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Vitamin D supplementation in adults — guidelines

Suplementacja witaminy D u dorosłych — zalecenia

Ewa Marcinowska-Suchowierska[1], Magdalena Walicka[1], Marek Tałałaj[1], Wanda Horst-Sikorska[2], Magdalena Ignaszak-Szczepaniak[2], Ewa Sewerynek[3]

[1]Clinic of Family Medicine, Internal and Metabolic Bone Diseases, Medical Centre of Postgraduate Education, Warszawa, Poland
[2]Chair and Department of Family Medicine, The K. Marcinkowski Medical University, Poznań, Poland
[3]Department of Endocrine Disorders and Bone Metabolism, The 1st Chair of Endocrinology, Medical University, Łódź, Poland

Abstract

Vitamin D is necessary in maintaining appropriate calcium and phosphate homeostasis in the body (classical function) and ensuring appropriate functioning of many tissues, organs and cells, unrelated to mineral economy (non-classical function). Vitamin D deficiency in adults may cause osteomalacia, increase fracture risk in osteoporosis, induce cardiovascular diseases, diabetes type 1 and 2, multiple sclerosis, Lesniowski-Crohn disease, and cancer, including colon, breast, and prostate cancer.

Possible causes of vitamin D deficiency in a healthy population include decreased cutaneous synthesis and an inadequate intake of vitamin D, both in food and in supplements. Vitamin D deficiency level (25(OH) D. < 20 ng/mL), is fairly widespread, being found in a substantial percentage of healthy subjects around the world, regardless of race, gender and age. Daily vitamin D dose, as determined by the Food and Nutrition Board in 1997, is now rather insufficient, the biggest problem being associated with maximal vitamin D levels (50 μg/day) in actually available food supplements. Nowadays, it is recommended that adults need a minimum of 800–1,000 U/day when their exposure to the sun is inadequate (in Poland from October to April). This dosage should be provided to all subjects who avoid sunlight, as well as to those aged over 65 because of their slower skin synthesis of vitamin D and for its proven anti-fracture and anti-fall effects.

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Key words: *vitamin D, food inadequacy, supplementation*

Streszczenie

Witamina D jest niezbędnym elementem do utrzymania właściwej homeostazy wapniowo-fosforanowej organizmu (rola klasyczna) i zapewnienia właściwego funkcjonowania wielu tkanek, narządów i komórek niezależnych od obrotu mineralnego (rola nieklasyczna). Niedobór witaminy D u dorosłych zwiększa ryzyko złamań kości w osteoporozie, może prowadzić do osteomalacji, choroby niedokrwiennej serca, cukrzycy typu 1 i 2, stwardnienia rozsianego, choroby Leśniowskiego-Crohna oraz nowotworów szczególnie jelita grubego, piersi i prostaty.

Przyczynami niedoboru witaminy D u zdrowej populacji jest prawdopodobnie zmniejszenie syntezy skórnej oraz niedostateczne spożywanie w diecie oraz suplementach. Niedobór witaminy 25(OH)D (stężenie < 20 ng/ml) występuje dość powszechnie u zdrowej populacji ogólnej niezależnie od rasy, płci i wieku. Dzienne zapotrzebowanie na witaminę D określone przez *Food and Nutrition Board* w 1997 roku, jest obecnie niewystarczająca. Najwiekszy problem wiąże się z maksymalnym stężeniem witaminy D (50 μg/dobę) w suplementach. Obecnie uważa się, że dzienne zapotrzebowanie osoby dorosłej wynosi 800–1000 j., jeżeli jej ekspozycja na słońce jest niewystarczająca (w Polsce od października do kwietnia). Taka dawka powinna być przyjmowana przez osoby unikające nasłonecznienia, jak również stosowana przez wszystkich w wieku powyżej 65 lat z powodu spowolnienia skórnej syntezy witaminy D, oraz ze względu na udowodnione działanie przeciw złamaniom i upadkom. **(Endokrynol Pol 2010; 61 (6): 723–729)**

Słowa kluczowe: *witamina D, niedobór w diecie, suplementacja*

The guidelines concerning vitamin D supplementation in adults have been approved by:
National Consultant for Internal Medicine — Assistant Prof. Jacek Imiela MD, PhD
National Consultant for Family Medicine — Prof. Witold Lukas MD, PhD
Chairman of the Polish Foundation of Osteoporosis — Prof. Janusz Badurski MD, PhD
Chairman of the Polish Society of Osteoarthrology — Assistant Prof. Edward Czerwiński MD, PhD
Chairman of the Multibranch Forum of Osteoporosis – Prof. Roman Lorenc MD, PhD

