

# Vitamin D in the Light of Current Knowledge

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## SUMMARY

Vitamin D, i.e. 1,25(OH)<sub>2</sub>D, is an essential factor, not only of homeostasis of calcium and phosphorus, but also of cell proliferation, differentiation and apoptosis, immune and hormonal regulation, as well as other body processes. Thus, its optimal presence in the body is of exceptional significance for health, both of children, as well as adults and elderly persons. Today, it is known that the lack of vitamin D, besides having negative effects on the skeleton and teeth, also contributes to the development of various malignancies, primarily of the large bowel, prostate and breasts, as well as of autoimmune and allergic diseases, diabetes mellitus type II, arterial hypertension and others. Considered from the biological aspect, physiological requirements in vitamin D are achieved by cutaneous synthesis from 7-dehydrocholesterol during sun exposure, while, except rarely, it is very scarce in food. Having in mind extensive evidence that sun exposure presents a high risk for the development of skin malignancies, primarily melanoma, it is clear that humans are deprived of the natural and basic source of vitamin D. In accordance, as well as based on numerous epidemiological studies showing the increase of diseases, in the basis of which vitamin D deficiency plays the important role, next led to the recommended dietary allowance of vitamin D, regardless of age. According to current attitudes, it is recommended that the daily dietary allowances of vitamin D, i.e. the quantity of oral intake that would safely cover the optimal body requirements should be 400 IU for ages 0-18 years, 600 IU for ages 19-70 years and 800 IU for persons aged over 70 years.

**Keywords:** vitamin D; physiological role; recommended dietary allowances

## INTRODUCTION

Vitamin D (calciferol) is the precursor of the steroid hormone calcitriol [1,25(OH)<sub>2</sub>D] responsible for the homeostasis of calcium and phosphorus, i.e. bone and tooth mineralization, cell proliferation, differentiation and apoptosis, immune and hormonal regulation, as well as other physiological processes [1, 2, 3]. Thus, its optimal presence in the body is of exceptional significance in the prevention of various diseases, both in children, adults and elderly persons [4-7]. In addition, adequate vitamin D overall level is an important factor in the normal prenatal growth and development, as well as in the preservation of pregnant and lactating women health [8-11].

Although vitamin D has been known to us for almost 100 years, it is still insufficiently understood [12]. This regards less to its physiological effects which are mostly recognized, but much more to its optimal requirements under current life conditions that are associated with limited sun exposure [13, 14, 15]. Numerous studies based on the determination of serum 25-hydroxyvitamin D [25(OH)D] indicate that vitamin D deficit presents a global occurrence and an important etiopathogenic factor in the development of various malignant, autoimmune, degenerative, allergic and other diseases [4, 13-17]. Consequently, with the aim to preserve health, the additional intake of vitamin D by foods or supplements

is currently considered indispensable [13-17]. This refers to all ages and particularly to the period of growth and development, pregnancy and lactation [9, 18-24]. This paper exposes the physiological significance of vitamin D from the current aspect, and presents up-to-date recommended dietary allowances.

## CHEMICAL ASPECTS AND RESOURCES OF VITAMIN D

Vitamin D is composed of two secosteroid derivatives of cholesterol, cholecalciferol (D-3) and ergocalciferol (D-2), which differ in origin, chemical composition and biological activity [2]. Both vitamin D isomers are formed by photolytic break of C<sub>9</sub>-C<sub>10</sub>, the B ring bond of the corresponding steroid precursors, i.e. 7-dehydrocholesterol (7-DHC) and ergosterol, to be converted into cholecalciferol and ergocalciferol, respectively [2]. Humans and higher animal species (vertebrates) produce cholecalciferol, while ergocalciferol is of plant origin. Unlike cholecalciferol, the side-chain of ergocalciferol contains an unsaturated bond placed at the position C<sub>22</sub>-C<sub>23</sub> and a methyl group at C<sub>24</sub> [25]. The difference in chemical structure and consequently in metabolism make cholecalciferol 2-3 times more active than ergocalciferol [2, 25-28].

