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REVIEW



Vitamin D, menopause, and aging: *quo vadis?*

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ABSTRACT

Menopause and aging are associated with changes in circulating gonadal steroid hormones, insulin sensitivity, body composition, and also lifestyle and social coordinates. Vitamin D status influences different metabolic adjustments, aside from calcium–phosphorus and bone metabolism. The main blood marker used to measure endogenous vitamin D status is 25-hydroxyvitamin D. Aging is associated with increases in serum parathyroid hormone and alkaline phosphatase, and a decrease of serum calcium, phosphorus, and vitamin D metabolites. 25-Hydroxyvitamin D status is also influenced by the circannual rhythm of sun irradiation. Results of clinical association studies have not correlated with intervention trials, experimental studies, and/or meta-analyses regarding the role of vitamin D on different outcomes in women during their second half of life and the vitamin D supplementation dose needed to improve clinical endpoints. Discordant results have been related to the method used to measure vitamin D, the studied population (i.e., sociodemographics and ethnicity), study designs, and biases of analyses. Vitamin D supplementation with cholecalciferol or calcifediol may improve some metabolic variables and clinical outcomes in young postmenopausal and older women. Studies seem to suggest that calcifediol may have some advantages over other forms of vitamin D supplementation. Further studies are needed to define interventions with supplements and effective food fortification.

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Introduction

The climacteric is a transitional period related to regressive ovarian estrogen synthesis. Progressive hypoestrogenemia causes a negative impact on the quality of life of young postmenopausal women (aged <60 years), due to the presence and intensity of menopausal symptoms (e.g. hot flashes, insomnia, mood swings, low self-esteem, muscle–joint pain), readjustments in social and occupational considerations, sleep disorders, changes in body composition, and an increased risk of the metabolic syndrome (METS) and related consequences. In woman aged 60 years or older, there is an increase in the prevalence and severity of urogenital symptoms (e.g. vulvovaginal atrophy, overactive bladder, dyspareunia, sexual dysfunction), musculoskeletal pain, a higher risk of neurodegenerative and cardiovascular diseases, and problems linked to body weight gain such as insulin resistance and type 2 diabetes mellitus (T2DM). In addition, there is a loss of muscle strength and coordination, and an increased risk of sarcopenia, osteoporosis, and related complications such as low-intensity fractures¹.

Vitamin D is a fat-soluble prohormone that affects the expression of more than 200 human genes. The endogenous

status is related to its synthesis induced at the skin by the sun and by the diet content (nutrition)². Vitamin D has traditionally been associated with alterations in bone metabolism, osteoporosis, and risk of fractures. Part of these risks are related to hypovitaminosis D, hypoestrogenism, and age-related readjustments in the secretion of parathyroid hormone (PTH). In recent decades it has been shown that all nucleated cells have specific receptors for vitamin D, which are sensitive to changes in vitamin D endogenous status; so, there is practically no organ or system exempt from different diseases and syndromes related to hypovitaminosis D^{2,3}. However, in most cases, no causal relationships have been demonstrated between hypovitaminosis D and such clinical or analytical findings. Moreover, much of the generated confusion has been related to the inappropriate mix of research of different rank and quality: 'it is like adding apples and oranges' without considering the nature or the rank of evidence. Another aspect that may have generated conflicting positions is the fact that vitamin D requirements may not necessarily be similar in a given tissue or cell type in order to maintain different functions.

In recent years we have moved between the exaggerated optimism of those who think that vitamin D is a miracle

balm for preventing aging and nihilists who think that 'well, a small dose of sun (using a suntan protector cream) is enough' or just 'a small amount of milk or cheese is enough'. Despite all these considerations, we would like to briefly discuss which clinical conditions might be improved – or maintained – by achieving a sufficient endogenous vitamin D status in postmenopausal women.

Vitamin D and parathyroid hormone

In nature, the two main forms of vitamin D are ergocalciferol (vitamin D₂), typical of vegetables and invertebrates, and cholecalciferol (vitamin D₃), typical of vertebrates. Vitamin D₂ is produced from ergosterol by several organisms: phytoplankton, fungi, and invertebrates in response to ultraviolet sunlight. The main natural source of vitamin D₃ is the cutaneous synthesis of 7-dehydrocholesterol through exposure to sunlight with a small amount of dietary animal foods such as fatty fish, eggs, and milk. The endogenous synthesis of the active hormone requires two hydroxylation reactions, one in the liver (25-hydroxylation) and the second at the kidney level (1- α -hydroxylation)^{2–4}.