Ewa Marcinkowska-Suchowierska MD, Clinic of Family Medicine, Internal and Metabolic Bone Diseases, Medical Centre of Postgraduate Education, Warszawa 02–097, Czerniakowska St. 231, tel.: 601 923 381, e-mail: ewa.marcinkowska@wp.pl

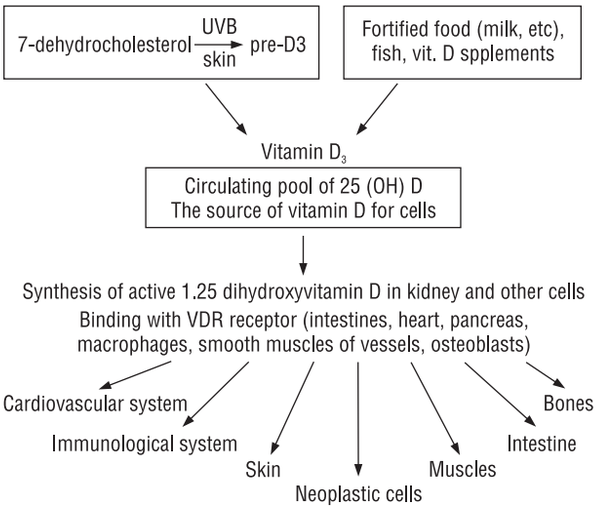

Figure 1. *Effects of vitamin D_3 (Schwalfenberg G. Can Fam Physician 2007; 53: 841–854)*

Rycina 1. *Efekty stosowania witaminy D_3 (Schwalfenberg G. Can Fam Physician 2007; 53: 841–854)*

Introduction

Vitamin D is necessary to maintain appropriate calcium and phosphate homeostasis in the body and to ensure appropriate functioning of many tissues, organs and cells, unrelated to mineral economy.

Vitamin D deficiency considered to be a risk factor for the following [1–17]: cardiovascular diseases, metabolic syndrome and obesity, immunological system disorders, neoplasms, osteoporosis, bone fractures and falling incidents.

Figure 1 shows how vitamin D participates in various processes in the body. D-1,25-dihydroxy-vitamin D [1,25$(OH)_2$D], an active form of vitamin D, after binding with the vitamin D receptor (VDR), exerts direct effects as a nuclear transcriptive factor. 1,25$(OH)_2$D acts also, either directly or indirectly, on more than 200 including those responsible for renin and insulin synthesis, the release of cytokines from lymphocytes and for the growth and proliferation of vascular smooth muscles and cardiomyocytes [18].

Vitamin D influences the circulation via the renin–angiotensin–aldosterone (RAA) system. Vitamin D deficiency activate the RAA system, resulting in an excessive proliferation of vascular smooth muscle cells and left ventricular hypertrophy. An association has been proven between hypovitaminosis D and myocardial infarction, cerebral stroke, cardiac insufficiency, hypertension, the occurrence of eclampsia and vascular sclerosis.

Low vitamin D concentrations predispose to insulin resistance, dysfunction of pancreatic beta-cells and, in consequence, to obesity and the metabolic syndrome.

The active form of vitamin D is produced in macrophages in response to inflammatory reaction. It suppresses inflammatory processes, influencing the cells, participating in autoimmunological reactions, and modulates lymphocyte responses. VDR receptor expression on macrophages enhances the processes of fagocytosis and increases cytokine production.

Decreased 1,25$(OH)_2$D levels have been found in multiple sclerosis, systemic lupus erythematosus and psoriasis. Low vitamin D levels are a risk factor for the development or progression of many neoplasms: breast, prostate, colon, kidney, lung and pancreatic cancer. Studies on tissue expression of 1α-hydroxylase coding CYP27B1 gene and on the calcium receptor (CaR) have demonstrated that local (extrarenal) synthesis of active 1,25$(OH)_2$D and the pool of extracellular Ca play a significant role in carcinogenesis, regulating the processes of proliferation and cell differentiation and stimulating apoptosis. It is regarded as the key regulator of cell functions in various types of tissues [8, 19, 20].

Vitamin D deficiency increases the risk of potential falls and, in their consequence, of bone fractures. A relationship has been confirmed between sarcopenia (defect of muscular fibres, replaced by adipose tissue), causing muscle power decrease with tendency to falls and vitamin D deficit. In this way, the anti-fracture efficacy of vitamin D is shown in the population above 65 [13, 17, 21].

