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# Проблемные вопросы диагностики и лечения дефицита витамина D у пожилых больных

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***АННОТАЦИЯ***

Витамин D — жирорастворимое соединение, которое человек получает с пищей или синтезирует самостоятельно при воздействии солнечного света с кожей.

Метаболизм витамина D модулируется многими внутренними и внешними факторами, включая генетический полиморфизм, тип кожи (пигментацию), возраст, состояние здоровья, время года, географическую широту, одежду и питание. Некоторые из них являются модифицируемыми, т.е. могут регулироваться человеком.

Для оценки уровня витамина D в организме рекомендуется использовать определение в сыворотке крови концентрации общего 25(OH)D — основной циркулирующей формы, которая отражает как поступление витамина D с пищей и нативными препаратами, так и синтезированный витамин D в коже под воздействием ультрафиолетового облучения.

Статья посвящена вопросам диагностики и лечения дефицита витамина D у пожилых пациентов. Проблема, обусловленная возрастом, связана с более частыми оперативными вмешательствами в анамнезе и хроническими заболеваниями, требующими приёма медикаментозной терапии, которая в свою очередь может влиять на метаболизм этого витамина. Дефицит витамина D у пожилых людей требует постоянного и длительного приёма колекальциферола, однако нельзя забывать о рисках лекарственного взаимодействия и полипрагмазии. Диагностика и терапия дефицита витамина D у пожилых людей должны проходить с учётом всех особенностей этой группы пациентов.

В статье обсуждаются особенности метаболизма витамина D в пожилом возрасте; представлены нозологии, предрасполагающие к развитию дефицита витамина D, способы диагностики и коррекции дефицита этого витамина, в том числе рассматривается взаимосвязь тяжёлого течения новой коронавирусной инфекции COVID-19 с уровнем витамина D.

Требуется дальнейшее изучение возможных лекарственных взаимодействий и возможных дополнительных эффектов витамина D, а также его вклад в течение сопутствующих заболеваний.

**Ключевые слова:** витамин D; остеопороз; питание; переломы; диагностика.

**Как цитировать**

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# Issues of diagnostics and treatment of vitamin D deficiency in older patients

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***ABSTRACT***

Vitamin D is a fat-soluble compound that a person obtains from food or synthesizes independently when the skin is exposed to sunlight.

Vitamin D metabolism is modulated by various intrinsic and extrinsic factors, including genetic polymorphism, skin type (pigmentation), age, health, season, latitude, clothing, and diet. Some of them are modifiable, i.e., they can be controlled by humans.

To assess the vitamin D level in the body, the recommendation was to determine the concentration of total 25(OH)D in the blood serum, the main circulating form, which reflects both the intake of vitamin D from food and native preparations and the synthesized vitamin D in the skin under the influence of ultraviolet irradiation. This study focused on the diagnosis and treatment of vitamin D deficiency in older patients.

The age-related problem is associated with a more frequent history of surgery and chronic diseases requiring drug therapy, which in turn can affect the metabolism of this vitamin. Vitamin D deficiency in older people requires constant and long-term use of cholecalciferol; however, the risks of drug interactions and polypharmacy should not be overlooked.

The diagnosis and treatment of vitamin D deficiency in older people should consider all the characteristics of this group. Moreover, this study presents the features of vitamin D metabolism in older people, nosologies predisposing to the development of vitamin D deficiency, methods for diagnosing and correcting vitamin D deficiency, and relationship between severe COVID-19 and vitamin D levels.

Further study of possible drug interactions, additional effects of vitamin D, and its contribution to comorbidities is warranted.

**Keywords:** vitamin D; osteoporosis; fractures; bone; food; diagnostic tests.

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## BACKGROUND

Vitamin D deficiency is a common problem. Approximately 40% of Europeans have vitamin D deficiency (plasma 25(OH)D concentration <20 ng/ml or <50 nmol/l), and 13% of them have severe vitamin D deficiency (plasma concentration <12 ng/ml or <30 nmol/l) [1]. In the Russian Federation, 70%–95% of adults were found to have plasma 25(OH)D levels <30 ng/ml (below the reference level of most laboratory tests) [2], which may be due to both a low level of endogenous vitamin D synthesis resulting from insufficient solar irradiation, and insufficient vitamin D consumption from food. Taking appropriate measures to improve vitamin D status and maintaining the optimal blood concentration of 25(OH)D in the population will improve the condition of the musculoskeletal system and reduce the risk and mitigate the course of certain chronic diseases [3].

Vitamin D and its metabolic effects have been known for a long time. Rickets as a classic disease associated with vitamin D deficiency was first described in the 17$^{th}$ century. In 1928, Adolf Otto Reinhold Windaus was awarded the Nobel Prize in Chemistry for the discovery of 7-dehydrocholesterol, a precursor of vitamin D [4].

