Therapeutic Advances in Endocrinology and Metabolism Review

Vitamin D supplementation after the menopause

Faustino R. Pérez-López, Peter Chedraui and Stefan Pilz

Ther Adv Endocrinol Metab

2020, Vol. 11: 1–13

DOI: 10.1177/2042018820931291

***Abstract*:** The purpose of this review was to assess recent evidence regarding the effects of low vitamin D levels on some highly prevalent clinical conditions of postmenopausal women. We reviewed and selected recent literature regarding menopause-related conditions associated with vitamin D deficiency and interventions to manage them. Low circulating 25-hydroxyvitamin D (25(OH)D) levels related to menopause are linked to diet, lifestyle, changes in body composition, insulin sensitivity, and reduced physical activity. Vitamin D supplementation increases serum 25(OH)D levels while normalizing parathyroid hormone and bone markers, and in women with serum 25(OH)D levels below 10 ng/ml supplementation may improve bone mineral density. Low vitamin D status has been associated with the metabolic syndrome, high triglyceride levels, and low high-density lipoprotein cholesterol levels. When compared with placebo, vitamin D supplementation may lower the risk of the metabolic syndrome, hypertriglyceridemia, and hyperglycemia. There is an inverse relationship between fat mass and serum 25(OH)D levels and, therefore, the dosage of supplementation should be adjusted according to the body mass index. Although vitamin D supplementation may improve glucose metabolism in prediabetic subjects, data regarding muscle strength are conflictive. There is evidence that vitamin D over-treatment, to reach extremely high circulating 25(OH)D levels, does not result in better clinical outcomes. The identification and treatment of vitamin D deficiency in postmenopausal women may improve their general health and health outcomes. Vitamin D supplementation should preferably be based on the use of either cholecalciferol or calcifediol.

Keywords: body composition, calcifediol, cholecalciferol, fracture, insulin resistance, menopause, metabolic syndrome, obesity, vitamin D

Received: 27 March 2020; revised manuscript accepted: 10 May 2020.

Correspondence to:
Faustino R. Pérez-López
Department of Obstetrics and Gynecology, Instituto de Investigaciones Sanitarias de Aragón, University of Zaragoza Faculty of Medicine, Domingo Miral s/n, Zaragoza, 50009, Spain
faustino.perez@unizar.es

Peter Chedraui
Instituto de Investigación e Innovación en Salud Integral, Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador, and Facultad de Ciencias de la Salud, Universidad Católica Nuestra Señora de la Asunción, Asunción, Paraguay

Stefan Pilz
Department of Internal Medicine, Medical University of Graz, Graz, Austria

Introduction

Vitamin D deficiency is considered a public-health problem because it has a high worldwide prevalence and may contribute to a variety of acute and chronic diseases. Nutritional guidelines have established dietary intake references for vitamin D based on skeletal health because vitamin D is effective in the prevention and treatment of rickets and osteomalacia. To date, it is unclear whether vitamin D exerts additional musculoskeletal effects such as improvements in bone mineral density (BMD) or reductions in fractures and falls as some recent meta-analyses of randomized controlled trials (RCTs) have questioned these previously proposed vitamin D effects. Moreover, there is accumulating evidence that vitamin D may also play a significant role in a variety of extra-skeletal diseases including for example, infections, cancer, or autoimmune and neurological diseases. While there are many open questions surrounding the potential role of vitamin D for overall human health, it is becoming increasingly clear that vitamin D supplementation is not a panacea for all diseases, but it is effective in certain sensitive populations including those with vitamin D deficiency. In this context, various RCTs and meta-analyses of RCTs have suggested that the beneficial effects of vitamin D are either restricted to, or particularly pronounced, in individuals with deficient (20–30 ng/ml) or insufficient (<20 ng/ml) circulating 25-hydroxyvitamin D (25(OH)D) (calcidiol, calcifediol) concentrations. However,

the biological active hormone is 1α,25 dihydroxy-vitamin D (1,25(OH)$_2$D) (calcitriol), which acts directly through binding to specific vitamin D receptors and indirectly by regulating the parathyroid hormone (PTH), and calcium and phosphate metabolism.[1,2]

While we refer to various reviews and meta-analyses in the current literature on general vitamin D effects with regard to clinically relevant health outcomes, the aim of the present article is to provide a narrative review on the current literature regarding specific characteristics of vitamin D status and metabolism in postmenopausal women, and on the health effects of vitamin D supplementation in this setting.

Postmenopausal women are of particular interest as they have a high prevalence of diseases with relevance for vitamin D, such as musculoskeletal diseases as well as changes in vitamin D metabolism, such as reduced skin synthesis of vitamin D, or changes in body composition that are relevant for vitamin D status and physiology. In detail, we aim to outline data on the prevalence of vitamin D deficiency in postmenopausal women and the specific characteristics that determine vitamin D status and its metabolism in this regard. We specifically aim to review and discuss data on the differences regarding vitamin D status and its effects in postmenopausal women compared with other populations. Moreover, we aim to summarize recent data from vitamin D RCTs and meta-analyses in postmenopausal women and the current recommendations regarding the testing and treatment of vitamin D deficiency in these women.

