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Review

# Vitamin D and menopause—A narrative review

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ABSTRACT

There is accumulating evidence that vitamin D (VD) has important effects besides its well-known role in calcium and bone metabolism. Hypovitaminosis D is associated with cardiovascular disease, the metabolic syndrome, type 2 diabetes mellitus, cancer as well as with increased mortality. Further, VD deficiency is related to depression and impaired cognitive function. Increasing age and elevated body fat mass contribute to an increased risk of VD deficiency. Further, some studies report a relationship between VD and estrogen metabolism.

During menopause, the decline of estrogens results in increased bone turnover, a decrease in bone mineral density and elevated fracture risk. Musculoskeletal discomfort might impair quality of life, mood disturbances do frequently occur and the risk of metabolic and cardiovascular disease increases. Moreover, body composition changes including increased fat mass and decreased lean mass, which results in an increased risk of VD deficiency. Conversely, VD deficiency might aggravate discomfort as well as diseases that occur during menopause.

There are precise recommendations regarding a sufficient VD intake in order to prevent bone loss in peri- and postmenopausal women. Considering the fact that VD deficiency and menopause share risk factors beyond bone health such as cardiovascular, metabolic, cognitive and affective disorders, a sufficient VD status should be obtained in all peri- and postmenopausal women. This might be beneficial not only considering bone health but also regarding cognitive, affective, metabolic and cardiovascular health of women.



**Contents**



*Abbreviations:* $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; CaD, calcium/vitamin D; β-CTX, beta-crosslaps; HRT, hormone replacement therapy; LDL-C, low density lipoprotein cholesterol; MetS, metabolic syndrome; OC, osteocalcin; PTH, parathyroid hormone; QoL, quality of life; RCT, randomized-controlled trial; SHBG, sexual-hormone binding globulin; VD, vitamin D; VDR, vitamin D receptor; VMS, vasomotor signs; WHI, Women's Health Initiative.

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## 1. Introduction

VD has been well-known for its function in maintaining calcium and phosphorus homeostasis and promoting bone mineralization but VD deficiency is also linked with an increased risk of cancer, cognitive impairment, diabetes and cardiovascular diseases indicating the importance of sufficient VD levels [1]. Apart from symptoms such as VMS and musculoskeletal disease, the incidence of certain conditions (e.g., coronary artery disease, diabetes, cancer) increases after menopause [2]. Thus, menopause and VD deficiency share several adverse health outcomes including but not limited to bone loss, mood disturbances, increased risk of cardiovascular disease and cancer.

The focus of this review is the examination of research evidence relating to VD status and supplementation and menopause. The review further discusses the adverse health outcomes related to both menopause and VD deficiency and the possible interaction of both risk factors in these conditions. The biologically plausible role of VD in female reproduction including estrogen metabolism has been comprehensively reviewed elsewhere [3,4].

## 2. Obesity

Cross-sectional studies show that menopause is associated with weight gain and altered body fat distribution. Weight gain occurs because women lose fat-free mass after menopause, tend to exercise less, and have greater increases in fat mass [5]. This rise in obesity and especially visceral fat accumulation results in an increased risk of metabolic and cardiovascular disease, cancer and consecutive increased mortality [6]. It was demonstrated in a 4-year longitudinal observational study that subcutaneous fat mass significantly increases over time but only postmenopausal women showed an significant increase in visceral fat mass [5], which has been attributed to estrogen effects on lipolysis and lipogenesis in visceral adipocytes [7] and the SHBG-lowering effect of estrogen deficiency resulting in increased free testosterone levels. Hyperandrogenemia is associated with visceral fat accumulation which has been extensively described in PCOS women who are frequently affected by hyperandrogenemia as well as central obesity [8–10]. Although not only estrogens but also androgen levels decline during menopause [11] the more pronounced reduction in estrogen levels might result in increased visceral fat accumulation [5].

Besides the effect of estrogens on body fat distribution, there might also exist an effect on energy balance, metabolic rate, fat oxidation and total body weight [2].