Metabolism of vitamin D in physiological conditions

The term 'vitamin D' refers to the group of chemical compounds of the steroid group with the general formula $C_{28}H_{43}OH$. Of these compounds, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are the most significant.

Vitamins D_2 and D_3 do not reveal biological activity. They are initial substances which — in the body — undergo an identical cycle of transformations with the production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D.] — calcitriol, commonly perceived to be the most active form of vitamin D.

We know that 1,25$(OH)_2$D production takes place not only in the kidneys but also in many cells and tissues, demonstrating the activity of 1α-hydroxylase (a non-classic effect). Renal synthesis is associated with the maintenance of normal calcium-phosphate homeostasis in the system (endocrine, systemic activity) by influencing such target tissues as: intestine, kidneys, bone (classical activity).

The locally produced 1,25$(OH)_2$D vitamin controls the proliferation and differentiation of cells and the process of apoptosis in, among others, keratinocytes, macrophages, muscle cells, mammary gland cells and in cells of intestinal epithelium (para- and autocrine activity). This form is released into circulation and acts sys-

temically in the course of sarcoidosis and tuberculosis. 1,25$(OH)_2$D affects also the secretion of insulin by the pancreas and of parathormone by the parathyroid glands [22, 23].

Sources of vitamin D

Vitamin D_3 is in 20% obtained from food (fish, eggs, animal livers, dairy products) and in 80% from skin synthesis as a product of skin 7-dehydrocholesterol transformations, induced by ultraviolet (UV) radiation. This synthesis proceeds in two stages:

— 7-dehydrocholesterol (7DHC) is converted into pro-vitamin D (pre-D_3) under the effects of UV radiation with a wavelength of 290–320 nm (UVB);
— pro-vitamin D is, under the influence of body temperature, converted into vitamin D_3.

Vitamin D_3, produced in deeper epidermal layers, in the vicinity of blood and lymphatic vessels, is bound by the vitamin D binding protein (DBP).

Vitamin D_2 is found in vegetables and mushrooms.

The amount of 0.025 mg of pure calciferol is the International Unit (IU) of vitamin.

In subjects with light pigmentation, 1 erythema dose (1 MED) i.e. 1 dose of UV radiation, causing minimal skin erythema leads to a ten-fold increase of vitamin D_3 level in blood serum, resulting from the release of approximately 30 mg of D_3 from 1 square metre of body surface within 24 hours. The level of vitamin D_3, increased after UV irradiation, returns to normal values after a few days. In healthy subjects, it is accompanied by a slight increase of 25(OH)D level, while in those with vitamin D deficits, a triple increase of 25(OH)D in blood is observed.

The effectiveness of skin synthesis gets weaker as the body ages; in subjects aged 70+, it is one quarter that of young people given identical exposure to the sun. The application of protective creams with anti-UVB filters also reduces the skin synthesis of vitamin D_3 [23, 24].

Metabolism of vitamin D

In contrast to the non-enzymatic synthesis of vitamin D in skin, the transformation of vitamin D into 25(OH)D and 1,25$(OH)_2$D requires the presence of enzymes — hydroxylases.

The first stage is hydroxylation of 25-hydroxyvitamin in the liver in position 25 of the lateral chain, leading to formation of metabolically inactive 25-hydroxyvitamin D — 25(OH)D in physiological concentrations. Hydroxylation to active 1,25$(OH)_2$D takes place in the kidneys, where trace amounts of 24,25$(OH)_2$D and of 25,26$(OH)_2$D are also formed [4,5].

The activity of hepatic 25-hydroxylase increases under the effect of pro-vitamin D, DBP concentrations and some drugs (e.g. antiepileptics) and decreases as a result of the activity of the final metabolites of this transformation. The activity of 1α-hydroxylase and/or 24α-hydroxylase increases under the influence of parathormone (PTH) and PTH-resembling peptide (PTHrP), prostaglandins and reduced calcaemia and phosphataemia.

The formation of active vitamin D form inhibits: the increase of 1,25$(OH)_2$D level, caused by PTH and PTHrP deficits, hypercalcaemia, hyperphosphataemia, calcitonin and metabolic acidosis.