In healthy subjects aged 20–89 years, serum PTH and alkaline phosphatase levels increase with age, while serum levels of calcium, phosphorus, 25-hydroxyvitamin D₃ (25(OH)D; calcidiol, calcifediol), and 1,25-di-hydroxyvitamin D₃ (1,25(OH)₂D; calcitriol) decrease. In addition, in subjects aged 38 years or older, significant correlations have been described between PTH and Ca²⁺ ($r = -0.223$), 25(OH)D ($r = -0.178$), and age ($r = 0.322$)⁵. Therefore, PTH secretion is regulated by both 25(OH)D and Ca²⁺ levels. Seasonal variations in sun ultraviolet radiation determine a sinusoidal trend or a circannual rhythm in vitamin D status. In addition, the body mass index (BMI) also regulates the circulating levels of vitamin D in women aged 19–80 years⁶.

The mechanism of the action of vitamin D is mediated by a nuclear receptor which responds to the heterodimer calcitriol-retinoid X, present in almost all human cell types^{2–4,7}. The extra-skeletal effects of vitamin D are related to the almost universal presence of vitamin D receptors in human organs and cells that are in charge of regulating normal and abnormal cell proliferation, immune function, and vascular and metabolic mechanisms^{4,7}.

Vitamin D metabolites are essential for calcium homeostasis of the entire body, maintaining serum calcium levels within a narrow range, regulating this process in the intestine, kidney, bone, and parathyroid gland. The production of the active hormone 1,25(OH)₂D is influenced by dietary intake of calcium and general conditions (e.g. growth, pregnancy, aging, or menopause). The action of 1,25(OH)₂D on calcium-regulated tissues is mediated by the vitamin D receptor, increasing intestinal calcium absorption in order to be used for bone mineralization⁸. Originally, vitamin D was described as a major regulator of calcium and phosphate homeostasis, in relation to bone metabolism. In addition, there is considerable evidence that 25(OH)D deficiency is associated with osteoporosis^{7,9}.

Body weight and metabolic syndrome

The METS is a set of disorders that includes at least three or more of the following factors: abdominal obesity, low high-density lipoprotein cholesterol, and high serum triglyceride, fasting glucose, and/or blood pressure levels. Abdominal obesity is the most frequent component of the syndrome that favors insulin resistance and is accompanied by a pro-inflammatory and prothrombotic state, a risk of developing diabetes, hypertension, and other chronic conditions¹⁰. During the menopausal transition, women tend to gain weight and this has been linked to an increase in the prevalence of the METS¹¹. On the other hand, obesity, hypercholesterolemia as compared to women with normal levels, hyperglycemia, and insulin resistance have been associated with low vitamin D serum levels¹².

METS rates have also been related to hormonal status (perimenopausal versus postmenopausal), lifestyle changes, and endocrine adjustments. Recent studies show that vitamin D deficiency is associated with the METS, and the combination of estrogens and vitamin D has protective effects against the METS. Thus, sufficient vitamin D levels in postmenopausal women taking calcium and vitamin D supplements are associated with a favorable lipid profile and low glucose and blood pressure levels. The odds ratio (OR) for the METS was 2.19 (95% confidence interval [CI]: 1.19–4.01, $p = 0.009$) for those with vitamin D deficiency as compared to those with normal levels¹³. In addition, postmenopausal women with hypovitaminosis D and T2DM have elevated triglyceride levels¹⁴.

In a working Japanese population aged 18–69 years, Akter *et al.*¹⁵ reported an inverse trend between circulating 25(OH)D levels and the METS. Indeed, compared to those with 25(OH)D serum levels of <20 ng/ml, the adjusted OR for the METS was 0.79 (95% CI: 0.55–1.15) and 0.52 (95% CI: 0.25–1.04) for those with serum 25(OH)D levels of 20–29 ng/ml and ≥ 30 ng/ml, respectively. In addition, these associations were detected in subjects aged 44 years or older, and the inverse association between serum 25(OH)D and the METS was more pronounced in subjects with high calcium intake.