In recent years, widespread media coverage about the potential health benefits of vitamin D supplementation has led to a significant increase in interest on the diagnosis and treatment of vitamin D deficiency. Herein, we consider older person, one of the most vulnerable risk groups for vitamin D deficiency, and the diagnostic, and therapeutic aspects that the clinician may deal with among this group of patients.

## VITAMIN D METABOLISM

Vitamin D is a fat-soluble vitamin that an individual can obtain from food or synthesize themselves after skin exposure to sunlight. There are two forms of the vitamin: $D_2$ and $D_3$. $D_3$, or colecalciferol, is the most important source for animals and is produced in human skin; $D_2$, or ergocalciferol, differs from $D_3$ by a methyl group in C24 and a double bond in C22–C23, and is produced by plants and fungi [5]. The two forms of vitamin D are biologically equivalent in terms of their ability to cure rickets, and most of the stages involved in their metabolism are identical. However, at high doses, vitamin $D_2$ is less effective than vitamin $D_3$ due to differences in pharmacokinetics [6, 7].

In humans, $D_3$ is produced from 7-dehydrocholesterol (7-DHC), an intermediate in cholesterol synthesis. Exposure to beta rays of ultraviolet light (ultraviolet B, UVB) in the range of 290–315 nm causes an electrocyclic rearrangement of the ring at the C9–C10 position, leading to the formation of previtamin D ($PreD_3$). After $PreD_3$ formation, thermal isomerization to vitamin $D_3$ ($VitD_3$) occurs due to a shift of the hydrogen atom from C19 to C9 [8]. The synthesis of colecalciferol depends on the concentration of 7-DHC, which, in turn, depends on the activity of 7-dehydrocholesterol reductase (DHCR7). This enzyme catalyzes the reversible reduction of 7-DHC to cholesterol [9].

According to most authors, the biochemical regulation of DHCR7 is a crucial aspect in the production of vitamin D, since reduced activity of this enzyme can redirect the pathway from cholesterol to vitamin D biosynthesis [10] (Fig. 1).