The hepatic metabolite, 25(OH)D, is eliminated by 24-hydroxylation and excretion with bile, following its previous conjugation with glucuronic or sulphuric acid. In physiological conditions, 3% of circulating metabolites are excreted with urine and faeces [23, 25].

Table I. *Evaluation of the organism supply with vitamin D, based on serum 25(OH)D concentration — terminology [23, 25]*

Tabela I. *Ocena zaopatrzenia w witaminę D na podstawie stężenia 25(OH)D w surowicy — terminologia [23, 25]*

Terminology	Serum 25(OH)D concentration	
	[nmol/L]	[ng/mL]
Deficiency	0–25	0–10
Deficiency	25–50	10–20
Hypovitaminosis D	50–75	20–30
Recommended level	75–200	30–80
Toxic level	> 250	> 100

Table II. *Causes of vitamin D deficits*

Tabela II. *Przyczyny niedoboru witaminy D*

Suppressed skin synthesis
Insufficient volume in diet and supplements
Obesity
Hepatic diseases
Renal diseases
Malabsorption syndromes
Genetic diseases
Anticonvulsant drugs

Vitamin D deficiency

Definition

Table I presents a proposed terminology, used in the evaluation of the system supply with vitamin D.

Causes of vitamin D deficits

See Table II for the causes of vitamin D deficiency.

Suppressed skin synthesis of vitamin D and its insufficient supplementation with food

Without staying in the sun or an additional supplementation, vitamin D needs to be obtained in dietary components: e.g. fatty fish, such as salmon (400 IU/100 g), mackerel and sardines; cod-liver oil (400 IU/teaspoon); and egg yolk (20 IU). Over recent years, changes for the worse have been observed in dietary contents and this has meant reduced consumption of vitamin D_3; at present, the components which dominate diets include saturated fats, highly processed products and fast foods which have a low vitamin D content.

Vitamin D production in the skin is limited in the northern European climate during autumn and winter. Because the angle of sun ray incidence is small, UVB photons are absorbed by ozone in the atmosphere. The synthesis is also suppressed by the use of creams with sun-filters. Bright skin colour is associated with more effective synthesis of vitamin B. The system's ability to produce vitamin D under UVB radiation decreases with age [24, 26, 27].

Vitamin D deficiency in obese people

Obese subjects reveal significantly lower 25(OH)D concentration levels, partly because of vitamin D acumulation in the adipose tissue and partly perhaps because of avoiding direct exposure to sunlight with impaired skin synthesis (vitamin D concentration after UVB radiation is 57% lower than in normoweight subjects). It may also be the result of an increased synthesis of D — $1,25(OH)_2D$, an active metabolite of vitamin D, in the kidneys (which, in the negative feedback mechanism, inhibits 25(OH)D production in the liver) [28, 29].

Vitamin D deficiency concomitant with other diseases

In subjects with poor absorption syndrome, uncontrolled liver cirrhosis, renal diseases or who are on anticonvulsant drugs, systemic vitamin D deficits result from elimination diet, impaired skin synthesis, disturbed hydroxylation, excessive catabolism and decreased sensitivity of target tissues to $1,25(OH)_2D$ (e.g. in consequence of receptor defect).

Barbiturates, phenydantoin and pyramidone are inducers of microsomal hepatic enzymes (e.g. glucuronidases). The induction of hepatic vitamin D hydroxylation accelerates the excretion of glucuronic vitamin D inactive metabolites with bile.

Disturbances of vitamin D metabolism at the level of 1α-hydroxylation lead to a considerable decrease of $1,25(OH)_2D$ and to symptoms of vitamin D deficit. They occur both in hereditary diseases (vitamin D-dependent rickets of type I, hypophosphatemic rickets) and acquired diseases (chronic renal insufficiency, severe tubulopathies, hypoparathyroidism, pseudo-hypoparathyroidism). The suppressed activity of 1α-hydroxylase is a cause of reduced $1,25(OH)_2D$ concentrations in osteoporosis, especially senile, and in disturbed secretion of GH, prolactin and insulin [30].

Vitamin D-dependent rickets of type II is a representative syndrome, caused by genetic disturbances of $1,25(OH)_2D$ receptor.

Epidemiology of vitamin D deficiency

Hypovitaminosis D seems to be an epidemic in many populations in the world. Vitamin D deficits are regarded as one of the major health problems in children and young adults, especially Afro-American, and in middle-aged and elderly subjects. It has been determined that a concentration of 25(OH)D below 20 ng/mL occurs in 36% of healthy subjects (aged 18–29), 42% of black women (aged 15–49), 41% of out-patients (aged 49–83) and in almost 57% of internal in-patients in the United States [31].