It has been extensively studied that obesity is associated with low VD levels. For a long time it was, however, not clear whether VD insufficiency is caused by obesity and/or if obesity is a consequence of VD insufficiency. A recent bi-directional Mendelian randomization analysis sheds light on this issue [12]. On the basis of a bi-directional genetic approach that limits confounding, that study suggests that a higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D increasing BMI are likely to be small.

Nevertheless there is an ongoing debate whether VD supplementation should be considered in strategies aiming at weight loss. As removal of adipocytes through apoptosis reduces body fat and can help in long-lasting maintenance of reduces body weight, the effect of $1,25(OH)_2D_3$ on apoptotic cell death is worth mentioning [13]. Further, studies using a murine diet-induced obesity model suggest that high VD and calcium intake decreases body and fat weight gain in diet-induced obesity [14]. Interestingly, VD supplementation led to body fat mass reduction compared to placebo without a change in body weight or waist circumference [15] and a higher dairy calcium intake as well as increased serum VD are related to greater diet induced weight loss [16].

Weight loss is recommended for subjects in order to prevent obesity associated comorbidities. Caloric restriction, however, is associated with a reduction of estrogen levels [17] as well as with decreased calcium absorption [18] which might explain bone loss often occurring during weight loss. Of note, VD supplementation increases calcium absorption and maintains calcium balance during weight reduction [18].

As increasing age as well as increasing fat mass result in lower VD levels, peri- and postmenopausal women are at risk of the development of VD deficiency. Further, physical activity and thus sun exposure, which is necessary for the synthesis of VD in the skin [1], decreases during menopause [2]. As VD as well as estrogens are important for calcium absorption during weight loss [18,19], a sufficient VD intake is of high importance in peri- and postmenopausal women in order to prevent bone loss during weight reduction.

## 3. MetS and cardiovascular disease

Cardiovascular events are not frequent among premenopausal women and the sex difference between cardiovascular events in young women and men may be caused by the postulated protective effects of endogenous estrogens. The decrease in estrogen levels during menopause might explain the unfavorable changes lipid and carbohydrate metabolism occurring at menopause resulting in the increased incidence of cardiovascular events [20]. Management of risk factors has been suggested in order to reduce the risk of cardiovascular disease in women. Despite the suggested protective effect of estrogens, cardiovascular risk associated with HRT exceeds the benefit in postmenopausal women. Thus HRT should not be used for the prevention of cardiovascular disease in women [2].

There is large evidence from observational studies linking low VD levels with cardiovascular risk factors as well as with cardiovascular events [1,21]. VD has been suggested to be involved in insulin resistance, type 2 diabetes and the MetS in premenopausal [22] as well as in postmenopausal women [1]. This association might in part be caused by the above mentioned relation of hypovitaminosis D with obesity. There are, however, mechanisms beyond obesity such as a beneficial VD effect on insulin action [1] and VD-related genetic variants are associated with insulin resistance and insulin sensitivity [23].

Apart from the association of VD deficiency with metabolic disease in observational studies, the role of VD supplementation on cardiovascular risk factors is less clear. Dietary VD intake is inversely associated with prevalence of MetS but was not independent of total calcium intake [24] and the risk of hypertension was lower in subjects with high dietary calcium and VD intake, but did not change with calcium or VD supplements [25]. Small RCTs report a beneficial VD effect on blood pressure [26]. Hypovitaminosis D has also been associated with hypercholesterinemia in several observational studies but recent RCTs did not show a significant improvement of lipid levels following VD supplementation [21]. However, recent results from the WHI CaD trial indicate that supplemental CaD decreases LDL-C and high VD concentrations are associated with a favorable lipid profile [27].