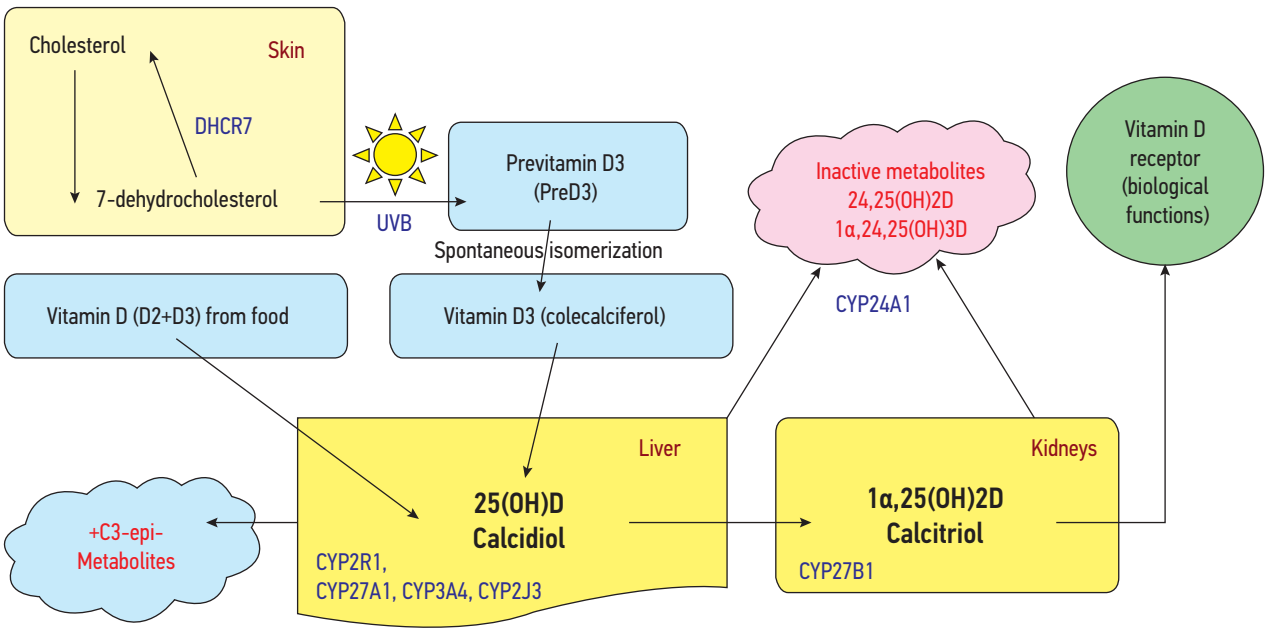


**Fig. 1.** Main stages of vitamin D metabolism.

Vitamin D metabolism is modulated by multiple intrinsic and extrinsic factors, including genetic polymorphism, skin type (pigmentation), age, health status, behavior under sun exposure, season, latitude, clothing, and diet. Some of these factors are modifiable, that is, can be controlled by humans. For example, complete avoidance of sun exposure, even because of fear of going out, can aggravate vitamin D deficiency [11]. On the other hand, prolonged exposure to sunlight can trigger the occurrence of skin cancer. The use of sunscreen for daily and recreational photoprotection does not interfere with the synthesis of vitamin D in the skin, even when applied under optimal conditions [12], and is associated with exposure to rays of different wavelengths. Due to the geographic and climatic conditions of Russia, the contribution of vitamin D synthesis in the skin under the action of sunlight is significantly limited for the majority of Russians [13].

Colecalciferol ($D_3$) and ergocalciferol ($D_2$) are biologically inert. To be activated and converted into their active forms, they must undergo two stages of hydroxylation [14].

The transport of vitamin D metabolites is mainly carried out by vitamin D-binding proteins (85%), whereas 15% of the transport is performed by albumin due to its lower affinity [15]. Vitamin D-binding protein is a highly polymorphic protein with at least 120 isoforms, isolated by electrophoresis [16]. Its concentration in blood serum significantly exceeds (up to 20 times) that of vitamin D metabolites; therefore, vitamin D-binding sites are occupied by only 5% of circulating vitamin D-binding proteins [17, 18].

The initial hydroxylation of dietary or skin-synthesized vitamin D occurs primarily in the liver. In the liver, with the involvement of the enzyme 25-hydroxylase, a hydroxyl group is attached to colecalciferol in the 25$^{th}$ position, and 25-hydroxycalciferol (calcidiol) is formed. There are several isoforms of 25-hydroxylase, such as CYP2R1, CYP27A1, CYP3A4, and CYP2J3 [19]. CYP2R1 expression is believed to be modulated by age and the metabolic environment. 25(OH)D levels decrease and are less responsive to therapy in elderly patients. Roizen et al. [20] attributed this finding to a decrease in CYP2R1 activity during aging, since the CYP2R1 mRNA, and protein content in the liver tissue of male mice decreased progressively with age. Moreover, the ratio of 25(OH)D to inactive colecalciferol was positively correlated with CYP2R1 mRNA and decreased steadily with age.

Calcidiol (25(OH)D) is the main circulating form of vitamin D; however, its activation requires additional hydroxylation, which results in the formation of calcitriol (1α,25(OH)2D). This second hydroxylation occurs predominantly in the kidneys, mediated by the CYP27B1 enzyme. In addition to the kidneys, keratinocytes, and immune cells that express CYP27B1 may be involved in this reaction. The regulation of 1,25(OH)2D production in non-renal cells occurs differently, as they can produce 1,25(OH)2D for their own needs in an autocrine and/or paracrine manner. If CYP27B1 activity is not controlled, it may lead to the overproduction of 1,25(OH)2D, which can lead to hypercalcemia and/or hypercalciuria (as in sarcoidosis) [21]. In the kidney, CYP27B1 activity is induced by parathyroid hormone and inhibited by fibroblast growth factor 23 (FGF23) and 1,25(OH)2D. In other tissues, CYP27B1 is mainly regulated by cytokines such as tumor necrosis factor and interferon-γ [22]. It is also known that dexamethasone inhibits CYP27B1, reducing both the concentration of CYP2R1 mRNA and protein in the liver (by 50% and 26%, respectively) and its production by alveolar macrophages [23].

To maintain a constant level of active vitamin D and avoid an excess of its active forms in blood plasma, several reactions of vitamin D inactivation are needed, such as the process of 24-hydroxylation, which is regulated reciprocally by 1α-hydroxylation. The enzyme CYP24A1 (24-hydroxylase) converts 25(OH)D and 1,25(OH)2D into non-biologically active metabolites excreted in the bile. CYP24A1 dysfunction leads to the production of elevated plasma levels of 1,25(OH)2D3 and is associated with idiopathic childhood hypercalcemia or kidney stones [24]. Other minor metabolic pathways of vitamin D have also been described. For example, under the action of 3-epimerase, metabolites with partial biological activity are formed [25]. Inactive metabolites (24,25(OH)2D; 1a,24,25(OH)3D) can also be formed in the liver [26].

