Marijana C Jandric Kocic[1]

VITAMIN D AND HYPERTENSION

Summary: Vitamin D is the name for a group of fat-soluble secosteroids, prohormones. Almost all tissues of the human body have vitamin D receptors. 3% of the human genome is under the influence of vitamin D. A significant number of epidemiological studies confirmed the integral connection of vitamin D and its metabolites with the value of blood pressure. Vitamin D lowers blood pressure by inhibiting the renin-angiotensin-aldosterone system, modulating the tone of vascular smooth muscle cells and influencing the vascular endothelium. The results of randomized controlled trials and meta-analyses of the same do not generally support the widespread use of vitamin D in the prevention and treatment of arterial hypertension. Nevertheless, a large number of experimental studies confirm the antihypertensive effect of vitamin D supplementation predominantly in people aged ≥ 50 years as well as obese people with vitamin D deficiency. Further research is needed to determine the potential benefit of vitamin D replacement therapy in hypertensive people.

Key words: vitamin D, blood pressure, hypertension

Vitamin D

Vitamin D (calciferol) is the name for a group of fat-soluble secosteroids, prohormones[1,2]. The two main forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol)[1-6]. Vitamin D2 is synthesized from ergosterol under the influence of ultraviolet B radiation predominantly in mushrooms and yeast[3]. Vitamin D3 is synthesized in the skin and is the main dietary source of vitamin D in foods of animal origin (fish, meat, eggs and milk)[3]. About 80% of the recommended daily amount of vitamin D is synthesized in the skin under the influence of ultraviolet B radiation (290–315 nm)[6]. Photochemical reaction from 7-dehydrocholesterol (provitamin D) produces precholecalciferol (previtamin D), which is converted into cholecalciferol (vitamin D) by isomerization[6-8]. Cholecalciferol enters the circulation

[1] Marijana C. Jandric-Kocic, Primary Health care Center Krupa na Uni, Republic of Srpska, BiH, marijanajandrickocic@gmail.com

where it binds to vitamin D binding protein and is thus transported to the liver[6-8]. The biosynthesis of the active form of vitamin D involves two hydroxylations[6-8]. The first hydroxylation takes place in the liver at the C-25 atom of cholecalciferol[6-8]. Under the action of the mitochondrial enzyme 25-hydroxylase, 25-hydroxycholecalciferol (the main circulating form of vitamin D) is formed[6-8]. The active form of vitamin D, 1,25-dihydroxycholecalciferol, is created in the kidney by hydroxylation on the C-1 atom of 25-hydroxycholecalciferol under the action of the mitochondrial enzyme 1α-hydroxylase[6-8]. Vitamin D activation is mediated by cytochrome P450 enzymes (cytochrome P450s, CYPs) including CYP27A1, CYP2R1, CYP3A4 and CYP2J3 (liver) and CYP27B1 (kidney)[8]. The mitochondrial enzyme 1α-hydroxylase is also present in extrarenal tissues (macrophages, keratinocytes, smooth muscle cells of blood vessels, β-cells of the pancreas, cells of the heart, colon, prostate, breast and brain)[7]. Extrarenal synthesis of 1,25-dihydroxycholecalciferol is limited by its bioavailability (independent of parathyroid hormone)[7]. The synthesis of 1,25-dihydroxycholecalciferol in the kidney is regulated by parathyroid hormone, fibroblast growth factor 23 and 1,25-dihydroxycholecalciferol itself[9].

It is believed that about 3% of the human genome is under the influence of vitamin D and that almost all tissues possess vitamin D receptors[7]. Vitamin D has a genomic and non-genomic effect[7]. It achieves its non-genomic effect by binding to the vitamin D membrane receptor, which causes the intracellular formation of a second messenger or the phosphorylation of intracellular proteins, the consequent activation of intracellular enzymes or ion channels and the modulation of cell activity7. It achieves its genomic effect by binding to the highly specific vitamin D receptor (ligand-dependent transcription factor)[7,10]. Vitamin D binding induces heterodimerization of the vitamin D receptor with the retinoid X receptor, translocation into the cell nucleus, binding to deoxyribonucleic acid and regulation of gene transcription[7]. Vitamin D, in addition to its regulatory role in bone mineralization and calcium metabolism, has autocrine and paracrine functions that are related to the immune, cardiovascular and neuroendocrine systems[11].