The majority of observational studies suggest an increased risk of cardiovascular events in subjects with low VD levels [21]. As low VD levels are associated with an unhealthy lifestyle such as few physical outdoor activities, a sedentary lifestyle and obesity it is difficult to interpret this findings. There are no large RCTs published that were specifically designed to analyze the effect of VD supplementation on cardiovascular events. Evidence from RCTs reporting cardiovascular events as secondary outcome is inconsistent and those RCTs have several methodological problems such as low VD doses or a combined VD and calcium supplementation. The latter one is a big problem as the effects of calcium supplementation

on cardiovascular parameters such as blood pressure, serum lipids and cardiovascular events are controversial and adverse effects of calcium supplementation on cardiovascular health have been suggested [28].

In summary, observational studies clearly suggest that VD deficiency is associated with cardiovascular risk factors as well as with cardiovascular events. In contrast, RCTs revealed conflicting results showing either a beneficial or no significant effects on cardiovascular effects.

Recognizing the fact that cardiovascular risk factors increase after menopause, which results in an increased risk of cardiovascular events, preventive strategies are warranted. As VD deficiency is also associated with cardiovascular disease, we hypothesize that VD deficiency and estrogen deficiency might act in concert leading to an increased risk of cardiovascular disease. This has been shown for men in whom a combined deficiency of androgens and VD was associated with an adverse outcome compared to men with only one hormone in the lower range [29] and results from the WHI suggest an interaction between HRT and CaD on hip fracture [30]. Thus, studies assessing the effect of VD supplementation on cardiovascular risk factors and events in peri- and early postmenopausal women are highly warranted.

## 4. VD, musculoskeletal symptoms, and bone

A lack of HRT has been suggested as risk factor for joint disease and women with HRT had a decreased chance of developing musculoskeletal symptoms such as aches and pain, joint pain, muscle stiffness, and skull and neck aching compared with those taking placebo [31]. Although the exact reason for musculoskeletal symptoms is uncertain, it is often attributed to estrogen depletion. While estrogen has no specific known effects on articular structures that would cause joint pain, it influences inflammation and neural processing of nociceptive input and exerts important antinociceptive effects [32].

Accelerated loss of bone mass occurs during the menopause as a result of naturally decreasing estrogen levels, putting women at risk of osteoporosis and fracture [2]. Women reach their peak bone mass around 25–30 years and BMD diminishes slowly between 30 and 50 years and tend to decline faster thereafter with a rapid loss of up to 3–4% per year around the menopause. Thus HRT has been suggested as effective tool against bone loss. However, studies show a similar fracture risk in HRT ex-users and never-users. It has therefore been suggested that HRT prevents fractures by reducing bone turnover at the time of likely fracture but does not lead to building bone for future. Thus, life style advice including adequate calcium and VD intake, physical activity, encouraging non-smoking and only moderate alcohol consumption has been recommended for bone health in perimenopause rather than the intake of HRT [2].

Most fractures appear as a consequence of a fall. Thus, besides a low BMD the second important risk factor for fractures are falls. There exist a large number of risk factors associated with an increased incidence of falls including age, sex, medical and psychological conditions such as cognitive impairment and depression, use of medications and lack of balance and muscle weakness. Therefore, optimal management of peri- and postmenopausal women should not only consider prevention of bone loss but also focus on reducing the risk of falls.

It has been suggested that VD has a dual effect on the musculoskeletal system: on bone mass/density/quality and on muscle mass/strength/function. In addition, adequate VD status reduces the risk of falling in older individuals, most likely by improving neuromuscular function [1]. In recent meta-analyses, VD supplementation was associated with improved muscle strength, body sway and physical performance [33] and decreased the risk of falls [34].

In children VD deficiency causes rickets whereas for adults the consequences of VD deficiency on bone health are a decrease in BMD due to the increased bone resorption by PTH as well as a mineralization defect causing osteomalacia [1]. Whereas this mineralization defect can be very subtle and often only determined by bone histology, the clinical manifestations of osteomalacia in adults include nonspecific throbbing aching bone pain and muscle weakness and muscle discomfort [35]. Hypovitaminosis D myopathy is a prominent symptom of VD deficiency, and severely impaired muscle function may be present even before biochemical signs of bone disease develop [35]. The literature reports that bone strength is modeled by muscle contractions in a way to achieve a degree of biomechanical homeostasis avoiding the spontaneous fracture incidents [36] and increases in muscle force results in increased bone strength reflecting the functional adaptation of bone to its function [37]. There is evidence showing that hormones including VD as well as sex hormones modulate the functional relation between bone and muscle tissues.

