



СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

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Paper Accepted*

ISSN Online 2406-0895

Review Article / Прегледни рад

Nedeljko Radlović¹, Petar Radlović², Zoran Leković^{3,4}, Marija Mladenović⁵, Biljana Vuletić^{6,7},
Siniša Dučić^{3,4}, Vladimir Radlović^{3,4,*}

Vitamin D: a comprehensive review

Витамин Д: свеобухватни преглед

¹Serbian Medical Society, Academy of Medical Sciences of the Serbian Medical Society, Belgrade, Serbia;

²Institute for Oncology and Radiology of Serbia, Belgrade, Serbia;

³University Children's Hospital, Belgrade, Serbia;

⁴University of Belgrade, Faculty of Medicine, Belgrade, Serbia;

⁵Singidunum University, Faculty of Health, Legal and Business Studies, Valjevo, Serbia;

⁶Kragujevac Clinical Center, Pediatric Clinic, Kragujevac, Serbia;

⁷University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

Received: December 4, 2024

Accepted: January 2, 2025

Online First: January 10, 2025

DOI: <https://doi.org/10.2298/SARH241204004R>

* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

***Correspondence to:**

Vladimir RADLOVIĆ

University Children's Hospital, Tiršova 10, 110000 Belgrade, Serbia

E-mail: vladar@botel.net

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SUMMARY

Vitamin D (calciferol), i.e. its active metabolite calcitriol [1,25(OH)₂D], apart from essential participation in calcium and phosphorus homeostasis, is an important factor in the regulation of cell proliferation, differentiation and apoptosis, angiogenesis, immune and hormonal activity and others processes in the human body. Hence, its optimal balance is extremely important for adequate prenatal and postnatal growth and development, as well as for the preservation of health in other phases of life. This article provides a brief overview of the natural source of vitamin D, its metabolism and physiological role, as well as current recommendations related to the coverage of its optimal needs.

Key words: vitamin D; physiological role; optimal need

САЖЕТАК

Витамин Д (калциферол), односно његов активни метаболит калцитриол [1,25(OH)₂D], осим есенцијалог учешћа у хомеостази калцијума и фосфора, битан је фактор у регулацији ћелијске пролиферације, диференцијације и апоптозе, ангиогенезе, иминске и хормонске активности и других процеса у људском организму. Отуда је његов оптимални биланс од изузетног значаја за адекватан пренатални и постнатални раст и развој, као и очувању здравља у осталим фазама живота. У овом чланку дат је кратак преглед природног извора витамина Д, његовог метаболизма и физиолошке улоге, као и актуелних препорука везаних за покриће његових оптималних потреба.

Кључне речи: витамин Д; физиолошка улога; оптимална потреба

INTRODUCTION

Vitamin D (calciferol), i.e. its active metabolite calcitriol [1,25(OH)₂D] is essential factor in ensuring calcium and phosphorus homeostasis and an important participant in the regulation of cell proliferation, differentiation and apoptosis, as well as immune, hormonal and other processes in human organism [1–7]. Hence, its optimal balance in the body is extremely important for normal prenatal and later growth and development, as well as for maintaining health in other phases of life [8–14]. This article provides a brief overview of the natural source of vitamin D, its metabolism and physiological role, as well as current guidelines related to meeting its optimal needs.

NATURAL SOURCES OF VITAMIN D

There are two major forms of vitamin D: vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol), which differ in origin and chemical structure. Both variants of vitamin D are the product of photolytic cleavage of the C₉-C₁₀ bond in the sterol B ring after exposure to ultraviolet-B (UV-B) rays of wavelengths 290–315 nm of the respective precursors, i.e. in the skin of man and most terrestrial vertebrates 7-dehydrocholesterol (7-DHC) to cholecalciferol and in yeast and other fungi ergosterol to ergocalciferol [1, 14, 15]. The origin of vitamin D in fish comes from from zooplankton and microalgae in the food chain in water, while some land animals, such as dogs and cats, get it by consuming others [16, 17]. Unlike cholecalciferol, the

side chain of ergocalciferol having an double bond at the position C₂₂-C₂₃ and a methyl group at C₂₄. A recent comparative analysis of the results of 20 studies showed that vitamin D₃, apart from more efficiently raising serum 25(OH)D concentration, has no advantage over vitamin D₂ [18].

