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An Overview on Vitamin D Deficiency and Menopause-Associated Symptoms in Postmenopausal Women

Ali El-Shabrawy Ali, Basem Mohammed Hamed, Ahmed Gamal El-Sayed Mohammed, Ahmed Metwally El-Kattawy

Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt

Abstract:

Menopause is an important period in women's life. It is characterized by many symptoms that affect women's quality of life. Vit D helps us to maintain our bones by absorbing calcium in menopause . It plays role in reducing inflammation and hot flushes and may have role in menopause-associated symptoms in postmenopausal women.

Keywords: Vitamin D deficiency, menopause-associated symptoms, postmenopausal women.

Introduction:

Vitamin D is a prohormone absorbed from food sources or supplements and also synthesized in the skin following exposure to ultraviolet light. The prohormone subsequently is converted to the metabolically active form in the liver and then the kidneys. Few foods naturally contain vitamin D. The principal food sources of vitamin D are fish that are oil rich, such as salmon, mackerel, and herring, as well as organ meats, liver, and egg yolk. **(1)**.

The chemical structure of vitamin D is almost identical to cholesterol, except that vitamin D has double bonds between (C-7 and C-8), (C-10 and C-19), and an open B ring structure. The two forms of vitamin D utilized in the human body, ergocalciferol (D2) and cholecalciferol (D3) begin with four intact rings. ***Ergocalciferol (vitamin D2)*** is principally synthesized in plants and invertebrates. It is typically consumed in the human diet as supplements or fortified products. ***Cholecalciferol (vitamin D3)*** is mainly of vertebrate animal origin and commonly consumed in the form of oily fish, also synthesized in human skin after exposure of 7-dehydrocholesterol to solar ultraviolet radiation. Endogenous and consumed vitamin D is stored in fat tissues and released into the circulation **(2).**

Vitamin D is acquired from dietary sources in two structural forms that only differ in side chain structure. Ergocalciferol or vitamin D2 is produced by yeast and mushrooms from the fungal precursor ergosterol when exposed to UVB light while cholecalciferol or vitamin D3 is produced in the skin of animal species from the precursor 7-dehydrocholesterol when exposed to UVB light. Both forms are metabolised in the same way and yield vitamin D activity.The content of cholecalciferol in animal meat is low in comparison to the content in fatty fish meat and lean fish liver **(3)**.

Dietary sources of ergocalciferol are few, with variable amounts in mushrooms, baker's yeast and animal products, but may contribute significantly to vitamin D status in countries with a low intake of cholecalciferol **(4)**.

Sunlight exposure and skin synthesis of vitamin D:

The major natural source of vitamin D is from skin photosynthesis following ultraviolet B solar irradiation . During exposure to sunlight, 7-dehydrocholesterol in the skin is converted to previtamin D3. Previtamin D3 immediately converts by a heat dependent process to vitamin D3. Excessive exposure to sunlight degrades previtamin D3 and vitamin D3 into inactive photoproducts **(5)**.

Storage of vitamin D:

Approximately 65% of body vitamin D is in the form of cholecalciferol, of which 75% is stored in adipose tissue. **(6)**.

Metabolism of vitamin D:

1- Synthesis of 1, 25-hydroxy vitamin D:

Vitamin D is obtained from exposure to sunlight, diet (fortified foods), and dietary supplements. When the skin is exposed to solar ultraviolet B radiation (wave length, 290 to 315 nm), 7-dehydrocholesterol is converted to previtamin D_3, which is rapidly converted to vitamin D_3 (cholecalciferol). Vitamin D from the skin and diet is transported in the blood by circulating vitamin D-binding protein (VDBP) to the liver. In the liver, vitamin D is metabolized by P 450 vitamin D-25-hydroxylase to 25-hydroxyvitamin D, which is the major circulating metabolite and used to determine a patient's vitamin D status **(7)**.