Recommended concentrations of 25-hydroxycholecalciferol in the blood of adults are > 30 ng/mL[11]. Concentrations lower than 30 ng/mL represent deficiency or insufficiency, lower than 20 ng/mL lack or deficiency of vitamin D[11]. An excess of vitamin D is present at a concentration > 100 ng/mL, intoxication at a concentration > 125 ng/mL in the blood[11]. The recommended daily amount of vitamin D for adults up to 50 years of age is 600 IJ/day[5-11]. People over 50 years of age require up to 800 IU/day[5-11]. Vitamin D deficiency is a significant public health problem[12]. It is believed that one billion people worldwide are deficient in vitamin D12. Initial therapy includes supplementation with 1,25-dihydroxycholecalciferol 6,000 IU/day or 50,000 IU/week for 8 weeks12. When the value of 25-hydroxycholecalciferol exceeds 30 ng/mL, a maintenance dose of 1,000 IU/day to 2,000 IU/day is recommended[12].

Arterial hypertension is the most common and poorly controlled mortality risk factor in the world[13-17]. More than one billion people worldwide have high blood pressure that requires some form of treatment[15]. Complications of arterial hypertension are associated with 10.4 million deaths per year[14]. The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) for the management of hypertension define arterial hypertension as values of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg[13]. In 90-95% of cases, arterial hypertension has no known etiology and is designated as essential (primary or idiopathic)[13]. Secondary arterial hypertension has an underlying cause that can be identified[13]. Essential arterial hypertension is a complex entity resulting from the interaction of genetic, behavioral, socio-economic and environmental factors[13]. The main pathophysiological mechanisms include activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, endothelial dysfunction, increased vascular reactivity and vascular remodeling[16].

A significant number of epidemiological studies confirmed the integral connection of vitamin D and its metabolites with the value of blood pressure[18-22]. Their findings are supported by pathophysiological mechanisms as well as the presence of vitamin D receptors in endothelial cells as well as smooth muscle cells of blood vessels[18-22].

Methods

The literature was searched using the keywords: vitamin D, blood pressure, and hypertension. The search was conducted for the period from 2001 to 2023 within the following databases: PubMed, Emabase and Scopus. Due to the limited number of available studies, no available filters were used in the database search. After the summaries were read, the papers were studied in more detail and those that did not correspond to the research objective were excluded.

Effect of vitamin d on blood pressure value

Vitamin D lowers blood pressure by inhibiting the renin-angiotensin-aldosterone system, modulating the tone of vascular smooth muscle cells and influencing the vascular endothelium[18].

Vitamin D acts as a proximal inhibitor of the renin-angiotensin-aldosterone system[18,19]. The vitamin D receptor inhibits renin gene expression by binding to the promoter site[20]. Increased concentrations of vitamin D are actively associated with lower renin and reduced angiotensin II concentration[18,20]. Vitamin D modulates vascular tone by changing calcium concentration in smooth muscle cells of blood

vessels (intracellular calcium accumulation inhibits renin secretion in juxtaglomerular cells)[18]. There is evidence that increased salt consumption increases vitamin D concentration and intravascular calcium concentration, which consequently decreases vascular tone and the activity of the renin-angiotensin-aldosterone system[18]. The exact pathophysiological mechanism of the mentioned interaction has not been clarified[18]. Vitamin D has a protective effect on the endothelium and smooth muscles of blood vessels [18,21,22]. It protects the endothelium from the end products of advanced glycation, improves the activity of nitric oxide, has anti-inflammatory and antiatherosclerotic effects[18,21,22]. Also, vitamin D is involved in the growth of vascular myocytes and the production of prostacyclin (through the cyclooxygenase pathway)[18].