Most of our vitamin D needs are met by production in the skin, while foods, excluding fish oil, fatty fish, liver, egg yolks, edible mushrooms treated with UV light, and fortified foods such as milk formulas, are poor sources of vitamin D. (Table 1) [1, 7, 19, 20, 21].

During photolysis of 7-DHC in epidermal keratocytes and dermal fibroblasts under the influence of sunlight, previtamin D₃ is formed, which is then isomerized to vitamin D₃ at skin temperature [1, 7, 13, 22]. The level of skin production of vitamin D depends on latitude and altitude, season, time of day, body surface area and length of exposure to the sun, amount of melanin in the skin, age and degree of protection from sunlight and genetic factors [1, 7, 13, 23, 24]. Apart from staying in the shade and using sun protection creams, cloudy weather and air pollution significantly reduce the skin's production of vitamin D₃ [1, 7, 24]. It is important to point out that excessive exposure to sunlight, especially sunburn, increases the risk of skin cancer, so it should be avoided [14, 25]. Bearing in mind the cumulative nature of sun damage, this is additionally true for the pediatric age group, and especially for infants under 6 months of age, who should not be exposed to direct sunlight due to the developmental hypersensitivity of the skin [26].

Vitamin D produced in the skin diffuses into the blood and, bound to vitamin D binding protein (DBP) and partly to albumin (10–15%), is transported to the liver, where it is hydroxylated into 25(OH)D (calcidiol), while the excess it is deposited, mainly (75%) in fatty tissue, and the rest in the liver, muscles and skeleton [1, 7, 22]. Holich suggests that exposing the arms and legs for 5 to 30 minutes (depending on the time of day, season, latitude, and skin pigmentation) between 10 and 3 p.m. twice a week is often enough to meet vitamin D needs [14]. Due to photoisomerization into non-toxic metabolites (lumisterol, tachysterol, suprasterol I and II and 5,6 trans cholecalciferol), the protective effect of melanin and skin desquamation, vitamin D intoxication through sun exposure is not possible [1, 7, 22, 25].

Vitamin D from food and supplements is absorbed in the small intestine by passive diffusion through micelles containing bile acids and then, incorporated into chylomicrons, exported from the enterocytes to the lymphatic system and transported to the systemic circulation [7]. The degree of intestinal absorption of vitamin D in a healthy person varies between 55 and 99% (on average about 80%), while in patients with fat malabsorption it is very low [7, 13, 22, 27]. After

entering the circulation, vitamin D is released from chylomicrons under the action of lipoprotein lipase and follows the same path as the fraction formed in the skin [7, 22]. Intestinal absorption of calcidiol, which is found in drugs intended for patients with fat malabsorption, as well as in variable amounts in some foods of animal origin, such as meat (0.8–16.4 IJ/100 g), liver (2.8–30.8 IJ/100 g) and kidney (3.6–93.2 IJ/100 g), since it is soluble in water, it is independent of the presence of bile acids and the formation of micelles and is therefore significantly more effective (about 93%) [22, 28]. The active metabolite of vitamin D, 1,25(OH)₂D (calcitriol), is found only in trace amounts in animal foods and does not contribute much to the biological activity of vitamin D [28]. Like other water-soluble substances, hydroxylated forms of vitamin D are absorbed directly from the proximal jejunum into the portal bloodstream and, bound to DBP and to a lesser extent to albumin, are distributed throughout the body [22, 28]. In contrast to vitamin D, which is mostly found in fat-tissue depots, 25(OH)D is more evenly distributed in the body (about 35% in fat tissue, 30% in blood, 20% in muscles and 15% in other tissues) [22]. According to research conducted on submarine personnel, the half-life of 25(OH)D in circulation in the absence of cholecalciferol supplementation is about two months [29].

Fetal need for vitamin D is met by placental transfer of hydroxylated forms of vitamin D, i.e. 25(OH)D and 1,25(OH)₂D [12]. At birth, human infants possess a small reserve of vitamin D in the form of 25(OH)D, which disappears during 6–8 weeks of postnatal life [7].