Almost all 25-hydroxyvitamin D is bound to circulating VDBP and is filtered by the kidneys and reabsorbed by the proximal convoluted tubules. In the kidney, megalin and cubilin, members of the LDL receptor superfamily, play essential roles in endocytic internalization of 25-hydroxyvitamin D. In the proximal renal tubules, 25-hydroxyvitamin D is hydroxylased at the position of carbon 1 of the A-ring by the enzyme 25-hydroxyvitamin D_3 1α-hydroxylase (CYP27B1) to its active form, 1, 25-hydroxyvitamin D. This enzyme is also found in extrarenal sites including the placenta, monocytes and macrophages **(7).**

2- Regulation of 1,25-hydroxy vitamin D:

The production of 1,25-hydroxyvitamin D is regulated by serum calcium and phosphorus levels, plasma parathyroid hormone (PTH) levels, and fibroblast growth factor 23 (FGF-23). Low serum calcium and phosphate levels result in enhanced activity of 1α-hydroxylase. PTH stimulates the transcription of 1α-hydroxylase and nuclear receptor 4A2 (NR4A2) is a key factor involved in the induction of 1α-hydroxylase transcription by PTH. 1, 25-hydroxyvitamin D in turn suppresses PTH production at the level of transcription **(1)**.

FGF-23 is a phosphaturic factor that promotes renal phosphate excretion by inactivating the sodium-phosphate cotransporter in the proximal tubule. 1, 25-hydroxyvitamin D stimulates the production of FGF 23 in the bone, and an increased level of FGF-23 suppresses the expression of 1α-hydroxylase in the kidneys. FGF-23 requires a klotho (a multifunctional protein involved in phosphate and calcium homeostasis) as a cofactor for FGF signaling, and 1, 25-hydroxyvitamin D upregulates klotho gene expression in the kidneys **(8)**.

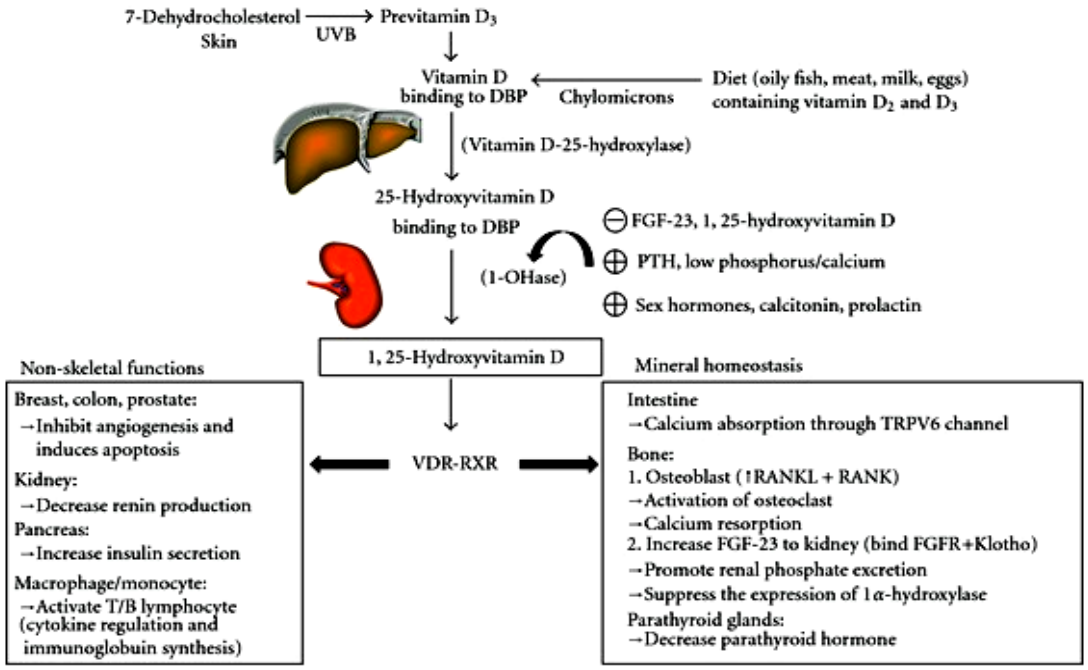

Figure (1): The synthesis and metabolism of vitamin D in the regulation of mineral homeostasis and nonskeletal functions **(7)**

3- VDBP:

Vitamin D signaling may occur by binding of circulating 1,25-hydroxyvitamin D to VDR or by local production from the main circulating form, 25-hydroxyvitamin D. VDBP (calbindin-D_{28K}), encoded by the Gc (group-specific component) gene, functions as a specific transporter of circulating vitamin D metabolites and is essential for vitamin D endocytosis and metabolism. VDBP is a highly polymorphic single-chain serum glycoprotein synthesized and secreted by the liver that forms a complex with vitamin D ensuring that circulating vitamin D is delivered to target tissues **(9)**.