The main mediator of the biological action of vitamin D is its receptor. The vitamin D receptor (VDR) is a 50,000 Da polypeptide comprising of a single amino acid chain. It is almost ubiquitous in the body, since it is expressed in at least 30 tissues involved in bone metabolism (intestine, bones, joints, kidneys) or other extraskeletal organs (heart, immune system, adipose tissue, and many others) [26]. Its binding sites can be located in various regions, including introns, and distal intergenic regions of regulated genes. Vitamin D receptor coregulators provide cell-specific genomic regulation [27, 28]. The vitamin D receptor functions as a transcription factor and can modulate genes encoding chromatin modifier enzymes, thereby modulating the human epigenome. For example, histone H3 lysine demethylase (KDM6B/JMJD3), which is essential in development, has been shown to be induced by 1,25(OH)2D/VDR, subsequently modulating vitamin D metabolism. Pereira et al. demonstrated that 1,25(OH)2D/VDR induces JMJD3 RNA in human colon cancer cells, indicating the role of 1,25(OH)2D in colon cancer epigenomic events [29].

## DIAGNOSTIC PROBLEMS IN VITAMIN D DEFICIENCY

To assess the level of vitamin D in the body, it is recommended to determine the concentration of total 25(OH)D in blood serum, as this is the main circulating form of vitamin D, with a half-life of approximately 2–3 weeks, which reflects both the vitamin D intake from food and native drugs, and that synthesized in the skin under the influence of ultraviolet irradiation [30].

Vitamin D is not subject to circadian changes; however, its concentration may vary depending on the time of the year.

The lowest 25(OH)D values are recorded in spring (in March for the Northern Hemisphere), and the highest values are noted after summer (August and September for the Northern Hemisphere) [31].

In certain clinical conditions, such as suspected CYP24A1 deficiency, hypophosphatemic syndrome, and granulomatous, or lymphoproliferative diseases, the blood serum levels of 1,25(OH)2D and 24,25(OH)2D can be measured as an additional diagnostic method. 1,25(OH)2D circulates in blood at concentrations up to 1,000 times lower than that of 25(OH)D and has a significantly shorter half-life of approximately 4 h. This metabolite is highly regulated by parathyroid hormone, FGF23 protein, calcium, and phosphorus in the blood and does not reflect the reserves of 25(OH)D in the body. The use of these methods is currently limited by the low prevalence and availability of these research methods [32–34].

The possible use of other markers of vitamin D level, such as free 25(OH)D (not bound to carrier proteins) or the 25(OH)D/24,25(OH)2D ratio, has been actively discussed. Due to the low evidence base and the relatively high cost in clinical practice of screening for vitamin D deficiency, their use is also not recommended [35]. However, if 24-hydroxylase deficiency is suspected, the determination of the 25(OH)D to 24,25(OH)2D ratio can be indicated as a screening method, as well as the determination of 24,25(OH)2D [32].

The first tests to assess vitamin D status in humans were performed manually. At the beginning of the XX century, the most popular biological method for vitamin D testing was the line test developed by McCollum et al. [36]. This analysis, performed entirely *in vivo* in rats, was time consuming, inconsistent, inaccurate, and cumbersome. The first *in vitro* test, a biological assay to measure 25(OH)D, was reported in 1971 by Haddad et al. [37], which became known as the "competitive protein-binding assay." Three decades later, in 2001, a fully automated form of the assay (Nichols Advantage) [38] was released. However, by 2005, the assay was eventually discontinued due to cross-reactivity of the vitamin D-binding protein with other metabolites derived from vitamin D, which led to an overestimation of the 25(OH)D values. In the early 1980s, the study team of B.W. Hollis [39] used an immunological approach based on the affinity between antibodies and antigens to quantify the concentration of 25(OH)D, which improved the specificity of 25(OH)D detection compared to the competitive binding assay.

Modern methods for determining the blood level of 25(OH)D can be divided into two large groups, namely immunoassay based (radioimmunoassay, chemiluminescent immunoassay, enzyme immunoassay, electrochemiluminescent immunoassay) and chromatographic methods (liquid chromatography mass spectrometry) [40]. The latest method for measuring vitamin D is the simultaneous analysis of eight vitamin D analogs using liquid chromatography mass spectrometry (LC-MS/MS). The new assay can be used to simultaneously measure the levels of six forms of vitamin D and two epimers, which is a significant improvement over existing methods. These features make this assay useful in research and clinical practice, where specific and accurate measurement of different forms is required [41]. The sensitivity and specificity of vitamin D assays have improved significantly in recent years, but analytical variation in samples due to matrix effects and antibody specificity is still a major concern. Due to these uncertainties, LC/MS/MS provides better separation and more accurate quantification of 25(OH)D, but its low throughput makes the method impractical for routine and large-scale use. The high cost and technical knowledge required to operate the HPLC/MS/MS (high-performance liquid chromatography combined with mass spectrometry) equipment make this method available only in specialized laboratories. Thus, a unified approach or method that combines the performance and convenience of immunoassays and the resolution and sensitivity of LC/MS/MS is essential to meet the growing demand and reduce the time and cost of vitamin D assays [42].