ACTIVATION OF VITAMIN D

Since it is a biologically inert compound, in order to express its effect, vitamin D must go through two hydroxylation processes, the first in the hepatocyte microsomes and the second in the mitochondria of renal proximal tubular cells. The first hydroxylation is catalyzed by the 25-hydroxylase, resulting in 25(OH)D, the major circulating form of vitamin D, which is bound to DBP and to a lesser extent to albumin and distributed to all cells of the body. The second reaction is mediated by 1 α -hydroxylase, which converts 25(OH)D to the biologically active hormone, 1,25(OH)₂D. Apart from the kidney, 1 α -hydroxylase is present in macrophages, monocytes and cells of the skeleton, teeth, breast, prostate, colon, pancreas, brain, adrenal glands, placenta and other tissues [1]. The half-life of 25(OH)D in circulation is about 15 days, while 1,25(OH)₂D is inactivated in 4 hours [7, 30]. Therefore, serum 25(OH)D levels are used as a reliable indicator of vitamin D status in the body [7, 31]. Table 2 shows the criteria of the Institute of Medicine (IOM, since 2015 the National Academy of Medicine of the United

States of America) regarding the level of 25(OH)D in serum and health [7]. Apart from the risk of a toxic effect of vitamin D, the IOM bases its recommendation regarding the upper reference value of the serum level of 25(OH)D on the absence of evidence to support that its level over 125 nmol/L results in additional health benefits [7]. The relevant associations of the Nordic and DACH countries, Australia and New Zealand, as well as the American Academy of Pediatrics and the Endocrine Society agree with the IOM guidelines regarding the lower limit of vitamin D adequacy based on serum 25(OH)D concentration, while the American Geriatrics Society, the International Foundation for Osteoporosis and some experts believe that it should be 75 nmol/L, respectively 100 nmol/L [30, 32, 33].

The activity of 1-alpha hydroxylase in the hydroxylation of 25(OH)D to 1,25(OH)₂D in the kidneys is primarily stimulated by parathyroid hormone (PTH), but also by hypocalcemia, hypophosphatemia, growth hormone, sex hormones, prolactin, and low levels of serum 1,25(OH)₂D, while the activity of this enzyme in extrarenal tissues is regulated by autochthonous factors, such as local growth factors, cytokines (gamma-interferon, tumor necrosis factor) and others [2, 5, 34]. A major suppressor of vitamin D activation is fibroblast growth factor-23 (FGF-23), a bone-derived hormone produced mainly by osteoblasts and osteocytes in response to increased extracellular phosphate and circulating 1,25(OH)₂D [1, 35]. FGF-23 reduces renal 1,25(OH)₂D synthesis by inhibiting the activity of 1 α-hydroxylase, which transforms 25(OH)D into 1,25(OH)₂D, and by stimulating 24-hydroxylase, which degrades both 25(OH)D and 1,25(OH)₂D [1, 35, 36]. Therefore, adequate concentrations of 1,25(OH)₂D in the body, in addition to regulating synthesis, are also achieved by controlling its inactivation. Inactivation of 1,25(OH)₂D is carried out by hydroxylation at C₂₄, not only in the kidneys, but also in the intestines, bones, cartilage, skin, prostate, placenta and other tissues, which results in the formation of inactive water-soluble products (calcitroic acid and 23-carboxylic derivatives) which are eliminated in bile and urine [2, 7, 22].

Due to efficient and unlimited intestinal absorption, high deposition in the body and extremely limited elimination, excessive oral intake of vitamin D leads to hypercalcemic heart rhythm disorders, the formation of renal stones, as well as soft tissue calcification and resultant renal and cardiovascular damage [7, 22, 37]. An identical problem occurs as part of a non-critically high parenteral change of vitamin D. Likewise, excessive vitamin D intake during pregnancy, in addition to preterm birth, can cause excessive transplacental transfer of 25(OH)D and life-threatening hypercalcemia in the newborn [38].