In postmenopausal Brazilian women, aged 45–75 years, with at least 1 year of amenorrhea (who were not taking vitamin D supplements) and with a diagnosis of cardiovascular disease, the METS prevalence was higher when the circulating 25(OH)D levels were below 20 ng/ml. In addition, those with the METS had high triglyceride and decreased low-density lipoprotein cholesterol levels when compared to women without the METS¹¹. After adjustment for age, BMI, time since menopause onset, and physical activity, women with low 25(OH)D levels doubled the odds of METS in comparison to those with sufficient circulating 25(OH)D levels¹¹. The same Brazilian research group¹⁶ more recently reported in a double-blind placebo-controlled trial that vitamin D supplementation (1000 IU/day for 9 months) improved the METS risk in postmenopausal women, finding a significant increase (45%) in circulating 25(OH)D levels in the treated group as compared with a reduction (–12%) in untreated women. Treated women showed a significant reduction in

triglycerides (-12.2% , $p = 0.001$), insulin (-13.7% , $p = 0.008$), and homeostasis model assessment of insulin resistance (HOMA-IR) values (-17.9% , $p = 0.007$). Women supplemented with vitamin D had a lower risk of the METS (OR 0.42, 95% CI: 0.21–0.83), hypertriglyceridemia (OR 0.43, 95% CI: 0.22–0.85), and hyperglycemia (OR 0.23, 95% CI: 0.10–0.52) as compared to the placebo group ($p < 0.05$)¹⁶.

A meta-analysis of 22 randomized controlled trials (RCTs) studied the effect of vitamin D supplementation on endothelial function among subjects with the METS and related disorders, finding that there is an increase of low-mediated dilatation without any other change in endothelial function (pulse wave velocity and augmentation index)¹⁷.

The precise mechanism of action of vitamin D on the METS is unknown. In mice, vitamin D signaling through Paneth cell defensins seems to maintain gut microbiota, hence improving metabolic disorders and hepatic steatosis¹⁸. Paneth cells maintain microbial diversity expression of antimicrobial peptides, especially human α -defensin-5, and have shown repressed secretory capacity in human obesity¹⁹.

Insulin resistance and type 2 diabetes mellitus

There are experimental and clinical data suggesting that hypovitaminosis D may be one of the factors involved in the initiation and progression of insulin resistance, although there are no results supporting the benefit of vitamin D supplementation in preventing T2DM and associated risks. Experimental studies have demonstrated that $1,25(\text{OH})_2\text{D}$ stimulates the pancreatic β -cell to secrete insulin, hence vitamin D deficiency could promote insulin resistance and inflammation. Indeed, vitamin D deficiency is associated with increased inflammatory markers and an increase in fat mass²⁰. Development of abnormal glucose tolerance and T2DM are associated with alterations in glucose tolerance, preceded by alterations in the function of pancreatic β -cells, insulin sensitivity, and systemic inflammation. Vitamin D deficit may contribute to the initial insulin resistance and later pancreatic β -cell death. Vitamin D may act by reducing inflammation (which favors insulin resistance), maintaining the epigenome, and increasing DNA demethylases that neutralize hypermethylation. When these mechanisms are not operative or are reduced, the risk of T2DM decreases²¹.

In healthy premenopausal women, vitamin D supplementation improves biochemical indexes of insulin function. In a RCT, healthy Austrian premenopausal women with low serum 25(OH)D levels were randomized to receive once weekly either 20,000 IU of cholecalciferol or placebo (2:1 ratio) over a total of 24 weeks²². Although the treatment did not have a significant effect on glucose levels and on some secondary outcomes, it had a significant effect on the HOMA-IR score and the quantitative insulin-sensitivity check index. There was no significant effect on the remaining secondary outcome parameters.

One RCT reported the effect of high dose of vitamin D treatment for 6 months in patients with prediabetes and hypovitaminosis D, finding a significant increase in serum 25(OH)D levels and a reduction in the HOMA-IR scores,

suggesting that vitamin D may improve insulin sensitivity²³. Another RCT reported similar results of vitamin D supplementation during 6 months in patients with T2DM and hypovitaminosis D²⁴. The intervention improved glycemic control as assessed with glycosylated hemoglobin (HbA1c), fasting plasma glucose, and post-prandial plasma glucose mean values. In addition, improvements in systolic and diastolic blood pressure and total cholesterol levels were measured in subjects under treatment with vitamin D.

There are several meta-analyses concerning the effects of vitamin D supplementation and different endpoints in individuals with T2DM. A meta-analysis of 24 prospective clinical trials reported the effect of improving the 25(OH)D status on glycemia and insulin resistance in T2DM patients²⁵. The treatment with a minimum of 4000 IU/day was associated with significant reductions of HbA1c, fasting plasma glucose, and HOMA-IR values, and a significant increase in serum 25(OH)D levels.

