

## The Effect of Vitamin D on the Physiological State of Women during Menopause

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**Abstract:** Vitamin D deficiency is one of the most common hypovitaminosis in the world. The article cites literature data showing that postmenopausal skin's ability to produce vitamin D is nearly quadrupled, and thus increases the risk of fractures from falls in older adults. Vitamin D is part of the complex therapy of postmenopausal osteoporosis, because its lack negatively affects the results of antiresorptive therapy: patients with low levels of vitamin D initially have a low level of growth during bisphosphonate therapy. For elderly people, a daily dose of vitamin D is required and blood There are no uniform standards for the concentration of vitamin D.

**Keywords:** vitamin D, osteoporosis, vitamin D deficiency.

One of the problems of modern medicine is related to the prevention of osteoporosis and the development of effective treatment methods. Statistical analysis of clinical studies shows that osteoporosis is diagnosed in about 10% of the population of the Russian Federation (14 million people), which is explained by the predominance of elderly people among the population [1]. Special attention is paid to the treatment of osteoporosis due to its serious consequences for human life: fractures of the vertebrae and bones of the peripheral skeleton, especially the femoral neck, resulting in an increase in disability and death among the elderly [2]. In North America, 76 percent of women with osteoporosis are vitamin D deficient, and 50 to 70 percent have a history of fracture. DC Gabaroi et al. (2010) conducted a study to determine the prevalence of joint factors (thyroid hormones, parathyroid hormones - PTH, 25(OH)-vitamin D) in bone loss in postmenopausal women with osteoporosis and to assess their contribution to disease severity. . 204 women with postmenopausal osteoporosis (mean age 64.9 years) were examined. It is known that the most important factors leading to the development of the disease in women are vitamin D deficiency in 82% of cases and increased PTH level (more than 65 pg/ml) in 35% [11]. The significant effect of vitamin D on the development of osteoporosis can be explained by its direct participation in the regulation of calcium-phosphorus metabolism. It is known that vitamin D deficiency is accompanied by a decrease in calcium and phosphorus in the blood due to a decrease in the efficiency of calcium absorption in the intestine and an increase in the level of PTH. this ultimately leads to impaired skeletal mineralization [20, 24, 26]. Increased PTH production mobilizes vital calcium stores from the skeleton and makes the spine more porous. If the body has enough calcium, the adult skeleton can maintain the size of the bone mass typical for each decade of life. in postmenopause, the balance of bone remodeling is disturbed towards the increase of bone resorption processes [21]. A significant decrease in the concentration of vitamin D in blood serum has been noted with age. In addition, in people over 65 years of age, due to the decrease in the concentration of 7-dehydrocholesterol, the ability of the skin to produce vitamin D decreases almost four times compared to young people [2, 24]. Factors affecting vitamin D levels include solar radiation and physical inactivity typical of modern urbanized society. ( $p=0.02$ ), which confirms the importance of insolation for its synthesis. Similar data were obtained from a survey conducted among the elderly population of the Ural region [3]. All patients (mean age 69 years) had some degree of vitamin D deficiency in hip fracture patients with severe (less than 12.5 nmol/l - 22%) and moderate (12.5-25 nmol / l) deficiency prevails. – 43% vitamin D deficiency, in single elderly people, average vitamin D deficiency in 45% cases, average vitamin D concentration in 53% was  $28.1\pm 10.1$  nmol/l in this group,