PHYSIOLOGICAL EFFECTS OF VITAMIN D

The physiologic effects of $1,25(\text{OH})_2\text{D}$ are mediated via the nuclear receptor (nVDR), i.e. by stimulating or inhibiting the transcription of more than 1000 human genes, and partly through membrane receptors (mVDRs) [1, 4, 13, 34, 39]. Both effects of $1,25(\text{OH})_2\text{D}$ work in synergy, with the fact that it is genomic, i.e. mediated by nVDR compared to membrane much slower [13]. Except in renal tubular cells, the presence of the nVDR has been evidenced in T and B lymphocytes, macrophages, cells of the pancreas, brain, breast, skin and other tissues [13, 39]. By modulating gene expression, the synthesis of various proteins responsible for the classic (calcitropic) and non-classic (non-calcitropic) effects of vitamin D is regulated [1, 4, 35]. Membrane (non-genomic) effects of $1,25(\text{OH})_2\text{D}$, also significant for cell function, are reflected in the regulation of cellular permeability to calcium and chlorine, as well as in raising the intracellular level of phospholipase C, cyclic guanosine monophosphate, protein kinase C and phosphoinositide metabolism [4, 34]. Through its main target tissues, the small intestine, kidneys and bones, vitamin D plays a key role in the regulation of calcium and phosphorus homeostasis [1, 4, 13]. In enterocytes and tubulocytes $1,25(\text{OH})_2\text{D}$ stimulates the synthesis of calcium channels, calbindin, Ca^{2+} ATP-ase, $3\text{Na}^+/\text{Ca}^{2+}$ ion exchanger and $2\text{Na}^+/\text{HPO}_4^{2-}$ cotransporter, thus enabling intestinal absorption and renal reabsorption of these ions and their transfer into the circulation [34]. The normal level of calcium and phosphorus in body fluids is of essential importance for numerous metabolic processes, neuromuscular function and mineralization of the skeleton and teeth [7]. In bone tissue, $1,25(\text{OH})_2\text{D}$ through nVDR and in cooperation with PTH induces the maturation of osteoclasts, which by remodeling bones release calcium and phosphorus into the circulation [1, 7, 34]. Although it represents to a certain extent a normal event, this process is particularly pronounced in conditions of insufficient intake, malabsorption or pathological loss of calcium [7]. In contrast, after the establishment of a normal serum calcium level, as well as during the period of growth and development, the genomic effect of vitamin D is primarily directed towards the maturation of osteoblasts and osteocytes [40]. In the renal tubule $1,25(\text{OH})_2\text{D}$ and PTH stimulate reabsorption of filtrated calcium, thus contributing to the maintenance of its homeostasis [7]. Therefore, the endocrine function of vitamin D is primarily aimed at increasing the absorption of calcium from food, while in conditions when this is not enough, at stimulating its renal reabsorption and mobilization from bones [1, 7]. In addition to calcitropic (classical), $1,25(\text{OH})_2\text{D}$ produced in the kidneys also has non-calcitropic (non-classical) effects, which are reflected in the modulation of T and B lymphocyte functions, reduction of renin expression, stimulation of insulin secretion and increased sensitivity of cells to its action and participation in the control of the synthesis and release of

thyrotropin hormone, atrial natriuretic peptide, osteocalcin and some other biomolecules [1, 5, 7, 11, 34]. The discovery that nVDR is present, not only in the cells of organs responsible for calcium and phosphorus metabolism, but also in many other cells in the body, and that they contain the enzyme responsible for the hydroxylation of 25(OH)D into 1,25(OH)₂D, and at the same time and the 24-hydroxylase that deactivates it, led to the knowledge of autochthonously (locally) regulated non-classical, primarily non-calcitropic, effects of vitamin D [1, 34]. Optimal autocrine (intracrine) and paracrine production of 1,25(OH)₂D, which is conditioned by the normal level of serum 25(OH)D, thanks to its antiproliferative, prodifferentiating and proapoptotic effect, significantly reduces the risk of malignant alteration [1, 7]. In addition, the autocrine effects of vitamin D are reflected in anti-neoangiogenesis and differentiation of malignant cells, which slows down the spread of malignant tissue, as well as stimulating the function of macrophages/monocytes and other components of innate immunity [1, 5, 31]. The endocrine and autocrine-paracrine effects of vitamin D are fully expressed prenatally. In addition to ensuring the fetal needs in calcium and phosphorus, 1,25(OH)₂D plays an important role in the development of the central nervous system, lungs, immunity and other systems [41, 42]. Hence, the optimal balance of vitamin D in a pregnant woman is extremely important, not only for her health and the normal course of pregnancy, but also for the proper growth and development of the fetus [41, 42]. Covering the needs in vitamin D during lactation, due to the additional requirement in calcium and phosphorus, has an important role in the prevention of demineralization of the skeleton and teeth in nursing mothers [41, 43]. Apart from its essential role in proper prenatal and later growth and development, a normal balance of vitamin D is an extremely important factor in the prevention of various diseases, both in children and in adults and the elderly. This is supported by numerous epidemiological studies which, in addition to hypomineralization of bones and teeth, confirm the connection between vitamin D deficiency and the appearance of some malignancies, especially of the colon, prostate, breast and ovaries, as well as autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus type I, but also arterial hypertension, diabetes mellitus type II and allergic, cardiovascular and neuromuscular diseases [11, 13, 31, 39, 43]. In addition, vitamin D deficit during pregnancy, besides side-effects on the fetal development, carries the increased risk of gestational diabetes, pre-eclampsia, C-section, preterm delivery, postpartum depression and other complications [1, 12, 41, 42, 43].