In addition, there is still a problem of standardization of 25(OH)D determination by different laboratory methods. Due to the insufficient coverage of methods for determining 25(OH)D by standardization, it is difficult to develop criteria for interpreting the vitamin D status in the entire range of results obtained, from deficiency to toxicity [43]. The VDSP (Vitamin D Standardization Program) international collaboration is working to provide a solution for this problem. It recommends that test kit manufacturers and large commercial or clinical laboratories should participate in a certification program developed by the Centers for Disease Control and Prevention (CDC) to ensure consistent results across different 25(OH)D assays. For smaller laboratories, there are performance testing schemes and external quality assessment programs such as the Vitamin D External Quality Assessment Scheme, including those developed by the College of American Pathologists (CAP) [44]. Under conditions of insufficient availability of standardized methods, it may be justified to use the same method for the dynamic assessment of the 25(OH)D level [2].

Immunoassay methods are more commonly used in clinical laboratories to measure the concentration of 25(OH)D because of their automation and fast results. However, when using these methods, cross-reactivity between various metabolites is possible, particularly with the inactive metabolite 24,25(OH)2D, which can reduce the test specificity. Chromatographic methods, in turn, do not always detect 3-epi-25(OH)D (a metabolite with partial biological activity), resulting in a decrease in the sensitivity of the above method [45].

Plasma vitamin D levels can be significantly reduced in the presence of inflammation, as almost all 25(OH)D values are below reference values when C-reactive protein levels are >40 mg/l, making interpretation difficult [46]. The optimal level of detectable vitamin D remains a matter of debate. Most researchers agree that 25(OH)D levels <12 ng/ml (30 nmol/l) are recognized as obviously insufficient for all ages, since they are associated with an increased risk of rickets

and osteomalacia, and levels >100 ng/ml (250 nmol/l) are potentially toxic, as they increase the risk of hypercalcemia and its consequences [31]. A blood concentration of 25(OH)D <20–30 ng/mL (50–75 nmol/L) is considered by most authors to be a sign of vitamin D deficiency [47, 48]. The classification of vitamin D levels, according to the recommendations of the Russian Association of Endocrinologists, is presented in Table 1 [2].

When correcting vitamin D deficiency, it is recommended to adhere to the target range of 30–60 ng/ml (75–150 nmol/l), since there is no evidence for additional positive effects with higher levels of 25(OH)D, and exceeding these values naturally in human is uncommon even in populations with year-round exposure to natural sunlight [2].

Repeated measurements of serum 25(OH)D levels should not be performed earlier than 8 weeks after the start of treatment [49, 50], but, according to some reports, even 12 weeks or more may be required before measurement [51].

## CHARACTERISTICS OF VITAMIN D METABOLISM IN ELDERLY PEOPLE

Chronic diseases and history of surgical interventions and other pathologies, including those requiring regular drug therapy, are more frequently reported in older people, and all these factors can affect vitamin D metabolism.

The ability of the skin to synthesize vitamin D decreases with age. This was demonstrated by measuring the levels of 7-dehydrocholesterol (provitamin $D_3$) in a certain area of the epidermis and dermis in people of different ages, and previtamin $D_3$ in their skin after UV exposure [52]. It was revealed that the skin's ability to produce vitamin D in elderly people is three times lower than that of young people [53], probably due to a change in DHCR7 activity, as described previously [10].

The risk of vitamin D deficiency is higher in patients who go out less often and those who try to completely avoid sun exposure [54]. As previously stated, the necessary use of sunscreen for daily and recreational photoprotection in such cases does not interfere with vitamin D synthesis [12].

Older persons tend to have a low intake of foods containing vitamin D, which is associated with the relative lactose intolerance in this group of patients. Conditions such as malabsorption, including celiac disease, short bowel syndrome, history of gastric bypass surgery, inflammatory bowel disease, chronic pancreatic insufficiency, and cystic fibrosis [55], and intake of drugs that disrupt the absorption of vitamin D precursors (cholesterol) in the intestine (Cholestyramine, orlistat) [56] also predispose to vitamin D deficiency due to impaired absorption. A history of gallectomy does not significantly affect vitamin D levels [57].

Vitamin D synthesis is disrupted by antiretroviral drugs [58] and drugs that induce p450 hepatic enzymes that activate vitamin D cleavage, such as phenobarbital, carbamazepine, dexamethasone, and other glucocorticosteroids, nifedipine, spironolactone, clotrimazole, and rifampicin [59].