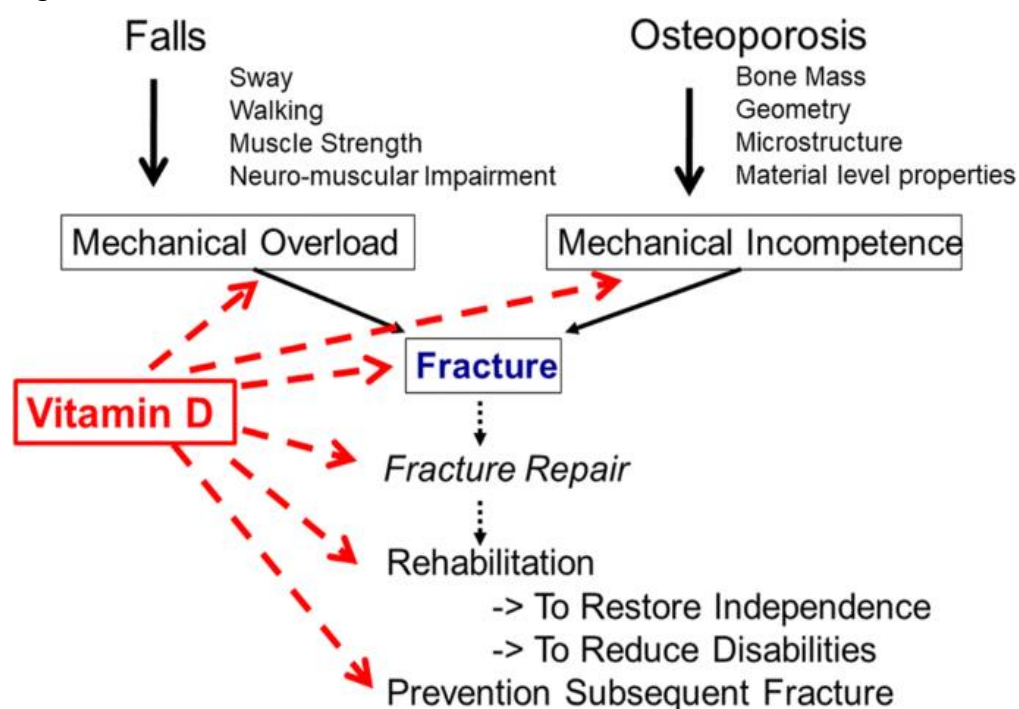
this number significantly higher mean levels of vitamin D ( $22.4 \pm 11.4$  nmol/l) than the group of fractured patients [21, 30].

Seasonal variation in vitamin D, PTH, and bone turnover markers was also reported in 55 healthy individuals living in southwest Germany at 49° latitude (volunteers aged 33 to 33) in a 2-year follow-up by Meier et al. (up to 78 years of age), for one year the authors studied the dynamics of PTH, vitamin D and bone mineral density (BMD) in two groups: in one group, subjects received 500 mg they took calcium. and 500 IU of vitamin D in winter, the other group did not receive therapy. In the intervention group, vitamin D and PTH levels, as well as normalization of bone metabolism was noted. Compared to the first year of follow-up, there was also an increase in BMD in the lumbar spine ( $p=0.04$ ) and femoral neck ( $p=0.05$ ), and a significant decrease in BMD in these areas in the untreated group [28].

A major cause of the worldwide epidemic of vitamin D deficiency is a lack of understanding that almost none of our food sources contain enough vitamin D to meet the body's daily requirement of 3,000 to 5,000 IU of vitamin D.

[24]. Our hunter-gatherer ancestors probably produced several thousand IU of vitamin D per day through exposure to the sun. It is known that the administration of 10,000 to 25,000 IU of vitamin D is equivalent to the effect of 1 minimal erythemal dose (slight pink coloration of the skin 24 hours after irradiation). All this explains the human need for ultraviolet radiation with low consumption of foods containing vitamin D. Interestingly, the Eskimos use the liver of polar bears and seafood, whale and seal oil in their diet, despite the negative effects, they meet the need for vitamin D. of the polar night [24].

Natural sources of vitamin D are oily fish, liver oil of some types of fish (cod, tuna, etc.). Mushrooms and yeast contain ergosterol, a precursor of vitamin D. When dried in the sun or exposed to ultraviolet light, ergosterol in mushrooms is converted to vitamin D [24]. Vitamin D fortification of milk is allowed in Sweden and Finland [18]. Fortification of milk with vitamin D, as well as some bakery products, orange juice, cereals, yogurt, and cheeses, is common in the United States and Canada [23, 29]. However, three studies examining the vitamin D content of milk in the US and Canada found that more than 70% of the samples studied did not contain the 80% vitamin D indicated on the package [24]. About 10% of the milk samples studied had no vitamin D at all, but vitamin D deficiency remains a major health problem in young children and the elderly, so in many European countries cereals, bread and margarine . Enriched with vitamin D.