Further, a recent meta-analysis reported that a VD intake of at least 800 IU/day together with 25(OH)D levels >60 nmol/L are effective in fracture prevention [38]. Recent results from the WHI indicate an interaction between HRT and CaD on hip fracture and CaD supplementation enhanced the antifracture effect of HT [30].

Besides the above mentioned studies on VD and bone health, there is evidence suggesting a relationship between osteoporosis, cardiovascular disease, and mortality. Bone turnover markers such as β-CTX and OC have been proposed as indicative of cardiovascular disease and mortality. This notion is supported by the fact that osteoporosis and atherosclerosis share common pathophysiological mechanisms suggesting an interplay between bone cells and the vascular system. Low VD levels are associated with increased bone turnover and low 25(OH)D levels are associated with increased risk of all-cause mortality and cardiovascular mortality [39].

As both menopause and VD deficiency are associated with musculoskeletal symptoms, one might speculate on a beneficial effect of VD supplementation on joint pain, muscle mass and function in peri- and postmenopausal women. Further, with improving muscle and body pain physical activity rate might increase and in turn prevent osteoporosis, obesity and cardiovascular disease. Moreover, VD supplementation might improve muscle function und mass directly leading to better BMD and a lower risk of falling. A further beneficial effect of vitamin supplementation might be the positive effect of VD on proposed risk factors of falls such as impaired cognitive function, depression, decreased mobility and medical conditions such as diabetes [1]. Thus, RCTs investigating VD effects in peri- and early postmenopausal women on musculoskeletal symptoms and diseases are highly warranted.

## 5. Climacteric symptoms

Hot flashes are the most commonly perceived and reported menopausal symptom. Although their precise pathophysiological mechanism is unknown, decreased estrogen levels are believed to cause an induction in noradrenergic hyperactivity, which leads to a heat loss response and the sensation of warmth throughout the body followed by sweats [40]. Apart from the adverse impact on QoL, VMS are also related to several diseases such as hypertension and osteoporosis. Systolic blood pressure may be higher among women with hot flashes than among women without hot flashes. Among early perimenopausal and late perimenopausal women, those with VMS had higher bone turnover and lower BMD than those without VMS [41,42]. Further, interindividual differences in estrogen “sensitivity” at the menopause transition have been

suggested. A higher sensitivity to the reduction in estrogen levels may underlie certain women having both frequent VMS and greater bone loss. Only sweating frequency and climacteric symptoms but not estradiol levels are independently associated with rate of bone loss [43].

There are several lines of evidence indicating shared complications of women affected by VMS and VD deficiency such as accelerated bone turnover, increased loss of bone mass, hypertension and depression. Nevertheless, today there is no RCT investigating the effect of VD supplementation in women with VMS regarding symptoms, mood and cardiovascular effects.

Considering the potential side effects of HRT, alternative strategies for treating VMS are of high interest. It is postulated that a contributor to hot flashes is a menopausal decline in serotonin, a neurotransmitter with known effects on thermoregulation. As VD can protect against experimental serotonin depletion in rats, one proposed mechanism for symptom alleviation is prevention of serotonin decline in menopause. A recent analysis of 530 women aged 51–80 years from the WHI CaD trial found borderline significant associations between 25(OH)D levels and total number of menopausal symptoms such as sleep disturbance, emotional well-being, and energy/fatigue, as well as individual symptoms were observed [44]. Polisseni et al. [45] compared the effects of HRT, tibolone and supplemental CaD (control) on QoL in symptomatic postmenopausal women and found an improved overall QoL in all groups suggesting improved QoL even in the control group. As recognized by the authors their selves, the use of VD in the control group may have affected the QoL because VD prevents osteoporosis, cardiovascular disease, diabetes, cancer, infections, and neurodegenerative diseases [1,21,46] although the dose used in the study was very low (200 IU). Further, as QoL was improved in all groups, the use of HRT and tibolone might be questionable considering the potential side effects of those medications. RCTs investigating the effect of VD supplementation using adequate doses in peri- or early postmenopausal women are warranted.