The prevalence of vitamin D deficiency in Europe is even higher. Following biochemical measurements, they have been diagnosed in 28–100% of healthy subjects and in 70–100% of hospitalised adults [32].

In Poland, we have no useful population data on the epidemiology of vitamin D deficits. However, deficits have been identified, during the winter, in nine out of every ten examined women in the OPTIFORD Project, performed in five European countries [10]. In a study performed on a small group of pregnant women in the third trimester, the mean 25(OH)D concentration was 9.93 ± 5.32 ng/mL during the winter and spring [33, 34].

Vitamin D deficiency in mothers during pregnancy result in hypovitaminosis D in newborns, because the developing foetus and then the newborn is entirely dependent on maternal stores of this vitamin. A strong correlation has been demonstrated between 25(OH)D concentrations in the mother and that in her newborn baby [28, 35].

Vitamin D deficiency is fairly common in subjects aged over 65 and in patients with osteoporosis. Studies of 8,532 post-menopausal women (mean age 74.2) from France, Belgium, Denmark, Italy, Poland, Hungary, Great Britain, Spain and Germany have shown a mean concentration of 24.4 ng/mL, with significant differences between countries. The lowest concentration of 25-hydroxyvitamin D was found in France (25.75 ng/mL), while the highest was in Spain (34 ng/mL). In the entire studied population, vitamin D deficit concerned 79.6% or 32.1% of subjects, according to whether 30 ng/mL or 20 ng/mL was regarded as the cut-off point [36, 37].

Guidelines for vitamin D supplementation in the population of adult subjects

Supplementation with vitamin D

1. An element of early prophylaxis in healthy population.
2. Vitamin D deficit treatment for individual recommendation in selected patients.

Supplementation with vitamin D in healthy population

Cause. The causes of vitamin D supplementation in the healthy population of Poland include reduced skin synthesis (associated with latitude, ageing processes, the use of sun-protection filters and lifestyle) and insufficient intake of vitamin D in the diet.

Goal. Supplementation with vitamin D is to maintain the level of 25(OH)D in serum above 30 ng/mL.

Prophylactics against vitamin D deficits

— Exposure to the sunlight.
— Oral vitamin D administration.
— Combined supplementation/skin irradiation and vitamin D supplementation.
— The optimal conditions of skin exposure to UV radiation in Poland occur from May until September. The duration of staying in the sun necessary for sufficient vitamin D synthesis is 20 minutes a day (without the use of protective filters); exposing unprotected face, hands and forearms (i.e. 15% of body surface) to sunlight is perfectly adequate. An alternative way to stimulate skin synthesis may be irradiation with a UVB lamp (1 erythema dose, two or three times a week).
— Oral vitamin D administration (minimum of 800–1,000 IU/day) is necessary during the period of insufficient skin synthesis, i.e. in Poland from October until April.
— Vitamin D (minimum of 800–1,000 IU/day) should be administered to all subjects who do not expose their skin, and to subjects aged over 65 throughout the whole year for the age-related decrease of skin synthesis and for the proven anti-fracture and anti-fall effects of the vitamin (see Table III).

Supplementation of vitamin D deficits in individual patients

Vitamin D deficiency may result not only because of insufficient skin synthesis or low supplementation in diet but also as a consequence of: disturbed absorption in the digestive tract, decreased hydroxylation (liver or kidney insufficiency), excessive catabolism (anticonvulsive drugs) or reduced sensitivity of target tissues to $1,25(OH)_2D$ (vitamin D-resistant rickets of type II).

Where there is too little exposure to sunlight or too little vitamin D intake in diet, it can be administered orally. In subjects, either non-compliant with medical recommendations or with poor tolerance of oral drug administration, parenteral administration of vitamin D is recommended.

In patients with disturbed absorption from the digestive tract, vitamin D is administered in large doses either orally or parenterally (the latter form is unavailable in Poland). The best effects of treating vitamin D deficiency in this group of patients, just as in patients with obesity combined with vitamin D deficit, are obtained by stimulation of skin synthesis, using artificial sources of UVB radiation and monitoring the levels of 25(OH)D every three months.

In patients with hepatic or renal dysfunctions, active metabolites of vitamin D are used; in cases of calcidiol deficiency for hepatic causes, calcifediol is used; and in cases of calcitriol deficit for renal causes. alphacalcidiol is used (see Table IV).