RECOMMENDED VITAMIN D INTAKES

Recommended dietary intakes of vitamin D for persons at risk for vitamin D deficiency, ie. in the absence of optimal sun exposure and upper level intake according to the recommendation of the IOM are given in table 3 [7]. The European Food Safety Authority fully agrees with these recommendations, as does the Endocrine Society (ES) [44, 45, 46]. Recommendations for dietary vitamin D intake for children and adolescents of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition, the American Academy of Pediatrics, and the Global Consensus on the Prevention of Nutritional Rickets are also in agreement with the IOM position [47, 48, 49]. The recommendations of other relevant associations are, to a greater or lesser extent, different [32, 50]. In contrast to the earlier position, the ES within the current Clinical Practice Guidelines on vitamin D recommends its routine supplementation for children and adolescents, pregnant women, adults with pre-diabetes and people older than 74 years, but not for healthy adults aged 19 to 74 years. [31, 45, 46]. These recommendations do not apply to people whose physiology of vitamin D was disrupted due to health reasons or therapeutic procedures, as well as those who live in countries where food fortification with vitamin D is not standard, which must provide its entry in accordance with IOM dietary reference intakes [45]. Also, within the framework of vitamin D supplementation, intake of low daily doses is recommended, because high intermittent (weekly or monthly) application can lead to unwanted effects [45]. In addition, the ES within the previous recommendations, published in 2011, suggests that obese children and adults ($BMI > 30 \text{ kg/m}^2$), due to the sequestration of vitamin D in adipose tissue, as well as patients taking anticonvulsant drugs, glucocorticoids, antifungals such as ketoconazole and AIDS drugs, due to the hypercatabolic effect on vitamin D, require at least two to three times higher vitamin D intake compared to the appropriate age group [31].

CONCLUSION

Vitamin D is an essential component of numerous processes in the body and, accordingly, of adequate growth and development, as well as the preservation of health in all phases of life. It achieves its physiological effect in small and narrowly defined amounts. Therefore, its deficit and excess can lead to numerous, and in severe forms, very serious health problems. Cutaneous production, i.e. photolysis of 7-DHC under the influence of sunlight, is the main source of vitamin D, while food, excluding fish oil, marine fish, liver, egg yolks and milk formulas, contains little of it. In accordance with this, in the absence of optimal sun exposure, as well as insufficient intake of vitamin D in food, it is necessary to meet his need in the form of a

supplement. Although the positions of the relevant international associations regarding optimal vitamin D intakes are not harmonized, the fact is that most of them fully or approximately align with the IOM recommendation from 2011.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