Song *et al.*²⁶ performed a meta-analysis of prospective observational studies assessing the association between 25(OH)D blood levels and the risk of incident T2DM. When comparing the highest and the lowest levels of 25(OH)D, the relative risk of T2DM was 0.62 (95% CI: 0.54–0.70), which did not differ by sex, duration of follow-up, sample size, diabetes diagnostic criteria, or measurement method for 25(OH)D. However, this inverse and significant relation between serum 25(OH)D, in diverse populations, does not fit with the results from the D2d trial by Pittas *et al.*²⁷. This study randomly assigned adults with at least two of three possible criteria for prediabetes and those with no diagnosis of diabetes to receive daily 4000 IU of vitamin D₃ or placebo, independent of baseline serum 25(OH)D levels. The target of 508 diabetes events was analyzed. After 2 months of treatment the intervention was associated with an increase of mean 25(OH)D from 27.7 ng/ml to 54.3 ng/ml, with no significant changes in the control group (28.2 ng/ml at baseline)²⁷. In this same trial, the hazard ratio for vitamin D treatment as compared to placebo was 0.88 (95% CI: 0.75–1.04, $p = 0.12$), suggesting that vitamin D supplementation in subjects with risk factors for diabetes may not reverse the ongoing endocrine-metabolic risks. It is also possible that the 25(OH)D levels in the placebo group were already 'sufficient' at the beginning of the study (28.8 ng/ml) and at the end of the study 2 years later (28.2 ng/ml). This selected population is quite different from that studied by Song *et al.*²⁶, showing an inverse association between 25(OH)D and diabetes risk in both men and women. In the D2d trial²⁷, the increase in serum 25(OH)D – from 27.7 to 54 ng/ml by month 24 in the treated group – suggests that 'more' circulating levels of vitamin D do not necessarily indicate 'better' concerning pancreatic endocrine function; even more if levels are within normal or sufficient range. The studied populations in both the Song *et al.*²⁶ and Pittas *et al.*²⁷ studies are not comparable in terms of baseline vitamin D status and risk of T2DM.

There are conflicting results concerning the effect of vitamin D supplementation on glucose metabolism in subjects with T2DM. A recent meta-analysis reported the effect of vitamin D supplementation versus placebo, showing that the

intervention reduced insulin resistance and HbA1c and insulin values. However, there were no significant differences in long-term follow-up with vitamin D intervention²⁸.

Vitamin D supplementation in T2DM patients can improve HbA1c, insulin resistance, and insulin values in a short-term intervention in people with low circulating vitamin D levels, suggesting that vitamin D can be considered an adjuvant therapeutic agent along with the other treatment options for T2DM.

Muscle mass and function

Skeletal muscle pain is among the most frequent complaint in postmenopausal women. It has long been recognized that vitamin D has a relevant role in muscle function, with anabolic and restorative properties over the muscle^{29,30}. Vitamin D has a special relevance at maintaining manual grip strength in middle-aged women³¹. Muscle weakness or dynapenia is very common during the second half of life, this phenomenon being partly linked to decreased estradiol secretion, changes in body composition, and alterations in vitamin D metabolism. Vitamin D deficiency alters muscle cell differentiation, intracellular calcium metabolism, and genomic mechanisms²⁹. Deficiency of muscle function is also related to insulin resistance as a consequence of the sedentary lifestyle observed among postmenopausal women³².

Muscle mass and function are influenced by age, gender, body weight, physical activity, and nutrition. Males have more skeletal mass than females, the gender difference being greater in the upper than the lower body. A significant decrease in skeletal muscle is detected at the end of the fifth decade³³. In young postmenopausal women with normal vitamin D levels, there is a reduction in hand grip strength related to age and time since menopause onset³⁴.

Hypovitaminosis D in older women (mean age 66.9 ± 8.5 years) was associated with significant differences in appendicular lean mass/BMI, total fat mass, visceral adipose tissue, hand grip strength, and other outcomes in comparison to those with normal 25(OH)D levels³⁵. Women with hypovitaminosis D had worse upper and lower limb muscle strength and physical performance than subjects with normal levels of 25(OH)D³⁶. Muscle weakness or fatigue is a complaint linked to hypovitaminosis D, especially if serum levels are <15 ng/ml. In general, doses of 800–1000 IU/day may improve muscle function^{37,38}. A protein-rich diet and vitamin D supplementation along with physical activity/exercise is recommended to maintain musculoskeletal health in postmenopausal women³⁹.