Given the high prevalence of vitamin D deficiency and deficiency in patients with postmenopausal osteoporosis, therapy for this disease requires a comprehensive approach. A generally accepted method in the treatment of postmenopausal osteoporosis is the use of first-line drugs - bisphosphonates in combination with calcium salts and vitamin D [2, 5]. However, the question of the adequate dose of vitamin D among the elderly is currently being widely discussed. The daily dose recommendations adopted in 1997 (400 IU per day for people aged 50 to 70 years, 600 IU per day for people aged 71 years and older) clearly contradict the current clinical practice of ambulatory observation and treatment of patients with osteoporosis. as the results of the following clinical studies convincingly prove [16].

HA Bischoff-Ferrari et al. A meta-analysis of double-blind randomized trials comparing the efficacy of oral forms of vitamin D (D, D) with and without calcium salts versus calcium salts alone and placebo in the prevention of nonvertebral hip fractures in the elderly (60 years and older). Sources included systematic reviews of Medline, Cochrane Controlled Trials Register (1960–2005) and EMBASE (1991–2005).

The analysis was based on 5 randomized controlled trials for hip fracture risk (n=9294) and 7 randomized controlled trials for non-vertebral fracture risk (n=9820). All studies used cholecalciferol. A daily vitamin D intake of 700 to 800 IU was found to reduce the risk of hip fracture by 26% (3 randomized controlled trials with 5572 subjects; hazard ratio - RR = 0.74; 95% confidence interval i - CI 0.61–0.88) and 23% compared with placebo or calcium for nonvertebral fractures (5 randomized controlled trials with 6098 subjects; RR = 0.77; 95% CI, 0.68 -0.87). Low-dose (400 IU) vitamin D (2 randomized controlled trials with 3,722 participants; RR for hip fracture, 1.15; 95% CI, 0.88 to 1.50; RR, 1.15% CI); 0.8–1.24) [8].

In 2009, a meta-analysis of randomized controlled trials was published to determine the effectiveness of vitamin D supplements and active forms of vitamin D in preventing falls in older adults with and without calcium supplements. Databases include Medline, the Cochrane Register of Controlled Trials, and BIOSIS. The analysis included eight randomized controlled trials (n=2426), with a mean age of 65 years, who received a fixed dose of vitamin D tablets: vitamin D (cholecalciferol) or vitamin D (ergocalciferol) or an active form of vitamin D (1 -  $\alpha$ -hydroxyvitamin D (1- $\alpha$ -hydroxycalciferol) or 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-dihydroxycholecalciferol). ) At the same time, patients were divided into two groups depending on the achieved concentration of 25 (OH) vitamin D. During therapy with different doses of vitamin D: 25 (OH) - vitamin D concentration less than 60 nmol / l (deficiency) and 60 nmol /L higher than normal (p = 0.005) intake of vitamin D resulted in a 19% reduction in the risk of falls (RR = 0.81, 95% CI 0.71 to 0.92; n=1921 in seven studies) , the risk of falling was reduced by 23% when serum 25(OH)-vitamin D concentration was 60 nmol/L or higher (RR=0.77, 95% CI 0.65 to 0.90). In the background of low doses of vitamin D (RR=1.10, 95% CI 0.89 to 1.35; n=505) or 25(OH)-vitamin D concentration less than 60 nmol/l (RR=1, 35, (95% CI 0.98 to 1.84) was not found to reduce the risk of falls. Two randomized controlled trials (n = 624) using active forms of vitamin D met the inclusion criteria. Treatment with active forms of the vitamin reduced the risk of falls by 22% (RR = 0.78, 95% CI 0.64 to 0.94). Thus, the authors concluded that a daily intake of 700-1000 IU of vitamin D reduced the risk of falls by 19% in the elderly, as was the case with treatment with active forms of vitamin D [7]. A daily dose of vitamin D below 700 IU does not reduce the risk of falls in the elderly [10].