A diagnosis of vitamin D deficiency requires the application of much higher doses of vitamin D (therapeutic), differentiated according to degree of deficit (see Table V). The therapeutic dose in severe depletion may amount to at least 5,000 IU/day to 10,000 IU/day (ab. 50,000 IU/week); in mild and moderate deficits it could be 2,000–3,000 IU/day. The supplementation time period varies between one and three months (depending on deficit degree). Having obtained the optimal concentration of 25(OH)D, a maintenance dose may be started. In the course of treatment, it is necessary to monitor 25(OH)D in serum and, in severe deficits, it is necessary to monitor calcium concentration, the activity of alkaline phosphatase and of 24-h urinary calcium excretion (calciuria).

Table III. *Supplementation of vitamin D for healthy adult population*
Tabela III. *Suplementacja witaminy D w populacji zdrowych dorosłych*

Supplementation of vitamin D		Skin synthesis		Oral administration	
Months		X–III	IV-IX	X–III	IV–IX
Adult subjects	Up to age 65	–	+	800–1.000 IU/d	–
	After 65	–	–	800–1.000 IU/d	

Table IV. *Causal treatment of patients with vitamin D deficit or disturbances of its metabolism*
Tabela IV. *Leczenie przyczynowe pacjentów z niedoborem witaminy D lub zaburzeniami jej metabolizmu*

Therapy	Vitamin D deficit - cause			Hydroxylation disorders - cause	
	Nutrition	Skin synthesis	↓ absorption GI	Liver	Kidney
UVB	+	+	+		
Oral administration of vit. D	+	+	+ (large doses)		
Parenteral administration of vit. D			+		
25(OH)D				+	
1α(OH)D 1,25(OH)$_2$D					+

GI — gastrointestinal tract

Table V. *Vitamin D deficiency (treatment/supplementation)*
Tabela V. *Niedobory witaminy D (leczenie/suplementacja)*

Serum level of 25(OH)D	< 10 ng/mL	10–20 ng/mL	20–30 ng/mL	> 30 ng/mL
Deficit degree	Severe	Moderate	Mild	Optimal concentration
Therapeutic dose of vitamin D*	+	+	+	–
Prophylactic dose of vitamin D	–	–	–	+
Follow-up every three months				
25(OH)D	+	+	–	–
Fa_s	+			
Ca_s	+			
calciuria	+			

*supplementation time — until an optimal level is obtained for the pleiotropic effect of vitamin D (25(OH)D > 30 mg/mL)

Table VI. *Vitamin D_3 commercial forms available on the Polish market*
Tabela VI. *Postacie handlowe witaminy D_3 dostępne na polskim rynku*

Agent	Dose in 1 mL	Dose in one drop or tablet
Devikap (Medana) 10 mL — drops	15.000 IU	500 IU
Juvit D_3 (Hasco-Lek) 10 mL — drops	20.000 IU	590 IU
Vigantol (Merk) 10 mL — drops	20.000 IU	670 IU
Vigantoletten 500 (Merk) tablet	n/a	500 IU
Vigantoletten 1000 (Merk) tablet	n/a	1000 IU
Vta D (Vitis Pharma)	n/a	400 IU

Table VII. *Active metabolites and analogues of vitamin D*
Tabela VII. *Aktywne metabolity i analogi witaminy D*

Name	Agent	Dose in 1 mL/tablet
25(OH)D calcifediol	Devisol 25 (drops)	0.15 mg
1a(OH)D alphacalcidol	Alfadiol Alfakalcydol IF (tabl.)	0.25 μg 1 μg
1,25(OH)$_2$D calcitriol	Kalcytriol (tabl.)	0.25 μg

Compensation of vitamin D deficiency — practical remarks

— The effect of vitamin D_2 is 30% lower than that of vitamin D_3.
— Vitamin D can be administered alternatively in appropriate doses: every week, or every two or four weeks (it acumulates in the system), as it ensures better compliance.
— The supplementing dose of vitamin D should be higher in elderly patients, in those with obesity, inhabitants of more northerly parts of the world, during autumn and winter and in subjects with dark skin pigmentation who use creams which protect against UVB which affects vitamin D metabolism.
— Calcitriol and alphacalcidol are not indicated to supplement vitamin D deficits in healthy people. They should be applied in disorders of vitamin D hydroxylation as a result of chronic liver or renal disease.
— Vitamin D should be administered together with meals, for more effective absorbtion.

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