Physiological requirements of humans in vitamin D are primarily satisfied by cutaneous

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**Table 1.** Vitamin D content in foods [29]

Food	Content (IU/100 g)
Human milk	2.5-3.0
Standard milk formulae	40-60
Hen egg yolk	125
Chicken liver	50
Mushrooms (champignons)	75
Shells (oysters)	320
Sea fish	200-650
Cod liver oil	8400

synthesis, while foods are a poor source of vitamin D, apart from fish oil, sea fish, liver, egg yolk and milk formulas (Table 1) [2, 13, 29]. During photolysis 7-DHC that is synthesized in epidermal keratocytes and dermal fibroblasts during exposure to solar ultraviolet B (290-315 nm) radiation, initially provitamin D is produced and then by its thermal isomerization vitamin D-3 [1, 30]. The degree of cutaneous production of vitamin D depends on geographical latitude, season of the year, time of day, amount to sun exposure, melanin quantity in skin, age and the degree of protection from sunlight [13]. Vitamin D produced in the skin enters the circulation where, bound to vitamin D binding protein (DBP), it is transported to the liver and other organs [1, 30]. By photoisomerization to non-toxic metabolites (lumisterol, tachysterol, suprasterol I and II and 5,6-trans-cholecalciferol), melanin protective effects, permanent skin desquamation and limited DBP transport capacity, vitamin D intoxication by sun exposure is not possible [30]. Vitamin D, by food or supplement intake, as well as other liposoluble substances, enters into the composition of chylomicrons to be transported into the circulation by the lymphatic system. Having in mind physiological significance and variable influx, any excess of vitamin D, of either cutaneous or alimentary sources, is stored in the liver, fat tissue, skeleton and muscles [1, 7]. Some reserves of vitamin D are also produced in the foetus, although they are small and disappear during the first weeks after birth [5]. Due to efficient and unlimited intestinal resorption, a high accumulation and the impossibility of adequate elimination, excessive oral intake of vitamin D may present a serious threat to health [31, 32]. Identical problem occurs in the parenterally administered vitamin D overdose.

## ACTIVATION AND PHYSIOLOGICAL EFFECTS OF VITAMIN D

To express its activity vitamin D, as a biologically inert compound, must be activated [1, 2]. Vitamin D and its derivatives are transported from the skin and storage pool by bondage to DBP, and only partly by albumin and plasma lipoprotein [4, 33]. Its activation is initiated by hydroxylation at C<sub>25</sub> in hepatocyte microsomes which is accompanied by the formation of 25-hydroxycholecalciferol [25(OH)D, calcidiol], the main circulating vitamin D derivative [33, 34]. Mediated by DBP, 25(OH)D enters the mitochondria of the renal proximal tubular cells, as well as macrophages, mono-

cytes and the cells of the skeleton, teeth, breasts, prostate, colon, pancreas, brain, adrenal glands, placenta and other tissues, where final (1- $\alpha$ ) hydroxylation occurs during which 1,25(OH)<sub>2</sub>D (calcitriol) is formed, the most potent vitamin D metabolite, i.e. a steroid hormone responsible for numerous and most significant physiological processes in the body [30, 33, 35-39]. Contrary to 25(OH)D, with half-life in the circulation of 10-20 days, 1,25(OH)<sub>2</sub> becomes inactivated within 4-7 hours [35]. Thus, 25(OH)D serum levels are used as a reliable indicator of vitamin D status in the body [19,38]. The activity of 1- $\alpha$  hydroxylase 25(OH)D in the kidney primarily stimulates the parathyroid hormone (PTH), but also hypocalcemia, hypophosphatemia, growth hormone, sex hormones, prolactin, and a low level of serum 1,25(OH)<sub>2</sub>D, while the activity of this enzyme in extrarenal tissues is regulated by autochthonous factors, such as local growth factors, cytokines (gamma-interferon, tumour necrosis factor) and others [2, 33, 40]. Adequate concentrations of 1,25(OH)<sub>2</sub>D in the body, beside being regulated by synthesis, are also achieved by control of inactivation. The inactivation of 1,25(OH)<sub>2</sub>D is carried out by hydroxylation at C<sub>24</sub> in the kidney, intestine, bones, cartilage, skin, prostate, placenta and other tissues, resulting in the formation of inactive hydrosoluble products (calcitroic acid and 23-carboxyle derivatives) which are eliminated in urine and bile [34, 38, 41, 42, 43].

The steroid hormone 1,25(OH)<sub>2</sub>D primarily expresses its activity through the nuclear vitamin D receptor (nVDR) by regulating, stimulating or inhibiting specific DNA sequences, transcription of about 500 different genes, and partially also by membranous receptors (mVDR) [2, 33, 44]. Both effects of vitamin D function in synergy, however, the genomic, i.e. nVDR mediated is much slower than the membranous effect [2, 44]. The presence of the nVDR has been evidenced in over 30 different cells in the body [2, 20]. By the modulation of gene expression, the synthesis of proteins responsible for classic (calcitropic) and non-classic (non-calcitropic) effects of vitamin D are regulated [2, 19, 20]. The membranous (non-genomic) effects of 1,25(OH)<sub>2</sub>D, also significant for cell function, are reflected in the increase of cell permeability of calcium and chloride, as well as in the increase of the intracellular level of phospholipase C, cyclic guanosine monophosphate, protein-kinase C and phosphoinositide metabolism [2, 33, 43].