According to the 2010 North American Menopause Society (NAMS), the minimum dose of vitamin D is 800 IU [27]. The serum vitamin D concentration needed to reduce the risk of fractures should be higher than 20 ng/ml, and to reduce the risk of falls - from 20 to 30 ng/ml [10, 12]. A blood level of 25(OH)-vitamin D less than 10 ng/ml (25 nmol/l) is usually diagnosed as osteomalacia [20]. However, according to the recommendations of the US National Institute of Medicine, the daily intake of vitamin D should be 600 IU for persons under the age of 71, and 800 IU for those 71 and older. At the same time, for the population of North America, vitamin D deficiency is a concentration of the latter from 12 to 20 ng / ml. A value of 20 ng/ml is accepted as a biologically reasonable norm, which was recorded in 97.5% of patients without osteoporosis [14]. In Canada, the recommended dose of the drug for

people over 50 years of age has been increased from 800 to 2000 IU per day [31]. In the clinical guidelines of the Russian Osteoporosis Association, the recommended dose of vitamin D is 800 IU per day [2].

In a randomized, placebo-controlled, double-blind study conducted by MF Holik, 1000 IU of vitamin D or vitamin D supplementation daily for 3 months resulted in a 10 ng/ml increase in blood vitamin D levels. shown. [18, 22]. The study involved 68 healthy people aged 18 to 84 from the Boston area. 60% of patients were vitamin D deficient (vitamin D concentration less than 20 ng/ml) and 87% were deficient (less than 30 ng/ml), approximately 47% of patients received 400 IU vitamin D and multivitamins. approximately 47% of subjects received 1.2 cups of milk. All participants were randomized into 4 groups: a placebo group that received 1,000 IU of vitamin D or vitamin D or a combination of 500 IU of vitamin D and 500 IU of vitamin D. For 11 weeks, the authors analyzed the dynamics of vitamin D concentration in blood serum. After 3 months, no significant changes in the level of vitamin D were noted in the placebo group, an increase in the concentration of vitamin D by 10 ng / ml was found in the groups that received 1000 IU of vitamin D daily, i.e. A daily intake of 1000 IU of vitamin D was associated with an increase in vitamin D concentration of 10 ng/ml. However, since the initial blood vitamin D level was 19 ng/ml, none of the subjects had a vitamin D concentration greater than 30 ng/ml. It appears that both children and adults require 2,000–3,000 IU per day to maintain vitamin D levels above 30 ng/ml in the absence of sunlight [22].

A number of studies have shown that during bisphosphonate therapy, patients with low levels of vitamin D initially had a low increase in BMD, i.e. To achieve the maximum antiresorptive effect from taking bisphosphonates, the level of vitamin D in the blood should be within the reference values.

After intensive therapy with vitamin D (500,000 IU for 5 weeks) diagnosed with vitamin D deficiency, the level of the latter reached normal values in 17 (85%). Of the 20 patients with insufficient vitamin D concentrations associated with a significant increase in BMD in the spine and femoral neck (3.0 and 2.7%, respectively);  $p < 0.2$ ). In patients with reduced vitamin D levels

A subsequent loss of BMD was noted. In a clinical study conducted by D. Grigori et al., it was also found that the rate of increase in BMD depends on the initial concentration of vitamin D [17]. Similar results were obtained in the work conducted by S. Adami et al. After 13.1 months of antiresorptive therapy (alendronate, risedronate, raloxifene), more than 75% of patients with postmenopausal osteoporosis were included in the study. Optimal vitamin D saturation has been shown to maximize the response to antiresorptive therapy for changes in BMD and fracture prevention in older postmenopausal adults ( $p = 0.004$ ). In a retrospective analysis by A. Deane et al. [13] also showed a lower BMD increase ( $p = 0.04$ ) in patients with low levels of vitamin D at baseline during bisphosphonate therapy.