4- VDR:

Vitamin D receptors were discovered in 1969. Inactivating mutations in VDRs result in Hereditary Vitamin D Resistant Rickets (HVDRR). Vitamin D exerts its actions in a variety of cell types through binding to the cytosolic/nuclear VDR , which is a member of the steroid/thyroid hormone receptor family that functions as a transcriptional activator of many genes. **(7)**.

5- Extrarenal 1, 25-hydroxyvitamin D production:

Vitamin D is characterized as a regulator of homeostasis of bone and mineral metabolisms. More than 200 genes are controlled by 1, 25-hydroxyvitamin D directly or indirectly to regulate cellular proliferation, differentiation, apoptosis, and angiogenesis. 1, 25-dihydroxyvitamin D inhibits renin synthesis, and increases insulin production, myocardial contractility, the reproductive system, and hair growth.Vitamin D may play an important role in modifying the risk of cardio metabolic outcomes, including type 2 DM, hypertension, and cardiovascular diseases **(7).**

Catabolism of vitamin D:

In a five-step oxidation pathway, calcitriol is catabolised to calcitroic acid, a truncated water soluble molecule excreted through the bile. The first step, and perhaps several other steps also, are catalysed by the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24A1). This enzyme also catabolises the much more abundant 25OHD, but has a stronger affinity to calcitriol **(10)**.

The physiological role of CYP24A1 is illustrated in humans with mutations causing reduced enzyme activity. These individuals display chronic or transient hypercalcaemia which may lead to soft-tissue calcifications and chronic kidney disease. CYP24A1 deficient mice display hypercalcaemia, nephrocalcinosis and a lethality of 50% **(11)**.

Factors affecting vitamin D levels:

Factors that can affect UVB exposure, and thus the skin's production of vitamin D, include altitude, season of the year, time of day, air pollution, cloud cover, melanin content of the skin, use of sunblock, age, and the extent of clothing covering the body. **(12)**.

Measurement of 25(OH) D level:

Some controversy exists regarding the best method for measuring 25(OH) D levels. Radioimmunoassay has been the most common method and was the method used in some of the large-scale population studies of vitamin D, such as the National Health and Nutrition Examination Survey (NHANES) and the Women's Health Initiative (WHI). The accuracy of measurement varies widely between individual laboratories and between different assay methods **(13)**.

The use of a standard cutoff value for adequate vitamin D status is problematic if applied to all laboratories and all methods. A single serum sample could be assessed as showing adequate vitamin D status in one laboratory and an insufficient level in another, with differences of up to 17 ng/mL. More recently; large medical laboratories have begun using liquid chromatography–tandem mass spectrometry, which identifies the 25-hydroxylated forms of both vitamin D_2 and D_3. The total 25(OH) D, which is the sum of 25(OH) D2 and 25(OH) D3, is used to evaluate vitamin D status **(13).**

Indications for vitamin D testing:

Measurement of serum 25(OH) D levels is indicated in selected circumstances. If clinical symptoms of rickets in children or osteomalacia in adults are present, measurement of 25(OH) D levels will confirm vitamin D deficiency. Such testing would be appropriate in adults or children with bone pain, elevated serum alkaline phosphatase or PTH levels, and low serum calcium or phosphorus levels. Persons of advanced age, those with osteoporosis, or those at increased risk of falls or fractures may also benefit from measurement of 25(OH) D levels **(13)**.

Vitamin D deficiency and menopause-associated symptoms in postmenopausal women

Natural menopause is defined as the absence of menstruation for one year in women without any other underlying causes. In the menopausal period, low estrogen and high follicle stimulating hormone (FSH) concentrations are observed due to the decrease or disappearance of ovarian follicles **(14)**.

This hormonal instability in menopausal period may cause a number of physical and psychological complaints such as vasomotor symptoms, genito-urinary symptoms, mood and sleep disturbance. These menopause-related symptoms can negatively affect the individual's quality of life, work life and personal relations **(15)**.