Regarding the major target tissues, small intestine, kidney and bone, vitamin D plays an important role in the regulation of calcium and phosphorus homeostasis [1, 19]. In enterocytes and tubulocytes 1,25(OH)<sub>2</sub>D stimulates the synthesis of calcium channels, calbindin, Ca<sup>2+</sup>ATPase, 3Na<sup>+</sup>/Ca<sup>2+</sup> ion exchanger and 2Na<sup>+</sup>/HPO<sub>4</sub><sup>2-</sup> cotransporter, thus enabling intestinal absorption and renal reabsorption of these ions and their transfer into the circulation [33]. The optimal concentration of calcium and phosphorus in body fluids is significant for numerous metabolic functions, neuromuscular transmission and the mineralization of the skeleton and teeth [1]. In bone tissue 1,25(OH)<sub>2</sub>D, through the VDR in association with PTH, influences the maturation of osteoclasts which by bone remodelling

release calcium and phosphorus into the circulation [33]. Although presenting to a certain degree a normal event, this is particularly manifested in the conditions of insufficient intake, malabsorption or pathological loss of calcium, and primary and secondary hyperparathyroidism [45, 46]. Contrarily, after establishing a normal overall level of calcium and calcemia, as well as during the period of growth and development, the genomic effect of vitamin D is primarily directed toward the maturation of osteoblasts and osteocytes [38]. In the renal tubule 1,25(OH)<sub>2</sub>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 reflected by the increase of calcium absorption from foods according to the requirements, while under special conditions, when it is insufficient, by its mobilization from bones and renal reabsorption. Beside calcitropic (classic), 1,25(OH)<sub>2</sub>D of renal source also manifests a non-calcitropic (non-classic) effect that is reflected by the modulation of T and B lymphocyte functions, suppression of rennin secretion, stimulation of insulin excretion and increase of cell sensitivity to its effects, as well as the regulation of synthesis and the release of PTH, TSH and some other hormones [19, 33, 43].

The discovery that nVDR is present, not only in tissue cells primarily responsible for calcium and phosphorus metabolism, but also in many other cells in the body, and that they contain an enzyme responsible for 1-alpha hydroxylation of 25(OH)D, thus having the ability to produce the active form of vitamin D, and also at the same time the enzyme system for its activation; this has led to the awareness about the autochthonously (locally) regulated non-classic, primarily non-calcitropic, effects of vitamin D [2, 19, 33, 44]. The optimal autocrine (intracrine) and paracrine production of 1,25(OH)<sub>2</sub>D, conditioned by the normal level of serum 25(OH)D, significantly decreases the risk of malignant alteration by their suppressive effect on cell proliferation and stimulation of cell differentiation and apoptosis [2, 19]. Besides, the autocrine effects of vitamin D are also reflected in the anti-neoangiogenesis and differentiation of malignant cells, which slows down the expansion of malignant tissue, and also increases both macrophage/monocyte function and other components of innate immunity [2, 19].

The significance of autocrine-paracrine effects of 1,25(OH)<sub>2</sub>D also reaches its full expression prenatally [9, 18, 20]. This does not only concern the assured provision of foetal requirements in calcium, but also to the development of the central nervous system, lungs, immunity and other systems [8]. Thus, the optimal bilans of vitamin D in a pregnant woman is significant, not only for health and normal pregnancy course, but also for the adequate growth and development of the foetus [8, 18]. Contrarily to this condition, the primary goal of covering the optimal vitamin D requirements during lactation is to prevent the demineralization of the skeleton and teeth in the pregnant woman [8].

All these facts clearly indicate that the optimal overall level of vitamin D is of essential significance for health, not only in childhood, but during the entire life. This is also supported by numerous epidemiological studies, which,

beside osteomalacia and osteoporosis, confirm the relation between vitamin D deficit and the development of some malignancies, particularly of the colon, prostate, breasts and ovaries, as well as of autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus type I and others, arterial hypertension, diabetes mellitus type II, and some allergic, cardiovascular, neuromuscular and psychiatric diseases [4, 13-16, 19]. In addition, there is exact evidence that vitamin D deficit during pregnancy, besides exerting side-effects on the foetus, also carries the increased risk of gestational diabetes, pre-eclampsia, surgical delivery, preterm birth and other complications [8-11].