Thus, studies conducted in recent decades have convincingly confirmed that vitamin D is an underappreciated and long-neglected, absolutely necessary for human health and survival [6, 19, 25]. The consequences of vitamin D deficiency are manifested in insufficient development and function of bones, disruption of neuromuscular transmission, which leads to falls and fractures [9].

Osteoporosis (OP) is a systemic skeletal disease characterized by decreased bone strength and increased fracture risk. In the European Union, approximately 21% of women aged 50–84 years have AP according to WHO criteria [1]. In Western Europe, postmenopausal women have a 40% incidence of fractures in the localization typical for AP, which is higher than the incidence of breast cancer (12%) and is close to the incidence of cardiovascular disease. According to the Federal Center for the Prevention of AP in the Russian Federation, 33.8% of women aged 50 and older living in cities have AP, 43.3% have osteopenia, and 24% already have fractures. The results of bone densitometry in a random sample of 45-70-year-old postmenopausal women in the Moscow region showed that opacity was detected in 26% of women in the spine, in the femoral neck and proximal femur - in 12%. In addition, 52-58% of subjects have osteopenia in these areas [3, 4]. Extrapolation of available epidemiological data to the population of the Russian Federation shows that AP affects 14 million people in the Russian Federation (about 10% of the country's population) and another 20 million

people have osteopenia. In the Russian Federation, 7 vertebrae are broken every minute, and 1 femur is broken every 5 minutes.

Calcium and vitamin D preparations are widely used in the prevention and complex treatment of AP, but despite extensive and long-term experience in studying the effectiveness and safety of this type of therapy, no consensus has been reached regarding the optimal doses, potential risks, as well as whether calcium and vitamin D should be used together, whether vitamin D supplementation is sufficient, and whether additional bioactive substances (collagen, micro and macronutrients) are needed to enhance the effects of vitamin D and calcium. In reviewing the literature, we tried to answer these questions based on the analysis and synthesis of modern scientific data.

### **Sources of calcium and vitamin D for humans**

A person receives 70-80% of calcium from dairy products, they also contain other components such as phosphorus and magnesium, which have a positive effect on bone remodeling processes [6], phosphoproteins from the main milk proteins [7], casein and estrogens [6, 8]. Therefore, getting enough calcium from dairy products is an important factor in maintaining bone health [9, 10]. In their review, DA McCarron and RP Heaney (2004) estimate that in the United States alone, consuming dairy products within the recommended limits would result in \$209 billion in budget savings due to reductions in health and social benefits, of which \$14 billion would result in cost savings. came to the conclusion that it will come. Treatment of fractures in patients with AP [11].

Vitamin D is a fat-soluble vitamin that is synthesized in humans from 7-dehydrocholesterol in the skin by exposure to ultraviolet light or obtained from certain foods. The production of vitamin D<sub>3</sub> depends on the severity of skin pigmentation, the width of the region, the length of the day, the time of year, weather conditions, and the area of skin not covered by clothing. For example, in countries located in northern latitudes, most of the ultraviolet radiation is absorbed by the atmosphere in winter, and vitamin D<sub>3</sub> is almost not synthesized between October and March [13]. Another important source of vitamin D is food. Oily fish (cod, tuna, etc.) are especially rich in vitamin D [13]. Ergosterol, a precursor of vitamin D, is found in mushrooms and yeast. When dried in the sun or exposed to ultraviolet light, ergosterol in mushrooms is converted to vitamin D<sub>2</sub> [14].

After 2 successive hydroxylation reactions in the kidneys, vitamin D forms an active metabolite, 1,25(OH)<sub>2</sub>D<sub>3</sub> - D-hormone, which binds to specific receptors of organs and tissues, and vitamin D has a biological effect related to its effect.

