardiovascular diseases. Arch Iran Med 19: 359-362.
28. Cosentino N, Campodonico J, Milazzo V, Monica De Metrio, Marta B, et al. (2021) Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. Nutrients 13(10): 3603.
29. Freundlich M, Li YC, Quiroz Y, Yanauri Bravo, Wacharee S, et al. (2014) Paricalcitol downregulates myocardial renin-angiotensin and fibroblast growth factor expression and attenuates cardiac hypertrophy in uremic rats. Am J Hypertens 27(5): 720-726.
30. Polly P, Tan TC (2014) The role of vitamin D in skeletal and cardiac muscle function. Front Physiol 16(5): 125.
31. Roffe Vazquez DN, Huerta Delgado AS, Castillo EC, José R Villarreal, Adrian M Gonzalez-Gil, et al. (2019) Correlation of Vitamin D with Inflammatory Cytokines, Atherosclerotic Parameters, and Lifestyle Factors in the Setting of Heart Failure: A 12-Month Follow-Up Study. Int J Mol Sci 20(22): 5811.
32. Cakal S, Çakal B, Karaca O (2021) Association of Vitamin D Deficiency with Arterial Stiffness in Newly 949 Diagnosed Hypertension. Blood Press. Monit 26: 113-117.
33. Barthelmes J, Nägele MP, Ludovici V, Ruschitzka F, Sudano I, et al. (2017) Endothelial Dysfunction in Cardiovascular Disease and Flammer Syndrome-Similarities and Differences. EPMA J 8(2): 99-109.
34. Latic N, Erben RG (2020) Vitamin D and Cardiovascular Disease, with Emphasis on Hypertension, Atherosclerosis, and Heart Failure. Int J Mol Sci 21(18): 6483.
35. Gallo G, Volpe M, Savoia C (2022) Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. Front Med 8: 798958.
36. Molinari C, Uberti F, Grossini E, Vacca G, Carda S, et al. (2011)1α,25- Dihydroxycholecalciferol Induces Nitric Oxide Production in Cultured Endothelial Cells. Cell Physiol Biochem 27(6): 661-668.
37. Andrukhova O, Slavic S, Zeitz U, Riesen SC, Heppelmann MS, et al. (2014) Vitamin D Is a Regulator of Endothelial Nitric Oxide Synthase and Arterial Stiffness in Mice. Mol Endocrinol 28(1): 53-64.
38. Jain SK, Micinski D, Huning L, Kahlon G, Bass PF, et al. (2014) Vitamin D and L-Cysteine Levels Correlate Positively with GSH and Negatively with Insulin Resistance Levels in the Blood of Type 2 Diabetic Patients. Eur J Clin Nutr 68(10): 1148-1153.
39. Nakai K, Fujii H, Kono K, Goto S, Kitazawa R, et al. (2014) Vitamin D Activates the Nrf2-Keap1 Antioxidant Pathway and Ameliorates Nephropathy in Diabetic Rats. Am J Hypertens 27(4): 586-595.
40. Bhat M, Ismail A (2015) Vitamin D Treatment Protects against and Reverses Oxidative Stress Induced Muscle Proteolysis. J Steroid Biochem Mol Biol 152: 171-179.
41. Calton EK, Keane KN, Newsholme P, Soares MJ (2015) The Impact of Vitamin D Levels on Inflammatory Status: A Systematic Review of Immune Cell Studies. PLoS One 10 (11): e0141770.
42. Kunadian V, Ford GA, Bawamia B, Qiu W, Manson JE (2014) Vitamin D Deficiency and Coronary Artery Disease: A Review of the Evidence. Am Heart J 167(3): 283-291.
43. Kalvandi F, Azarbayjani MA, Azizbeigi R, Azizbeigi K (2022) Elastic Resistance Training Is More Effective than Vitamin D_3 Supplementation in Reducing Oxidative Stress and Strengthen Antioxidant Enzymes in Healthy Men. Eur J Clin Nutr 76(4): 610-615.
44. Asemi Z, Samimi M, Tabassi Z, Shakeri H, Esmaillzadeh A (2013) Vitamin D Supplementation Affects Serum High-Sensitivity C-Reactive Protein, Insulin Resistance, and Biomarkers of Oxidative Stress in Pregnant Women. J Nutr 143(9): 1432-1438.
45. Timar A, Saberi Karimian M, Ghazizadeh H, Parizadeh SMR, Sabbaghzadeh R, et al. (2019) Evaluation of the Serum Prooxidant-Antioxidant Balance before and after Vitamin D Supplementation in Adolescent Iranian Girls. Adv Med Sci 64(1): 174-180.
46. De Medeiros Cavalcante IG, Silva AS, Costa MJC, Persuhn DC, Issa CTMI, et al. (2015) Effect of Vitamin D_3 Supplementation and Influence of BsmI Polymorphism of the VDR Gene of the Inflammatory Profile and Oxida-

tive Stress in Elderly Women with Vitamin D Insufficiency Vitamin D_3 Megadose Reduces Inflammatory Markers. Exp Gerontol 66: 10-16.

47. Scholten S, Sergeev I, Birger C, Song Q (2015) Effects of Vitamin D and Quercetin, Alone and in Combination, on Cardiorespiratory Fitness and Muscle Function in Physically Active Male Adults. Open Access J Sport Med 6: 229-239.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.50.007886

Kali Makedou. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php