Paper accepted

REFERENCES

1. Wimalawansa SJ. Physiology of vitamin D – focusing on disease prevention. *Nutrients*. 2024;16(11):1666. [DOI: 10.3390/nu16111666] [PMID: 38892599]
2. Radlović N, Mladenović M, Simić D, Radlović P. Vitamin D in the light of current knowledge. *Srp Arh Celok Lek*. 2012;140(1–2):110–4. [DOI: 10.2298/SARH1202110R] [PMID: 22462359]
3. Carlberg C, Velleuer E. Vitamin D and the risk for cancer: A molecular analysis. *Biochem Pharmacol*. 2022;196:114735. [DOI: 10.1016/j.bcp.2021.114735] [PMID: 34411566]
4. Voltan G, Cannito M, Ferrarese M, Ceccato F, Camozzi V. Vitamin D: An overview of gene regulation, ranging from metabolism to genomic effects. *Genes (Basel)*. 2023;14(9):1691. [DOI: 10.3390/genes14091691] [PMID: 37761831]
5. Giannini S, Giusti A, Minisola S, Napoli N, Passeri G, Rossini M, et al. The immunologic profile of vitamin D and its role in different immune-mediated diseases: An expert opinion. *Nutrients*. 2022;14(3):473. [DOI: 10.3390/nu14030473] [PMID: 35276834]
6. Danese VC, Pepe J, Ferrone F, Colangelo L, De Martino V, Nieddu L, et al. The mutual interplay between bone, glucose, and lipid metabolism: The role of vitamin D and PTH. *Nutrients*. 2023;15(13):2998. [DOI: 10.3390/nu15132998] [PMID: 37447323]
7. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US); 2011. [PMID: 21796828]
8. Gracia-Marco L. Calcium, vitamin D, and health. *Nutrients*. 2020;12(2):416. [DOI: 10.3390/nu12020416] [PMID: 32041090]
9. Wimalawansa SJ. Infections and autoimmunity—the immune system and vitamin D: a systematic review. *Nutrients*. 2023;15(17):3842. [DOI: 10.3390/nu15173842] [PMID: 37686873]
10. Passeri G, Giannini S. Benefits of vitamin D in health and diseases. *Nutrients*. 2023;15(11):2419. [DOI: 10.3390/nu15112419] [PMID: 37299383] [PMCID: PMC10254656]
11. Arshad R, Sameen A, Murtaza MA, Sharif HR, Iahtisham-Ul-Haq, Dawood S, et al. Impact of vitamin D on maternal and fetal health: A review. *Food Sci Nutr*. 2022;10(10):3230–40. [DOI: 10.1002/fsn3.2948] [PMID: 36249984]
12. Radlović N, Leković Z, Radlović V, Simić D, Ristić D, Vuletić B. Food allergy in children. *Srp Arh Celok Lek*. 2016;144(1–2):99–103. [DOI: 10.2298/sarh1602099r] [PMID: 27276868]
13. Rebelos E, Tentolouris N, Jude E. The role of vitamin D in health and disease: A narrative review on the mechanisms linking vitamin D with disease and the effects of supplementation. *Drugs*. 2023;83(8):665–85. [DOI: 10.1007/s40265-023-01875-8] [PMID: 37148471]
14. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–81. [DOI: 10.1056/NEJMra070553] [PMID: 17634462]
15. Nair R, Maseeh A. Vitamin D: The “sunshine” vitamin. *J Pharmacol Pharmacother*. 2012;3(2):118–26. [DOI: 10.4103/0976-500X.95506] [PMID: 22629085] [PMCID: PMC3356951]
16. Björn LO, Wang T. Vitamin D in an ecological context. *Int J Circumpolar Health*. 2000;59(1):26–32. [PMID: 10850004]
17. Zafalon RVA, Ruberti B, Rentas MF, Amaral AR, Vendramini THA, Chacar FC, et al. The role of vitamin D in small animal bone metabolism. *Metabolites*. 2020;10(12):496. [DOI: 10.3390/metabo10120496] [PMID: 33287408]
18. van den Heuvel EG, Lips P, Schoonmade LJ, Lanham-New SA, van Schoor NM. Comparison of the effect of daily vitamin D2 and vitamin D3 supplementation on serum 25-hydroxyvitamin D concentration (total 25(OH)D, 25(OH)D2, and 25(OH)D3) and importance of body mass index: A systematic review and meta-analysis. *Adv Nutr*. 2024;15(1):100133. [DOI: 10.1016/j.advnut.2023.09.016] [PMID: 37865222]