### **Prevalence and role of calcium and vitamin D deficiency as risk factors for AP and fractures**

The average amount of calcium for women aged 19-50 and men aged 19-70 is 1000 mg/day, for women over 50 and men over 70 - 1200 mg/day [15, 16]. According to the interim results of the Russian osteoscreening program, the average intake of calcium in women and men is 683±231 and 635±276 mg, respectively. Only 9% of women and 6% of men consume 50% or less of the daily calcium requirement in most cases. An analysis of the level of calcium consumption in food products among 1,712 residents of the Moscow region aged 20-87 years showed that 42.3% of women consume dairy products once a day, 33.7% less than once a day consume or do not consume at all, and only 24% of women include dairy products in their diet several times a day. All age groups 40 years and older show deficient calcium intake, with minimal intake after 80 years of age [18].

In patients with AP and in people with osteopenia, the level of calcium intake is much lower than in the healthy population - 901 mg/day versus 715 mg/day, respectively [19]. Another risk group for insufficient calcium intake in our country can be considered medical workers: a survey conducted among 842 doctors aged 20-72 in 16 regions showed that their average calcium intake moli is only 445 mg per day, and a deficiency has been found in intake. in 90% of cases [19].

Calcium deficiency is an important risk factor for the development of AP and fractures [20-22]. Low calcium intake is associated with significant social consequences of hip fracture, so increasing dairy consumption may be effective in reducing the adverse health effects of hip fracture in the general

population [23]. In addition to beneficial effects on bone mineral density (BMD) and moderate antiresorptive effects, adequate calcium intake in postmenopausal women is associated with a reduced risk of colorectal cancer, hypertension, kidney stones, and obesity [ 24 ].

Men and women under 70 should get at least 600 IU per day, and those over 70 should get at least 800 IU per day [25]. The prevalence of vitamin D deficiency increases significantly in old age. With aging, the time spent in the sun and the skin's ability to synthesize vitamin D<sub>3</sub> decrease, and the level of 1,25(OH)<sub>2</sub>D produced in the kidneys due to impaired kidney function decreases - all of which contribute to its prevalence. prevalence of vitamin D deficiency in the elderly. In particular, Russian studies have shown high levels of vitamin D deficiency among postmenopausal women in Moscow [26] and elderly residents of the Ural region [27]. Because vitamin D is essential for adequate calcium absorption and normal bone metabolism, chronic deficiency leads to secondary hyperparathyroidism, increased bone resorption, and rapid loss of BMD, and is associated with an increased incidence of falls.

Efficacy of calcium and vitamin D supplementation in preventing AP and fractures: monotherapy or combination?

Food should be the main source of calcium [1, 24]. However, due to the apparent deficiency of calcium intake from food sources, the appropriateness of calcium salts supplementation is questioned. There are separate studies on the positive effect of calcium supplements on BMD and the risk of fractures, but in general, calcium in the form of monotherapy combined with vitamin D is characterized by weaker clinical potential in the prevention and complex treatment of AP. [28, 29]. Some evidence suggests that adequate postmenopausal calcium intake slows bone loss due to estrogen deficiency and even reduces the risk of bone fractures [25, 30]. In particular, R. Recker et al. (1996) concluded that 600 mg of calcium per day for 4 years in independent living elderly women reduced the risk of developing vertebral fractures, especially if there was a history of such fractures (in the treatment group versus the placebo group, risk). fracture 2 .45, 95% confidence interval (CI) 1.42–4.20) [30]. A meta-analysis of 59 articles published by B. Shea et al. (2000) showed that monotherapy with calcium salts has a positive effect on BMD only at high doses - 2-3 g per day, and there are no reliable data on the positive effect of calcium monotherapy on fracture incidence. ]. In addition, according to the results of a recent meta-analysis, the use of calcium supplements without concomitant vitamin D intake is associated with a 30% increased risk of myocardial infarction [32]. In this regard, the amount of calcium obtained from any source should not exceed the age-recommended norm, and calcium salts should be used together with vitamin D preparations [1, 20].

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