## 6. Cancer

The incidence of cancer rises in women with increasing age. Besides other factors, this is aggravated by several lifestyle aspects such as reduced physical activity, a sedentary lifestyle, increased caloric and alcohol intake as well as obesity [2].

The association of VD with cancer has already been comprehensively reviewed elsewhere [46]. There is accumulating evidence from experimental as well as from observational studies showing that VD deficiency is a causal risk factor for cancer and cancer-related mortality [46]. High 25(OH)D levels are associated with decreased mortality in patients with cancer, which is well documented in women with colon and breast cancer. Further, higher vitamin D intake was associated with decreased risk of lung and breast cancer [47,48]. The pathophysiological background for this association might be explained by VD effects such as antiproliferative and apoptotic effects on cancer cells, inhibition of metastatic dissemination and tumor invasion and increased sensitivity to radiation and chemotherapy [46].

Considering the increased risk of VD deficiency in peri- and early postmenopausal women as well as the fact that underlying risk factors are also related to increased risk of cancer, one might speculate that a sufficient VD status in those women might also be beneficial regarding risk of cancer.

## 7. Brain function

It has been extensively studied that women are at a higher risk than men to develop mood disorders and depression, which has been attributed to fluctuating estrogen levels that occur during reproductive cycle events. Interestingly, several studies reported an increased incidence of depression as well as anxiety in women across the menopausal transition and estradiol levels are significantly lower in depressed women [49]. The role of HRT in treating or prevention of depression during menopausal transition has been evaluated in several RCTs in peri- and postmenopausal women diagnosed with depression. Those studies revealed conflicting results. A recent review on this topic [49] suggest that transdermal estrogen has beneficial effects on mood, and could be a viable treatment option for women with and without prior mood disturbances, and may also serve as a treatment for women with depression.

There are clinical data suggesting that VD may affect mood and cerebral function and VD deficiency is associated with vascular neuropathology [1]. Several neuroprotective mechanisms have been suggested, including increased phagocytosis of amyloid plaques, regulation of neurotrophins, antioxidative effects, neuronal calcium regulation, immunomodulation and vascular protection [50] and alterations in calcium homeostasis [51]. Observational and small RCTs, with some methodological limitations, have suggested a positive effect of sunlight and/or adequate VD levels on memory, cognition, all-cause dementia and Parkinson disease risk [50–52].

VD has also been linked with depression and VD deficiency has been proposed as one underlying factor of the higher prevalence of seasonal affective disorders such as depression associated with winter at high latitudes [51] although results of small interventional studies are inconsistent. Findings of observational studies reporting an increased risk of depression is subjects with VD deficiency are difficult to interpret due to the fact that subjects suffering from depression frequently have a lifestyle such as less outdoor activity that predispose them for VD deficiency (reverse causality). Further evidence comes from prospective studies that are less likely to be contaminated by reverse causality and show an association of low VD level at baseline with incident depression [53] [54].

As outlined above, VD deficiency and the decline in estrogens during menopausal transition are conditions associated with increased risk of mood disorders such as depression. However, there are no RCTs investigating the effect of VD supplementation in perimenopausal women.

## 8. Conclusion

VD deficiency is a common finding that is related to obesity, increasing age and unhealthy lifestyle. Menopause and VD deficiency are both associated with musculoskeletal, cardiovascular and metabolic disease as well as with psychological and cognitive disturbances. A sufficient VD status might be beneficial regarding bone, cardiovascular and overall health. Thus, large RCTs investigating the effects of VD supplementation in peri- and postmenopausal women are highly warranted.

## Contributors

Elisabeth Lerchbaum was responsible for article conception and design, drafting of article, revising the article for important intellectual content and has seen and approved the final version of the manuscript.

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