19. Cashman KD. Global differences in vitamin D status and dietary intake: a review of the data. *Endocr Connect*. 2022;11(1):e210282. [DOI: 10.1530/EC-21-0282] [PMID: 34860171] [PMCID: PMC8789021]
20. Souci SW, Fachmann W, Kraut H. *Food Composition and Nutrition Tables*. 6th ed. Stuttgart: Medforum; 2000.
21. Polzonetti V, Pucciarelli S, Vincenzetti S, Polidori P. Dietary intake of vitamin D from dairy products reduces the risk of osteoporosis. *Nutrients*. 2020;12(6):1743. [DOI: 10.3390/nu12061743] [PMID: 32532150]
22. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA); Turck D, Bohn T, Castenmiller J, de Henauw S, Hirsch-Ernst KI, Knutsen HK, et al. Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate. *EFSA J*. 2023;21(8):e08145. [DOI: 10.2903/j.efsa.2023.8145] [PMID: 37560437]
23. Fan P, Wang Q, Li J, Lu C, Xu Y, Cao H, et al. Poor status of vitamin D: A survey of area with lowest sunlight radiation in Sichuan, China. *Front Endocrinol (Lausanne)*. 2021;12:626983. [DOI: 10.3389/fendo.2021.626983] [PMID: 33732216]
24. Neville JJ, Palmieri T, Young AR. Physical determinants of vitamin D photosynthesis: A review. *JBMR Plus*. 2021;5(1):e10460. [DOI: 10.1002/jbm4.10460] [PMID: 33553995]
25. Greinert R, de Vries E, Erdmann F, Espina C, Auvinen A, Kesminiene A, et al. European Code against Cancer 4th Edition: Ultraviolet radiation and cancer. *Cancer Epidemiol*. 2015;39 Suppl 1:S75–83. [DOI: 10.1016/j.canep.2014.12.014] [PMID: 26096748]
26. Council on Environmental Health; Section on Dermatology, Balk SJ. Ultraviolet radiation: a hazard to children and adolescents. *Pediatrics*. 2011;127(3):588–97. [DOI: 10.1542/peds.2010-3501] [PMID: 21357336]
27. Nikolic A, Radlovic N, Dinic J, Milosevic K, Radojkovic D. Clinical presentation of mild cystic fibrosis in a Serbian patient homozygous for the CFTR mutation c.1393-1G>A. *J Cyst Fibros*. 2014;13(1):111–3. [DOI: 10.1016/j.jcf.2013.07.001] [PMID: 23933162]
28. Schmid A, Walther B. Natural vitamin D content in animal products. *Adv Nutr*. 2013;4(4):453–62. [DOI: 10.3945/an.113.003780] [PMID: 23858093]
29. Vieth R. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. *Eur J Clin Nutr*. 2020;74(11):1493–7. [DOI: 10.1038/s41430-020-0697-1] [PMID: 32704098]
30. Sempos CT, Binkley N. 25-Hydroxyvitamin D assay standardisation and vitamin D guidelines paralysis. *Public Health Nutr*. 2020;23(7):1153–64. [DOI: 10.1017/S1368980019005251] [PMID: 32301688]
31. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911–30. [DOI: 10.1210/jc.2011-0385] [PMID: 21646368]
32. Giustina A, Bilezikian JP, Adler RA, Banfi G, Bikle DD, Binkley NC, et al. Consensus statement on vitamin D status assessment and supplementation: Whys, whens, and hows. *Endocr Rev*. 2024;45(5):625–54. [DOI: 10.1210/endrev/bnae009] [PMID: 38676447]
33. McCartney CR, McDonnell ME, Corrigan MD, Lash RW. Vitamin D insufficiency and epistemic humility: An Endocrine Society guideline communication. *J Clin Endocrinol Metab*. 2024;109(8):1948–54. [DOI: 10.1210/clinem/dgae322] [PMID: 38828961]
34. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol*. 2005;289(1):F8–28. [DOI: 10.1152/ajprenal.00336.2004] [PMID: 15951480]
35. Pons-Belda OD, Alonso-Álvarez MA, González-Rodríguez JD, Mantecón-Fernández L, Santos-Rodríguez F. Mineral metabolism in children: Interrelation between vitamin D and FGF23. *Int J Mol Sci*. 2023;24(7):6661. [DOI: 10.3390/ijms24076661] [PMID: 37047636]
36. Radlović V, Smoljanić Z, Radlović N, Leković Z, Ristić D, Ducić S, et al. X-linked hypophosphatemic rickets: case report. *Srp Arh Celok Lek*. 2014;142(1–2):75–8. [DOI: 10.2298/sarh1402075r] [PMID: 24684036]
37. Radlović N, Leković Z, Ristić D, Radlović V, Djuričić G, Dimitrijević A, et al. Case report of acute vitamin D intoxication in an infant. *Srp Arh Celok Lek*. 2014;142(11–12):736–9. [DOI: 10.2298/sarh1412736r] [PMID: 25731008]