Vitamin D supplementation in hypertension therapy

A significant number of experimental studies found that vitamin D supplementation has an antihypertensive effect[18]. A randomized, double-blind study of normotensive individuals aged ≥60 years with vitamin D deficiency in Switzerland found that vitamin D supplementation at a dose of 800 IU/day and 2000 IU/day over two years resulted in a reduction of mean systolic pressure by 3,94 and 2,75 mmHg[23,24]. A multicenter randomized, double-blind study (DO-HEALTH) in Switzerland, France, Germany, Portugal, and Austria observed that vitamin D supplementation at a dose of 2000 IU/day or 800 IU/day over three years reduced systolic pressure by 8,6 and 7,9 mmHg, in hypertensive persons aged ≥ 70 years with vitamin D deficiency[24,25]. A study in Germany found that supplementation with calcium at a dose of 1200 mg/day and vitamin D at a dose of 800 IU/day for eight weeks in women over 70 years of age with a plasma 25-hydroxycholecalciferol level < 50 ng/ml reduced systolic blood pressure of 9,3%[26]. These results have clinical significance since each 10 mmHg reduction in systolic pressure causes a 17% reduction in coronary heart disease, 27% in stroke, 28% in heart failure, and 13% in all-cause mortality[24]. In addition to monotherapy, vitamin D was used in combination with conventional antihypertensives therapy27,28. A 2-year double-blind randomized controlled clinical trial of hypertensive individuals aged 18 to 75 years in Iran found that vitamin D supplementation (1000IU/week for vitamin D concentrations of 20 to 30 ng/mL and 50,000IU/week for vitamin D concentrations <20 ng/mL mL) of antihypertensive therapy for two months causes a significant decrease in systolic blood pressure[27]. Similar results were obtained by a group of researchers in India using 33,000 IU of vitamin D every 2 weeks for 3 months in addition to conventional antihypertensive therapy in patients with vitamin D deficiency[28]. A double-blind, randomized, controlled clinical trial in the United States of America among overnourished or obese children with vitamin D deficiency aged 10 to 18 years found that administration of vitamin D at a dose of 1000IU/day for 6

months resulted in a significant reduction in systolic blood pressure[29]. A meta-analysis of 22 randomized controlled trials in China found that vitamin D supplementation reduced systolic blood pressure in people over 50 years of age or obese with vitamin D deficiency[30]. A meta-analysis of 30 randomized controlled studies confirmed that vitamin D supplementation in a dose > 800IU/day for a period longer than 6 months significantly lowers systolic and diastolic blood pressure in people aged ≥ 50 years with vitamin D deficiency[31].

On the other hand, a single-center, double-blind, placebo-controlled study of the effect of vitamin D supplementation at a dose of 2800 IU/day for eight weeks in Austria observed an inverse association of the achieved concentrations of 25-hydroxycholecalciferol with the values of 24h systolic blood pressure, but not a statistically significant reduction in 24h of systolic blood pressure in adults with vitamin D concentration > 30 ng/mL[32]. A double-blind, placebo-controlled study in Brazil found that single vitamin D supplementation at a dose of 200,000 IU in women aged > 70 years did not reduce resting blood pressure after seven days[33]. A double-blind, placebo-controlled study in New Zealand found that vitamin D supplementation for 18 months (200,000 IU/month for two months and 100,000 IU/month) had no statistically significant effect on blood pressure values in healthy adults (predominantly white) with no significant vitamin D deficiency[34]. A meta-analysis of 46 randomized controlled studies by authors from several countries did not identify a statistically significant effect of vitamin D supplementation on blood pressure values[35]. A meta-analysis of 27 randomized controlled trials in China had identical results[36].

Conclusion

A significant number of epidemiological studies confirmed the integral connection of vitamin D and its metabolites with the value of blood pressure. Their findings are supported by pathophysiological mechanisms as well as the presence of vitamin D receptors in endothelial cells as well as smooth muscle cells of blood vessels. The results of randomized controlled trials and meta-analyses of the same do not generally support the widespread use of vitamin D in the prevention and treatment of arterial hypertension. Nevertheless, a large number of experimental studies confirm the antihypertensive effect of vitamin D supplementation predominantly in people aged ≥ 50 years as well as obese people with vitamin D deficiency. Further research is needed to determine the potential benefit of vitamin D replacement therapy in hypertensive people.