Methods

We conducted a selective literature search of the years 2018 through to February 2020 in PubMed, using the search terms 'vitamin D', 'menopause', 'postmenopausal women', 'body composition', 'metabolic syndrome', and 'aging'. In addition, secondary searches for specific topics were performed. In this review we will discuss different clinical conditions related to low vitamin D levels in postmenopausal women, some of which may have slowly developed years before menopause onset. This narrative review also included publications of crucial importance that pre-date 2018. To facilitate text reading, serum 25(OH)D results in nmol/L were converted to ng/ml, being 2.5 nmol/L = 1 ng/mL. In addition, 1 µg of calcifediol is equivalent to 60 IU.

Prior to the examination of the various clinical conditions prevalent in postmenopause that may be related to vitamin D, the problem of serum vitamin D measurement should be mentioned. Despite being much facilitated in the 21st century, there are important variation coefficients observed among methods, even within a particular method there may be a high degree of variation.[3,4] There is a need for 25(OH)D immunoassay methods in each center to be calibrated against standardized liquid chromatography-tandem mass spectrometry or international reference preparations.

Results and discussion

Vitamin D and bone metabolism

In postmenopausal women aged 50–65 years, low 25(OH)D blood levels are associated with alterations in bone turnover markers and supplementation with vitamin D may normalize these parameters. In a double-blind, placebo-controlled RCT performed by Nahas-Neto *et al.*,[5] postmenopausal women were supplemented with 1000 IU/day of vitamin D$_3$ or placebo for 9 months. They found an increase in circulating 25(OH)D levels from 15.0 ± 7.5 ng/ml to 27.5 ± 10.4 ng/ml (+45.4%) in the supplemented group while in the placebo group 25(OH)D levels decreased from 16.9 ± 6.7 ng/ml to 13.8 ± 6.0 ng/ml (–8.5%). At the same time, the supplemented group displayed decreases in serum levels of PTH, C-terminal telopeptide of collagen type I, and procollagen type I N-terminal propeptide; there were no significant changes in total calcium, alkaline phosphatase, and calciuria levels.[5]

Bislev *et al.*[6] performed a double-blind, placebo-controlled RCT in healthy postmenopausal women in which a short-term vitamin D$_3$ supplementation (2800 IU/day for 3 months) was administered during the winter months. The intervention was effective in increasing circulating 25(OH)D and 1,25(OH)$_2$D levels by 23.6 ng/ml and 19 pmol/l, respectively, while reducing PTH by 0.7 pmol/L (all $p < 0.001$). These changes were associated with an increase in trabecular bone score in the trochanter region and femoral neck as measured by quantitative computed tomography, suggesting that vitamin D supplementation correlates with increases in trabecular bone thickness, stiffness, and failure load. Despite the aforementioned, there were no benefits on muscle function.

The mismatch between 25(OH)D and PTH levels in cases of vitamin D deficiency is associated with increases in cortical bone porosity. Osima *et al.*[7] reported that increased PTH (not reduced 25(OH)D) was the link between femoral cortical bone porosity and increased odds for fracture risk in women with a mean age of 68 years, with higher serum PTH levels compared with controls (4.6 ± 2.4 pmol/L *versus* 4.1 ± 1.8 pmol/L; $p = 0.01$), after adjustment for season of blood sampling (winter *versus* summer). In addition, decreased 25(OH)D and increased PTH are associated with fracture risk, independently of age, weight, calcium supplementation, calcemia, and cortical porosity. However, the majority of intervention studies have failed to demonstrate the benefits of vitamin D supplementation on BMD and fracture prevention.[8] This is probably because vitamin D status (as an inclusion criterion) was not defined in studied subjects.[9] Jorde *et al.*[10] reported the effect of supplementation with 20,000 IU/week of vitamin D_3 *versus* placebo for 4 months in subjects with baseline 25(OH)D levels of 13.6 ng/ml. Mean serum 25(OH)D levels increased to 35.6 ng/ml and there were no significant changes in the placebo group. In addition, there was a small but significant decrease in serum procollagen type I N-terminal propeptide in the vitamin D-supplemented group compared with the control group, but there were no significant differences between groups for C-terminal telopeptide collagen type 1, sclerostin, tumor necrosis factor-alpha, osteoprotegerin, receptor activator of nuclear factor κB ligand, or leptin.

LeBoff *et al.*[11] reported the results of the VITamin D and OmegA-3 TriaL (VITAL) study, a double-blind, placebo-controlled RCT carried out among men ⩾50 and women ⩾55 years. After 2 years of vitamin D supplementation (2000 IU/day) there was no effect on BMD at the spine, femoral neck, total hip, or whole body. In this population, the effect did not vary by sex, ethnicity, or body mass index (BMI). This study was designed to study the effect of vitamin D supplementation on cancer risk. Mean baseline 25(OH)D levels were 30.8 ± 10.0 ng/ml, about 87% of treated subjects had normal 25(OH)D levels, and most of the supplemented subjects attained serum 25(OH)D levels of 40 ng/ml or more after the first year of follow up. In other words, nearly 87% of the treated subjects had normal 25(OH)D levels.[12] No data were disclosed on the number of subjects with severe 25(OH)D insufficiency (<10 ng/ml). Therefore, it seems we cannot expect that supplementation with 25(OH)D levels ⩾20 ng/ml will have benefit on bone metabolism.