In patients with chronic liver diseases such as cirrhosis, 25-hydroxylation may be impaired, resulting in active vitamin D deficiency [60]. In hepatic insufficiency, vitamin D deficiency can also occur due to a decrease in the level of serum transport proteins and an acceleration of its catabolism [61].

An increased depletion of vitamin D reserves in the body may occur in chronic granulomatous diseases, primary hyperparathyroidism, and some types of lymphomas, due to acceleration of its conversion into the active form (1,25(OH)2D) [62, 63].

Among kidney diseases, nephrotic syndrome potentiates the loss of vitamin D in urine and its binding to proteins [64]. In chronic kidney disease, there may be an impairment of vitamin D activation [30].

In addition to the difficulties in absorption and metabolism of vitamin D, which exacerbate the development of vitamin D deficiency in the elderly, there are several diseases in which an optimal level of vitamin D can improve the disease outcomes. First, vitamin D deficiency is associated with osteoporosis. In Russia, osteoporosis occurs in approximately 30% (34% of women and 27% of men) of individuals aged 50 years and older, while its incidence increases with age [65]. Osteoporosis can lead to fractures of the vertebral bodies and other bones of the skeleton, most often long bones, which entails high material costs in the field of healthcare, leads to incapacity for work and disability, and increases mortality [66].

**Table 1.** Interpretation of the concentrations of 25(OH)D, according to the Russian Association of Endocrinologists

| Classification | Blood 25(OH)D concentration |
|---|---|
| Severe vitamin D deficiency | <10 ng/ml (<25 nmol/L) |
| Vitamin D deficiency | <20 ng/ml (<50 nmol/L) |
| Vitamin D insufficiency | ≥20 and <30 ng/ml (≥50 and <75 nmol/L) |
| Target levels of vitamin D | 30–60 ng/ml (75–150 nmol/L) |
| Adequate vitamin D levels | 30–100 ng/ml (75–250 nmol/L) |
| Levels with possible vitamin D toxicity manifestation | >10 ng/ml (>250 nmol/L) |
| Vitamin D-associated toxicity (hypercalcemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, ectopic calcification) | Any 25(OH)D levels |

Low vitamin D levels can lead to reduced intestinal absorption of calcium, resulting in secondary hyperparathyroidism with increased mobilization of calcium from bones, decreased bone mineral density, and osteoporosis. Vitamin D supports the formation and metabolic processes in muscle tissue, especially at the level of fast muscle fibers, which predisposes persons with vitamin D deficiency to falls [67, 68]. Although vitamin D preparations are not considered as drugs for the treatment of osteoporosis, they should be administered at doses of at least 800 IU per day, in combination with calcium preparations (500–1000 mg/day), during anti-osteoporotic therapy, as the efficiency of this combination of anti-osteoporotic therapy has been demonstrated by the results of a randomized controlled trial [66]. The combination of vitamin D and calcium also appears to be beneficial in preventing falls in older adults with 25(OH)D levels <50 nmol/L (20 ng/mL), which may be relevant to fracture prevention measures [69].

Vitamin D levels may also influence the course of Parkinson's disease. This neurodegenerative disorder is characterized by neuronal death in the substantia nigra pars compacta, which reduces the ability to synthesize dopamine, resulting in tremor, postural instability, bradykinesia, and rigidity. Parkinson's disease commonly affects older people, and an older age is a major risk factor for developing this condition [70, 71]. Vitamin $D_3$ supplementation may improve motor and non-motor symptoms of Parkinson's disease, thereby improving quality of life [72].

Vitamin D is involved in the maintenance of innate and adaptive immunity, and an impairment of vitamin D metabolism or vitamin D insufficiency can lead to dysregulation of the immune response [73].

There is evidence that vitamin D deficiency may be a predictor of increased incidence of acute respiratory infections in institutionalized older adults, and that vitamin D supplementation may reduce the risk of morbidity [74].

The relationship between COVID-19 infection and vitamin D levels has been extensively studied, and not all retrospective studies have shown such a correlation after adjusting for confounding variables. However, there is insufficient evidence to associate severity and mortality from COVID-19 with vitamin D sufficiency [75]. Interpretation of these studies is difficult due to the finding that plasma levels of vitamin D can be significantly lowered by inflammation, as almost all 25(OH)D levels are below the reference values when the C-reactive protein level >40 mg/l [46]. Therefore, patients with higher levels of C-reactive protein may be erroneously classified as vitamin D deficient, and high levels of C-reactive protein may potentially be a marker of severe COVID-19 infection [76].