## VITAMIN D REQUIREMENTS

Considered from the biological aspect, vitamin D requirements in humans are primarily satisfied by sun exposure, while standard foods, generally speaking, are insufficient to cover such needs [2, 13]. Some studies have reported that daily, even 2-3 times a week, a direct 5-15 min to sun exposure of 5-15% of skin surface, which corresponds to the surface of the face and hands or hands and legs during summer-time noon in moderate climate regions, ensures Caucasians' requirements in vitamin D [31, 47]. The degree of cutaneous synthesis of calciferol in coloured persons is, depending on the quantity of melanin in the skin, 5-10 times lower [20, 48]. This is also partly true in regard to the constitutional pigmentation of the Caucasians, as well as to persons who are continually exposed to the sun. However, the fear of malignant skin diseases, particularly melanoma, has resulted in the avoidance of a direct sun exposure or the usage of sunbathing ointments with high protective factors, particularly during the first six months after birth, and even in later childhood when vitamin D relative requirements are also the highest [49]. This, as well as the modern lifestyle associated with long-term stay in closed spaces, have considerably decreased the natural source of vitamin D, which has led to the necessity of its additional oral intake, either as a food additive or in the form of supplements (Table 2) [21, 24]. The optimal vitamin D requirements of the preterm neonate, as well as the one with a low body weight for the gestational age at birth, are also 400 IU daily [50]. Up-to-date most vitamin D preparations are offered in the form of calciferol, because, as a human natural product, its biological activity is much higher and safer as compared to ergocalciferol [26, 27, 28].

**Table 2.** Recommended dietary allowances for vitamin D

Category		Institution	
		AAP, CN, 2008	IM, FNB, 2010
Children (years)	<1	400 IU	400 IU*
	2-18	400 IU	600 IU
Adults (years)	19-70	-	600 IU
	>70	-	800 IU
Pregnant women		-	600 IU
Lactating women		-	600 IU

AAP, CN – American Academy of Pediatrics, Committee on Nutrition, 2008 [21]; IM, FNB – Institute of Medicine, Food and Nutrition Board, 2010 [24]  
\* adequate intake

## CONCLUSION

Vitamin D is an essential factor of numerous processes in the human body. Considered from the biological aspect, vitamin D physiological requirements are fulfilled by cutaneous synthesis, while foods, except for rare exceptions, are a very poor source of vitamin D. However, due

to circumstances the modern man is mostly left without the essential source of vitamin D, and thus, accordingly, as well as based on numerous studies indicating the increase of diseases with underlying basic participation of its lack, recommendations have been established for the necessary additional dietary allowance of vitamin D, regardless of age.

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## Витамин Д у светлу савремених сазнања

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### КРАТАК САДРЖАЈ

Витамин Д, односно  $1,25(OH)_2D$ , јесте есенцијални чинилац не само хомеостазе калцијума и фосфора, него и пролиферације, диференцијације и апоптозе ћелија, имунске и хормонске регулације и других процеса у организму. Отуда је његов оптималан ниво у телу човека веома значајан за здравље, како деце, тако и одраслих и старих људи. Недостатак витамина Д, поред лоших последица на скелет и зубе, доприноси појави различитих малигнитета, пре свега дебелог црева, простате и дојке, затим аутоимунолошких и алергијских обољења, дијабетеса тип II, артеријске хипертензије и др. Посматрано са биолошког аспекта, физиолошке потребе за витамином Д остварују се кутаном синтезом из 7-де-хидрохолестерола током сунчања, док је храна, сем ретких изузетка, веома оскудна у њему. Имајући у виду бројне до-

казе да је излагање сунцу велики ризик за појаву малигнитета коже (превасходно меланома), јасно је да је човек остао без свог природног и основног извора витамина Д. У складу с тим, као и на основу разних епидемиолошких истраживања која указују на повећање броја обољења у чијој основи битно учешће има недостатак витамина Д, уследиле су препоруке да се он, без обзира на животно доба, мора уносити. Према савременим ставовима, препоручена дневна доза витамина Д, тј. количина која орално унета задовољава оптималне потребе организма, јесте 400 ИЈ у узрасту до 18 година, 600 ИЈ у периоду између 19. и 70. године, односно 800 ИЈ после 70. године.

**Кључне речи:** витамин Д; физиолошка улога; препоручени дневни унос

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