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REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Vitamin D: a comprehensive review

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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 other 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 sources of vitamin D, its metabolism and physiological role, as well as current recommendations related to the coverage of its optimal needs.
Keywords: vitamin D; physiological role; optimal need

INTRODUCTION

Vitamin D (calciferol), i.e. its active metabolite calcitriol [1,25(OH)2D] is an 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 the 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 sources 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 D_2 (ergocalciferol) and vitamin D_3 (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 zooplankton and microalgae in the food chain in water, while some land animals, such as dogs and cats, get it by consuming prey which stores vitamin D_3 in the liver and adipose tissue [16, 17]. Unlike cholecalciferol, the side chain of ergocalciferol has a 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 D_3, apart from more efficiently raising serum 25(OH)D concentration, has no advantage over vitamin D_2 [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].

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

During photolysis of 7-DHC in epidermal keratocytes and dermal fibroblasts under the influence of sunlight, previtamin D_3 is formed, which is then isomerized to vitamin D_3 at skin temperature [1, 7, 13, 22]. The level of skin production of vitamin D depends on latitude and

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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 D_3 [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 six months of age, who should not be exposed to direct sunlight due to the developmental hypersensitivity of the skin [26].

Holick [14] suggests that exposing the arms and legs for 5–30 minutes (depending on the time of day, season, latitude, and skin pigmentation) between 10 a.m. and 3 p.m. twice a week is often enough to meet vitamin D needs. 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 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 is deposited, mainly (75%) in fatty tissue, and the rest in the liver, muscles, and skeleton [1, 7, 22].

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 IU/100 g), liver (2.8–30.8 IU/100 g) and kidney (3.6–93.2 IU/100 g), since it is soluble in water, 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 six to eight 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 1α-hydroxylase, which converts 25(OH)D to the biologically active hormone, 1,25(OH)2D. Apart from the kidney, 1α-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 four 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].

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

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 1α-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) that 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 administration 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 physiological effects of 1,25(OH)2D 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(OH)2D work in synergy, although the genomic effect (i.e., mediated by nVDR) is much slower than the membrane effect [13]. 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(OH)2D, 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(OH)2D stimulates the synthesis of calcium channels, calbindin, Ca2+ATP-ase, 3Na+/Ca2+ ion exchanger and 2Na+/HPO42– 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(OH)2D 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(OH)2D and PTH stimulate reabsorption of filtered calcium, thus contributing to the maintenance of its homeostasis [7]. Hence, 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(OH)2D 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 these cells contain the enzyme responsible for the hydroxylation of 25(OH)D into 1,25(OH)2D, as well as 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 that, in addition to finding hypomineralization of bones and teeth, confirm an association between vitamin D deficiency and the appearance of some malignancies, especially those of the colon, prostate, breast, and ovaries, as well as autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, and arterial hypertension, type 2 diabetes mellitus, and allergic, cardiovascular, and neuromuscular diseases [11, 13, 31, 39, 43]. In addition, vitamin D deficit during pregnancy, besides side effects on 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, i.e. 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 19–74 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 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].

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

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

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 its 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 in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

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Витамин Д: свеобухватни преглед

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САЖЕТАК

Витамин Д (калциферол), односно његов активни метаболит калцитриол [1,25(*OH*)2*D*], осим есенцијалног учешћа у хомеостази калцијума и фосфора, битан је фактор у регулацији ћелијске пролиферације, диференцијације и апоптозе, ангиогенезе, имунске и хормонске активности и других процеса у људском организму. Отуда је његова оптимална равнотежа изузетно значајна за адекватан пренатални и постнатални раст и развој, као и за очување 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 у вези са обезбеђивањем његовог оптималног уноса.

Кључне речи: витамин Д; физиолошка улога; оптимални унос