In the elderly, there is an association between vitamin D deficiency and increased risk of heart failure [77], and evidence that vitamin D supplementation may improve depression indices in patients over the age of 60 years [78]. The authors explain this by the fact that there are many vitamin D receptors associated with depression in the hippocampus, and that vitamin D metabolites can cross the blood-brain barrier.

A possible relationship between vitamin D deficiency and sarcopenia is also being discussed. However, whether vitamin D supplementation has beneficial effects in patients with sarcopenia, such as the suppression of muscle atrophy and increased muscle strength, remains controversial, partially due to the complex mechanisms underlying the effect of vitamin D on muscle tissue [79]. It is probable that the effect of vitamin D on muscle strength and physical performance depends on the level of physical activity of older people. Therefore, older people are advised to avoid both physical inactivity and vitamin D deficiency [80].

Obesity is accompanied by a decrease in the bioavailability of vitamin D, and as the body mass index increases, patients experience a decrease in the serum concentration of 25(OH)D and an increase in the level of parathyroid hormone in the blood. In the prevention and treatment of vitamin D deficiency in obese individuals, higher doses of colecalciferol are required. Pathogenetically, this increased need for vitamin D is due to the distribution of the vitamin in a larger volume of adipose tissue [81].

The pleiotropic effect of vitamin D on body tissues is of considerable interest due to the possible role of its metabolism in the development of pathological conditions and diseases. However, the levels of 25(OH)D concentration in blood serum necessary to achieve extraosseous effects may not coincide with the levels that are sufficient to achieve classical effects, and in cases where the contribution of an insufficient level of vitamin D is proven, they should be investigated as part of the development of appropriate therapeutic measures [82].

General population screening for vitamin D deficiency is not currently recommended, but most authors agree that 25(OH)D should be investigated in patients of certain risk groups. Groups of patients at high risk of severe vitamin D deficiency and for whom biochemical screening is indicated include [2]: elderly patients (>60 years) with history of a fall or low energy fracture; obese patients (body mass index ⩾30 kg/m$^2$); patients with malabsorption syndrome, inflammatory bowel disease (Crohn's disease, ulcerative colitis), celiac disease, cystic fibrosis, after bariatric surgery, with radiation enteritis; patients with chronic kidney disease stage C3a and above (glomerular filtration rate <60 ml/min); patients with hepatic insufficiency stage II–IV; patients with granulomatous diseases (sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidioidomycosis); patients with lymphoproliferative diseases (lymphomas); patients with bone diseases (rickets, osteomalacia, osteoporosis); patients with hyperparathyroidism (of any origin); patients with dark skin; patients taking glucocorticoids, antiretrovirals, antifungals, antiepileptic drugs, cholestyramine, orlistat); and pregnant and lactating women.

According to Pludowski et al. [83], biochemical screening is also indicated for patients with musculoskeletal pain;

chronic autoimmune diseases (multiple sclerosis, rheumatoid arthritis); hospitalized patients; and older people with a history of falls or low-traumatic fractures.

## CORRECTION OF VITAMIN D DEFICIENCY

As a supplement, most people are advised to use colecalciferol rather than ergocalciferol [84]. If a patient refuses to take colecalciferol for any reason (veganism, history of allergic reactions), measurements by HPLC, standardized VDSP, or LC-MS/MS analysis will be required to monitor 25(OH)D levels during ergocalciferol therapy.

According to most recommendations, consider the optimal dose of colecalciferol for the adult population is at least 800–1000 IU [2, 83, 85]. With a reduced vitamin D level, higher doses of colecalciferol (up to 6000–7000 IU daily) can be used for up to 1–3 months while controlling blood 25(OH)D levels. Certain groups of patients (e.g., patients with obesity and malabsorption syndrome, individuals with dark skin pigmentation) may require up to 4,000 IU daily to prevent the development of deficiency [83].

In chronic kidney disease and some progressive liver diseases, vitamin D activation may be impaired, which will require therapy with its active metabolites [30], namely calcitriol in severe liver lesion (since this form of the hormone does not need additional metabolic steps to acquire biological activity), and alfacalcidol in patients with end-stage chronic kidney disease accompanied by a decrease in 1α-hydroxylase activity [86].

According to Russian recommendations for the correction of vitamin D deficiency [2], the indications for prescribing its active metabolites include: secondary hyperparathyroidism in end-stage chronic kidney disease, hypoparathyroidism (autoimmune, congenital, postoperative, etc.), pseudohypoparathyroidism (a rare genetic disease, manifested by an impairment of phosphorus-calcium metabolism due to resistance to parathyroid hormone), vitamin D-resistant rickets, vitamin D-dependent rickets, and severe hypocalcemia.