The meta-analysis by Bolland *et al.*⁴⁰ including clinical trials on the effect of vitamin D supplementation has not confirmed some of the predicted results from association studies. They concluded that vitamin D supplementation does not prevent falls and fractures, and has no significant effect on bone mineral density. However, subjects with 25(OH)D levels below 10 ng/ml achieved a significant increase in lumbar bone mineral density with daily doses of 400 IU and 1000 IU, and in hip bone mineral density with a daily dose of 1000 IU⁴¹. Furthermore, 70% of treatments used

doses of 1000 IU/day or lower, which seem not to be enough to promote a sufficient level of circulating 25(OH)D⁴¹. Other limitations in the Bolland *et al.* meta-analysis have been related to the method of 25(OH)D measurement, the influence of ethnicity, and the so-called *p*-hacking effect in meta-analytic procedures^{42–44}.

A meta-analysis of 46 cohort studies assessed at baseline the incidence of prefrailty and frailty among community-dwelling adults aged 60 years or older⁴⁵. A total 13.6% of non-frail subjects who survived a median follow-up of 3 years became frail, with an incidence rate of 43.4 cases per 1000 person-years. The incidence of frailty is higher in prefrail subjects. In addition, frailty and prefrailty rates are significantly higher in women than in men: 44.8% versus 24.3% cases per 1000 person-years for frailty; and 173.2 versus 129 cases per 1000 person-years for prefrailty, respectively⁴⁵. Therefore, there is a gender difference with worse risks for postmenopausal and older women.

Vitamin D supplementation

It has been reported repeatedly that many of the associations between hypovitaminosis and different risks or clinical conditions are related to lifestyle, mainly linked to outdoors activities and dietary habits rather than to diseases and metabolic alterations. In addition, postmenopausal women have some gender-related risks as compared to men (osteoporosis, falls, changes in body composition, etc.). Since many metabolic processes and regulatory mechanisms are disrupted by hypovitaminosis D, interventions aimed at improving endogenous vitamin D status should be encouraged. Of course, vitamin D, *per se*, is not the sole preventive factor of T2DM, muscle dysfunction, or any other health condition. However, it may improve different metabolic functions. Vitamin D supplementation should take into consideration the basal health status and 25(OH)D levels, age, lifestyle, BMI, and comorbidities.

The risk of hypervitaminosis D (vitamin D toxicity) under most circumstances requires 25(OH)D levels to be at least 150 ng/ml, as indicated by the Endocrine Society Practice Guidelines⁴⁶.

Cholecalciferol

The European Menopause and Andropause Society and other scientific organizations recommend the use of a small daily supplement of vitamin D starting at 50 years of age or during postmenopausal years^{37,47}. In older subjects, 1 year of treatment with cholecalciferol or ergosterol (1600 IU/day or 50,000 IU/month) does not produce toxicity and measured 25(OH)D levels of <30 ng/ml persist in 20% of individuals. In addition, there are different individual responses in terms of achieved serum 25(OH)D levels⁴⁸. However, no routine monitoring is mandatory during vitamin D treatment due to its large therapeutic index, although 25(OH)D levels can be measured after 3–6 months to adjust the recommended dose⁴⁹.

It seems that vitamin D₃ (cholecalciferol) is more effective at raising serum 25(OH)D levels than vitamin D₂ (ergocalciferol), with the first being considered the best choice^{50,51}. Moreover, the use of ergocalciferol creates a problem with the measurement of serum 25(OH)D using conventional methods, and preference should be given to supplementation with cholecalciferol (D₃) instead of ergocalciferol (D₂). On the other hand, daily doses should be preferred to high monthly doses since daily dosages may approach the normal expected values if subjects are exposed to sunlight while bolus doses may induce 24-hydroxylation⁴².

In older adults randomized to placebo and two cholecalciferol doses (750 µg or 1500 µg) taken monthly for 12 months, levels of C-reactive protein, interleukin-10, leptin, and adiponectin were not significantly altered⁵².