Vitamin D is a fat-soluble vitamin that has important roles in calcium metabolism and musculoskeletal system. In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. In this regard Vitamin D deficiency can cause many infectious, autoimmune and cardiovascular diseases. It was also shown that Vitamin D has a protective impact againsts cardiovascular risks in women **(16**).

In addition, **Foti et al. (17)** showed that there may be a relationship between vitamin d deficiency and hot flushes, irritability and genitourinary sypmtoms. **Arvold et al. (18)** showed a correlation of severe vitamin D deficiency with anxiety, depression and impaired functionning in their randomized control trial in men and women population.

LeBlanc et al. (19) examined the association between baseline serum 25(OH)D levels and menopausal symptoms. They could not find an association between menopausal symptoms and serum vitamin D levels. They identified some menopausal symptoms, then participants rated these symptoms according to intensity of the symptom. The reason they failed to report any association between vitamin D levels and menopausal symptoms could be explained by the high number of women with menopause duration of more than ten years.

Vitamin D taken in diet or synthesized in the skin is biologically inactive and requires enzymatic conversion to active metabolites. It was shown that estrogen plays a role in the increase of vitamin D activating enzyme. Therefore, it could be thought that the decrease of estrogen levels in postmenopausal period might worsen the symptoms of subclinical vitamin D deficiency such as neuropsychiatric symptoms **(20**).

There are few data evaluating the neuroprotective role of vitamin D. **Siebert et al. (21)** investigated the effect of menopause on behavioral status found that menopause could cause an impairment in memory. **Siebert et al. (22)** showed that vitamin D supplementation reverses the hippocampal cytoskeletal changes caused by ovariectomy, in vivo. In another animal testing, increasing calcidiol levels by vitamin D supplementation in ovariectomized rats was reported to reduce the hippocampal inflammatory mediators such as nuclear factor-kappa B and interleukin-6.

Besides the hippocampal effects, cholecalciferol was concluded as an anxiolytic agent in ovariectomized rats. Depressive mood and irritability scores of the subjects were significantly higher in the deficiency group. Furthermore, anxiety score was also higher in this group although it was not statistically significant. Evaluating the total psychiatric score, a significant difference had been already encountered in the deficiency group **(23)**.

Similarly, in a report with a high patient population discoursing vitamin D and symptoms in menopause, it was mentioned that 25-OH vitamin D levels were low and depression scores were high in the postmenopausal period **(24**).

In a cross-sectional study from Turkey using MRS, **Tan et al. (25)** reported that BMI higher than 30 kg/m2 was signifacntly associated with higher depressive mood score. In a study including both patients in pre and postmenopausal periods, pelvic floor muscle strength was calculated lower in postmenopausal patients with vitamin D levels lower than 20 ng/mL. Urinary incontinence score was higher in women with vitamin D deficiency, but they could not find statistical difference **(26**). Unlike that study, **Foti et al. (17)** concluded that prevelance of low urinary tract symptoms was significantly higher in women with low vitamin D levels comparison to those with normal levels. Moreover, the siginificant improvement of lower urinary symptoms in postmenopausal patients treated with high dose vitamin D for one year was documented in a randomized controlled trial published by **Oberg et al. (27)**.

Somatic symptoms like hot flashes could often be challenging for menopausal women. Regardless of vitamin D levels, most of the women complain about these symptoms. Vitamin D was described to prevent seratonin depletion in rats. Seratonin was known as a neurotransmitter playing role in thermoregulation, a decline seratonin levels might cause hot flashes **(28)**.

In this context, high levels of vitamin D might protect against somatic symptoms, especially hot flashes, during menopause. In addition, it was mentioned that menopausal symptoms are less common in women with normal vitamin D levels than in women with vitamin D deficiency **(29)**.

Erturk and Kender Erturk (30) demonstrated that low levels of vitamin D in menopausal period might aggravate menopause-related symptoms. It could be considered that menopausal women with a high intensity of symptoms might benefit from vitamin D supplementation.

Hakim et al. (31) evaluated the relation between vitamin D levels and menopause-related symptoms and concluded that vitamin D deficiency is an alarming issue among postmenopausal women. It was not associated with menopause-related symptoms.

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