Active vitamin D metabolites in secondary hyperparathyroidism due to chronic kidney disease, and in combination therapy for osteoporosis can be used as relative indications [2]. However, even in patients with end-stage renal insufficiency and hereditary disorders of vitamin D metabolism, including those receiving therapy with active vitamin D metabolites, with an established decrease in the concentration of 25(OH)D, its correction with native vitamin D (colecalciferol) is an obligatory stage of treatment [2].

Active vitamin D metabolites and their analogs are not detected in significant amounts when studying vitamin D concentration in the blood serum. Therefore, while taking these drugs, it is necessary to control the calcium content in blood serum and urine, and to adjust the dose of the drug in case of hypercalcemia/hypercalciuria [87, 88].

The routine use of vitamin K supplements in the treatment of vitamin D deficiency and insufficiency is not recommended, and although some randomized controlled trials have shown its possible benefits (increased bone mineral density, reduced levels of undercarboxylated osteocalcin), this does not provide clear conclusions about its benefits [89].

For the treatment of established vitamin D deficiency, the Endocrine Society recommends 50,000 IU of vitamin D weekly for 8 weeks, followed by maintenance with 50,000 IU vitamin D every 2 weeks continuously. It is important to note that individual responses to a given dose of vitamin D vary greatly depending on weight, medications taken, health conditions, genetics, the method of 25(OH)D measurement, and others. This is the reason why it is recommended to check the serum concentration of 25(OH)D after 3–6 months of vitamin D intake for possible dose adjustments [90].

Daily, weekly, or monthly dosing regimens may be used as they result in similar serum 25(OH)D concentrations [91, 92]. However, some experts prefer daily doses, as native vitamin D itself may be biologically significant, and its half-life is only approximately 24 h. In randomized controlled trials using high doses of vitamin D, both the absence and an increase in the incidence of falls and fractures were reported [93]. A meta-analysis of vitamin D supplementation and musculoskeletal health outcomes revealed no difference between daily and intermittent doses of vitamin D [94].

Russian recommendations for the correction of vitamin D deficiency suggest choosing the optimal dosage regimen, taking into account the patient's preferences for the maximum expected adherence to treatment [2]. For the correction of vitamin D deficiency (serum 25(OH)D ⩾20 and <30 ng/mL), it is recommended to use half the total loading dose (100,000 IU cumulatively over 1 month) followed by maintenance doses. Patients with obesity, malabsorption syndrome, and those taking drugs that disrupt the metabolism of vitamin D are recommended to take higher (2–3 times) loading doses of colecalciferol to treat deficiency (800,000–1,200,000 IU) and insufficiency (400,000–600,000 IU) of vitamin D, with a transition to a maintenance dose of at least 3,000–6,000 IU/day [2].

It is noteworthy that, in the VITAL study, there were no safety problems with regard to hypercalcemia, kidney stones, or renal failure with daily intake of 50 μg (2000 IU) of vitamin D [95]. Single doses above 50,000 IU of vitamin D should be avoided [83].

Adequate intake of the required amount of colecalciferol with food is limited by its low content in food stuff, and the low availability of food grown in natural conditions. For comparison, some foods rich in vitamin D can be cited as an example (Table 2) [96].

Given the high prevalence of vitamin D deficiency and insufficiency among older people, requiring constant, and long-term intake of colecalciferol, the risks of drug interactions and polypharmacy should also be considered. For example, the use of thiazide diuretics in combination with calcium and vitamin D supplements may cause hypercalcemia in

**Table 2.** Examples of high vitamin D foods

| Product | Vitamin D content, IU |
|---|---|
| Cod liver oil | 400–1,000 in 1 teaspoon |
| Salmon, freshly caught in the wild | 600–1,000 per 100 g |
| Salmon, fresh, farm-raised | 100–250 per 100 g |
| Canned salmon | 300–600 per 100 g |
| Canned sardines | 300 per 100 g |
| Canned mackerel | 250 per 100 g |
| Canned tuna | 236 per 100 g |
| Egg yolk | 20 in 1 yolk |

older individuals or those with impaired renal function or hyperparathyroidism. Atorvastatin, a lipid-lowering drug, increases the concentration of 25(OH)D, and the simultaneous use of vitamin D with atorvastatin reduces the concentration of the latter. Undoubtedly, further studies are required to elucidate potential drug interactions with vitamin D, especially for drugs metabolized by cytochrome P450 3A4 (CYP3A4) [97].

## CONCLUSIONS

The diagnosis and treatment of vitamin D deficiency in the elderly should take into account all the characteristics of this group of patients. Further study of possible drug interactions and possible additional effects of vitamin D, and its contribution to comorbidities, is required.

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