Literature

1. Kalil G, Haynes W. Sympathetic nervous system in obesity-related hypertension: mechanisms and clinical implications. Hypertens Res. 2012;35:4–16. Available from: https://doi.org/10.1038/hr.2011.173
2. 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):255. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8074587/
3. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, DelValleet HB, Breiner H, Bandyal A et al editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US); 2011.3. Overview of Vitamin D. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56061/
4. Ružić M, Shek Vugrovečki A, Špoljarić D, Špoljarić B, Šimpraga M, Žura Žaja I. Uloga vitamina D u ovaca. Veterinsrska stanica. 2023;54(1). Available from: https://hrcak.srce.hr/file/396721
5. Kendić S, Salihagić A. Fiziološka uloga vitamina D u prevenciji nastanka i razvoja hroničnih nezaraznih bolesti. Zbornik Islamskog pedagoškog fakulteta u Bihaću. 2019;10.
6. Naumović N. Fiziološki značaj vitamina D. Med Pregl. 2010;63(5-6):301-304. Available from: https://scindeks-clanci.ceon.rs/data/pdf/0025-8105/2010/0025-81051006301N.pdf
7. Laktašić-Žerjavić N, Koršić M, Crnčević-Orlić Ž, Anić B. Vitamin D: vitamin prošlosti, hormon budućnosti. Liječ Vjesn. 2011;133:194–204. Available from: https://hrcak.srce.hr/file/253427
8. Jovičić S, Ignjatović S, Majkić-Singh N. Biochemistry and metabolism of vitamin D. Journal of Medical Biochemistry. 2012;31(4):309-15. Available from: https://scindeks.ceon.rs/article.aspx?artid=1452-82581204309J
9. Latic N, Erben RG. FGF23 and Vitamin D Metabolism. JBMR Plus. 2021;5(12):e10558. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8674776/
10. Kongsbak M, Levring TB, Geisler C, von Essen MR. The Vitamin D Receptor and T Cell Function. Frontiers in Immunology. 2013;4. Available from: https://doi.org/10.3389/fimmu.2013.00148
11. Milešević J. Razvoj prediktivnog modela obogaćivanja prehrambenih proizvoda vitaminom D u Srbiji– doktorska disertacija. Univerzitet u Novom Sadu, tehnološki fakultet. 2019. Available from: https://rimi.imi.bg.ac.rs/bitstream/handle/123456789/1122/1119.pdf?sequence=1&isAllowed=y
12. Sizar O, Khare S, Goyal A, et al. Vitamin D Deficiency. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532266/33.
13. Ninković Mrđenovački O. Faktori koji utiču na postignute vrednosti krvnog pritiska osoba sa dijagnostikovanom arterijskom hipertenzijom na nivou primarne zdravstvene zaštite – doktorska disertacija. Univerzitet u Novom Sadu, medicinski fakultet. 2017. Available from:http://nardus.mpn.gov.rs/bitstream/handle/123456789/8649/Disertacija11498.pdf?sequence=1&isAllowed=y.

14. Jelaković B, Bajer V, Banadinović M, Bilajac L, Capak K, Ćatić Ćuti E et al. Epidemiologija arterijske hipertenzije i unos kuhinjske soli u Hrvatskoj (EH-UH 2). Projekt Hrvatske zaklade za znanost (IP-06-2016). Medix. 2018;24(133/134):117-127. Available from:https://www.kardio.hr/wp-content/uploads/2019/05/Medix-133-134_117-127.pdf
15. Hall JE, Granger JP, Jones DW, Hall ME. Patophysiology of hypertension. In: Fuster V, Harrington RA, Narula J, Eapen ZJ. eds. Hurst's The Heart, 14e. McGraw Hill; 2017. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=2046&-sectionid=176572779
16. Oparil S, Zaman AM, Calhoun DA. Pathogenesis of Hypertension. Ann Intern Med.2003;139:761-776. Available from: https://www.acpjournals.org/doi/10.7326/0003-4819-139-9-200311040-00011 17.
17. Pavletić Peršić M , Vuksanović-Mikuličić S, Rački S. Arterijska hipertenzija. Medicina fluminensis. 2010;46(4):376-389. Available from: https://hrcak.srce.hr/file/94522
18. Vaidya A, Forman JP. Vitamin D and Hypertension. Current Evidence and Future Directions. Hypertension. 2010;56:774–779. Available from: https://www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.109.140160
19. Cervellin G, Salvagno G, Bonfanti L, Bonelli P, Guidi GC, Lippi G. Association of Hyponatremia and Hypovitaminosis D in Ambulatory Adults. J Med Biochem. 2015t;34(4):450-454. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4922356/
20. Grundmann SM, Schutkowski A, Schreier B, Rabe S, König B, Gekle M, Stangl GI. Vitamin D Receptor Deficiency Does Not Affect Blood Pressure and Heart Function. Front Physiol. 2019;10:1118. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6727788/
21. Pavlović D, Josipović J, Pavlović N. Vitamin D and hypertension. Period biol. 2011;113(3):299-302. Available from: https://hrcak.srce.hr/file/110014
22. Yaniel CT, Pérez AF, Puerta RC, Valdez MV, Castillo IS. Déficit de la vitamina D e hipertensión arterial. Evidencias a favor. Revista Colombiana de Cardiología. 2016;23(1):42-48. Available from: https://www.elsevier.es/es-revista-revista-colombiana-cardiologia-203-articulo-deficit-vitamina-d-e-hipertension-S0120563315001278
23. Abderhalden LA, Meyer S, Dawson-Hughes B, Orav EJ, Meyer U, de Godoi Rezende Costa Molino C, et al. Effect of daily 2000 IU versus 800 IU vitamin D on blood pressure among adults age 60 years and older: a randomized clinical trial. Am J Clin Nutr. 2020;112(3):527–37. Available from: https://doi.org/10.1093/ajcn/nqaa145
24. Chen S, Gemelga G, Yeghiazarians Y. Is Vitamin D Supplementation an Effective Treatment for Hypertension? Curr Hypertens Rep. 2022;24(10):445-453. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9509305/#CR28
25. Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, da Silva JAP, Blauth M, Felson DT, McCloskey EV et al. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. JAMA. 2020 Nov 10;324(18):1855-1868. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7656284/.

26. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a Short-Term Vitamin D_3 and Calcium Supplementation on Blood Pressure and Parathyroid Hormone Levels in Elderly Women. The Journal of Clinical Endocrinology & Metabolism. 2001;86(4): 1633–1637. Available from: https://academic.oup.com/jcem/article/86/4/1633/2848459
27. Sheikh V, Mozaianimonfared A, Gharakhani M, Poorolajal J. Effect of vitamin D supplementation versus placebo on essential hypertension in patients with vitamin D deficiency: a double-blind randomized clinical trial. J Clin Hypertens.2020;22:1867– 1873. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jch.13926
28. Goel RK, Lal H. Role of Vitamin D Supplementation in Hypertension. Ind J Clin Biochem. 2011;26;88–90. Available from: https://doi.org/10.1007/s12291-010-0092-0
29. Rajakumar K, Moore CG, KhalidAT, Vallejo AN, Virji MA, Holick MF et al. Effect of vitamin D_3 supplementation on vascular and metabolic health of vitamin D–deficient overweight and obese children: a randomized clinical trial. The American Journal of Clinical Nutrition. 2020;111(4):757–768. Available from: https://academic.oup.com/ajcn/article/111/4/757/5707680#
30. He Silu BS, Hao Xiyuan MS. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: A system review and meta-analysis. Medicine. 2019;98(19):p Available from: https://journals.lww.com/md-journal/Fulltext/2019/05100/The_effect_of_vitamin_D3_on_blood_pressure_in.11.aspx#JCL-P-23
31. Golzarand M, Shab-Bidar S, Koochakpoor G, Speakman JR, Djafarian K. Effect of vitamin D3 supplementation on blood pressure in adults: An updated meta-analysis. NMCD. 2016;26(8):663-673. Available from: https://www.nmcd-journal.com/article/S0939-4753(15)30123-X/fulltext
32. Theiler-Schwetz V, Trummer C, Grübler MR, Keppel MH, Zittermann A, Tomaschitz A et al. Effects of Vitamin D Supplementation on 24-Hour Blood Pressure in Patients with Low 25-Hydroxyvitamin D Levels: A Randomized Controlled Trial. Nutrients. 2022;14(7):1360. Available from: https://doi.org/10.3390/nu14071360
33. Silu BSH, Xiyuan MSH. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: A system review and meta-analysis. Medicine. 2019;98(19):p e15284. Available from: https://journals.lww.com/md-journal/fulltext/2019/05100/the_effect_of_vitamin_d3_on_blood_pressure_in.11.aspx
34. Scragg R, Slow S, Stewart AW, Jennings LC, Chambers ST, Priest PC et al. Long-Term High-Dose Vitamin D3 Supplementation and Blood Pressure in Healthy Adults. Hypertension. 2014;64:725–730. Available from: https://www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.114.03466#
35. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM. Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. JAMA Intern Med. 2015;175(5):745–754. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2195120?resultClick=1
36. Zhang D, Cheng C, Wang Y, Sun H, Yu S, Xue Y, et al. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials. Prev Chronic Dis 2020;17:190307. Available from: https://www.cdc.gov/pcd/issues/2020/19_0307.htm