Calcifediol

Oral administration of calcifediol increases serum 25(OH)D levels faster than oral cholecalciferol. It is also three times more potent than cholecalciferol, has a higher rate of intestinal absorption, and has a linear dose–response curve that is independent of basal 25(OH)D levels. This is in contrast with cholecalciferol in which intestinal absorption is lower when 25(OH)D is close to normal levels. On the other hand, while oral cholecalciferol is transported by chylomicrons and reaches the general circulation via the lymph pathway, calcifediol is almost 100% absorbed by the intestine and then passed to the bloodstream via the portal vein which may explain the rapid and higher reached peak of plasma calcifediol as compared to oral cholecalciferol intake. Also, calcifediol may be of particular interest in subjects with decreased intestinal absorption, in subjects with excessive body weight (due to its low trapping in adipose tissue as compared with other vitamin D compounds), and in subjects receiving treatments that interfere with liver cytochrome p-450 enzymes (which may decrease the synthesis of calcifediol)⁵³.

Calcifediol treatment (20 µg/day) had a greater improvement in gait speed in healthy postmenopausal women with low serum 25(OH)D levels, as compared to cholecalciferol supplementation (20 µg/day = 800 IU/day vitamin D₃), which was significantly correlated with blood 25(OH)D levels, although a benefit on trunk sway could not be demonstrated⁵⁴. A significant increase in serum levels of 25(OH)D, appendicular muscle strength, and physical performance has been reported in older postmenopausal women receiving calcifediol (20 µg/day) for a 6-month period. At 6 months, the percentage of fallers was lower, although not significant ($p = 0.078$), whereas there was a significant reduction both in the percentage of recurrent fallers and in the mean number of falls³⁶.

In most osteoporosis clinical practice guidelines it is advised that serum levels of 25(OH)D should be above 20 ng/ml, and even exceed 30 ng/ml⁵⁵. High doses of calcifediol could be used intermittently (every month or more frequently every 2 or 3 weeks)^{56,57}. Patients that receive calcifediol dosages (0.266 mg = 15,960 IU) every 15 or 30 days for at least 1 year usually reach or surpass these levels.

Indeed, the percentage of subjects reaching 25(OH)D levels higher than 20 and 30 ng/ml was respectively 100% and 92% with doses given every 15 days; and 97% and 80% respectively with doses given every 30 days⁵⁸.

In patients with chronic renal failure, calcifediol may neutralize hypovitaminosis D and reduce secondary hyperparathyroidism without concomitant changes of calcium, phosphorus, or other so-called safety parameters⁵⁹. As in any clinical situation, vitamin D supplementation should be monitored to prevent hypercalcemia as recommended by clinical guidelines and health authorities⁶⁰.

Food fortification

The promotion of healthy measures through outdoor activities and dietary consumption of vitamin D-rich foods may not be enough. It is unlikely that the almost epidemic hypovitaminosis D may be reduced by conventional vitamin D supplementation in the general human population, and specifically in women during the second half of their life. The design of such supplementation programs should consider climatological conditions, ethnicity, and lifestyle⁶¹. In general, adherence to the continued consumption of nutritional supplements should be encouraged, especially among the population with the lowest purchasing power. On the other hand, the risk of overdosing cannot be ruled out in some cases. Despite the advantages of vitamin D food fortification, one must bear in mind that this measure should be established after an analysis of the population characteristics and should be a public health decision, as it has been done in some countries such as Finland, Canada, and India^{62,63}.

Fish and eggs are probably the few foods naturally rich in vitamin D. Currently, supplementing animals with a diet rich in vitamin D has been suggested to indirectly increase the vitamin D intake from 'natural' diet products. It seems that dietary calcifediol (not cholecalciferol) can increase 25(OH)D in eggs and increase the vitamin D content more intensively. This approach, intended to increase the vitamin D content in food, is currently under investigation⁶⁴.

Conclusion

Postmenopausal and older women are at risk of different metabolic alterations and health limitations that may reduce quality of life and physical independence associated with low vitamin D levels. By maintaining an adequate endogenous status of vitamin D, it could be plausible to improve skeletal muscle function and different metabolic outcomes within the normal range in postmenopausal and older women. Cholecalciferol and calcifediol may be used to maintain a sufficient endogenous vitamin D status. Vitamin D food fortification is only possible in some countries with unified health protocols and appropriate health care systems. Results of clinical association studies have not correlated with intervention trials, experimental studies, and/or meta-analyses regarding the role of vitamin D in different outcomes in women during their second half of life basically due to blood measurement methods, different study designs,

ethnicity, and a diversity of socioeconomic factors that may influence the skin production of vitamin D and individual health status.

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