38. Karacan Küçükali G, Keskin M, Savaş Erdeve Ş, Çetinkaya S. Perinatal outcomes of high-dose vitamin D administration in the last trimester. *Turk J Obstet Gynecol.* 2021;18(2):159–162. [DOI: 10.4274/tjod.galenos.2021.90023] [PMID: 34083750]
39. Carlberg C. Vitamin D and its target genes. *Nutrients.* 2022;14(7):1354. [DOI: 10.3390/nu14071354] [PMID: 35405966]
40. Morris HA, Anderson PH. Autocrine and paracrine actions of vitamin D. *Clin Biochem Rev.* 2010;31(4):129–38. [PMID: 21170259] [PMCID: PMC2998276]
41. Pérez-López FR. Vitamin D: the secosteroid hormone and human reproduction. *Gynecol Endocrinol.* 2007;23(1):13–24. [DOI: 10.1080/09513590601045629] [PMID: 17484507]
42. Durá-Travé T, Gallinas-Victoriano F. Pregnancy, breastfeeding, and vitamin D. *Int J Mol Sci.* 2023;24(15):11881. [DOI: 10.3390/ijms241511881] [PMID: 37569256]
43. Botelho J, Machado V, Proença L, Delgado AS, Mendes JJ. Vitamin D deficiency and oral health: A comprehensive review. *Nutrients.* 2020;12(5):1471. [DOI: 10.3390/nu12051471] [PMID: 32438644]
44. European Food Safety Authority (EFSA). Dietary reference values for vitamin D. EFSA Panel on Dietetic Products, Nutrition and Allergies. 2016. Available at: <https://efsa.onlinelibrary.wiley.com/> [DOI: 10.2903/j.efsa.2016.4547]
45. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, et al. Vitamin D for the prevention of disease: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2024;109(8):1907–47. [DOI: 10.1210/clinem/dgae290] [PMID: 38828931]
46. Shah VP, Nayfeh T, Alsawaf Y, Saadi S, Farah M, et al. A systematic review supporting the Endocrine Society Clinical Practice Guidelines on vitamin D. *J Clin Endocrinol Metab.* 2024;109(8):1961–74. [DOI: 10.1210/clinem/dgae312] [PMID: 38828942]
47. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al; ESPGHAN Committee on Nutrition. Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr.* 2013;56(6):692–701. [DOI: 10.1097/MPG.0b013e31828f3c05] [PMID: 23708639]
48. Golden NH, Abrams SA; Committee on Nutrition. Optimizing bone health in children and adolescents. *Pediatrics.* 2014;134(4):e1229–43. [DOI: 10.1542/peds.2014-2173] [PMID: 25266429]
49. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab.* 2016;101(2):394–415. [DOI: 10.1210/jc.2015-2175] [PMID: 26745253]
50. Kimball SM, Holick MF. Official recommendations for vitamin D through the life stages in developed countries. *Eur J Clin Nutr.* 2020;74(11):1514–8. [DOI: 10.1038/s41430-020-00706-3] [PMID: 32820241]

Table 1. Vitamin D content in foods [20, 21]

Food	Content (IU/100 g)
Human milk	2.5–3
Standard milk formulae	40–60
Cow's milk	4
Chicken	15–20
Beef	30–50
Chicken liver	50
Hen egg yolk	125–215
Mushrooms, champignons*	75
Mushrooms, chanterelle*	210–570
Fish	200–990
Cod liver oil	8400–10,000

*Exposed to UV light

Table 2. Serum 25(OH)D concentrations and health [7]

nmol/L*	ng/mL*	Health status
< 30	< 12	Associated with vitamin D deficiency, which can lead to rickets in infants and children and osteomalacia in adults
30 to < 50	12 to < 20	Generally considered inadequate for bone and overall health in healthy individuals
≥ 50	≥ 20	Generally considered adequate for bone and overall health in healthy individuals
> 125	> 50	Linked to potential adverse effects, particularly at >150 nmol/L (> 60 ng/mL)

*One nmol/L = 0.4 ng/mL, and 1 ng/mL = 2.5 nmol/L

Table 3. Dietary reference intakes for vitamin D [7]

Life stage group (years)	Recommended dietary allowance (IU/day)	Upper level intake (IU/day)
0–6 months	400*	1000
6–12 months	400*	1500
1–3 years	600	2500
4–8 years	600	3000
9–18 years	600	4000
19–70 years	600	4000
> 70 years	800	4000
Pregnant/nursing women	600	4000

*For infants adequate intake is 400 IU/day for 0–12 months of age