Vitamin D and fracture risk

Although there is some controversy, combined vitamin D and calcium supplementation has been recommended to prevent osteoporosis and subsequent fracture risk. However, some clinicians are reluctant to use calcium supplements.[13] In addition, some RCTs have reported conflicting results regarding optimal doses and regimens of supplementation. In one meta-analysis of clinical trials, Bolland *et al.*[14] found that vitamin D supplementation does not prevent falls and fractures and has no significant effect on BMD. Nonetheless, subjects that had 25(OH)D levels below 10 ng/ml achieved a significant increase in lumbar BMD with daily doses of 400 IU and 1000 IU, and in hip BMD with a daily dose of 1000 IU. Furthermore, 70% of the trials used low daily doses of vitamin D which seem not to be enough to promote a sufficient level of circulating 25(OH)D.[15] Other limitations in the Bolland *et al.*[14] meta-analysis have been related to the method used to measure 25(OH)D, the influence of ethnicity, and the possible presence of the 'so-called' *p*-hacking effect of meta-analytic procedures.[15–18]

Further criticisms of the Bolland *et al.*[14] meta-analysis include the limited observation period to detect a recognizable effect on long-term events, the inclusion of subjects with low facture risk, and the lack of control of adherence to treatment. However, the two most relevant limitations were first that the majority of included studies had enrolled subjects with baseline 25(OH)D levels >20 ng/ml, and secondly, the small proportion of patients with vitamin D deficiency at baseline who did not even attain sufficient levels throughout the studies (>30 ng/ml), thus being unlikely to experience any benefit from the supplementation.[19] Therefore, subjects who are not vitamin D deficient would obtain hardly any benefit from vitamin D supplementation. This could erroneously induce elderly subjects, who have osteoporosis and do not receive active bone-forming agents, to stop vitamin D intake. If this population is deficient in vitamin D, supplementation would be essential as an anti-fracture agent.[20,21]

The Kahwat ***et al.***[22] meta-analysis of RCTs or observational studies analyzed vitamin D, calcium, or combined supplementation for the primary

prevention of fractures among community-dwelling adults without known vitamin D deficiency, osteoporosis, or prior fracture. Supplementation with vitamin D alone or in combination with calcium was not associated with a reduction in fracture risk in studied subjects. Vitamin D with calcium was associated with an increase incidence of kidney stones.

Another more recent meta-analysis[23] compared vitamin D or vitamin D and calcium with controls. It was based on studies involving at least 200 fracture cases and RCTs enrolling at least 500 participants (59.9% women, mean age 77.1 years, baseline blood 25(OH)D levels ranging from 10.6 ng/ml to 26.3 ng/ml, and reporting at least 10 incident fractures). In 11 observational studies, the combined (vitamin D + calcium) supplementation was associated with an adjusted lower relative risk (RR) for any fracture (RR 0.93; 95% CI 0.89–0.96) and for hip fracture (RR 0.80; 95% CI 0.75–0.86), for each increase in 10 ng/ml in serum 25(OH)D levels. Supplementation with vitamin D alone in 11 RCTs, with a mean serum 25(OH)D difference of 8.4 ng/ml, was not associated with a reduction in the risk of any fracture or hip fracture, although there were heterogeneous doses of vitamin D supplementation. Contrary to this, the meta-analysis of six RCTs of combined supplementation with vitamin D at daily doses of 400–800 IU/day (median serum difference of 25(OH)D 9.2 ng/ml) and calcium (1000–1200 mg/day) found a significant reduction (6%) for any fracture risk (RR 0.94; 95% CI 0.89–0.99), and a 16% reduction for hip fracture risk (RR 0.84; 95% CI 0.72–0.97).[23]

This overview of successive meta-analyses regarding the effect of vitamin D supplementation on fracture risk highlights the limitations of heterogeneous meta-analyses in terms of sample size, events, and low basal vitamin D levels, and sufficient change in serum vitamin D levels as confirmatory effects of clinical intervention, high adherence to interventions, and appropriate statistical approaches to the same clinical problem.

Recently a retrospective study performed by Zhuang *et al.*[24] analyzed in postmenopausal women (aged 50–98 years) the effect of age, BMI, BMD, and 25(OH)D serum levels over hip fracture risk when the femoral neck reached the threshold of osteoporosis. According to logistic regression analysis age, low femoral neck BMD, and low serum 25(OH)D levels were independent risk factors for fragile hip fracture with the condition that femoral neck BMD had reached the threshold of osteoporosis. Therefore, it seems reasonable to suggest that vitamin D supplementation may be a positive intervention to reduce the risk of fragile femoral neck. The recent Consensus Statement on vitamin D concluded that "vitamin D supplementation with adequate calcium intake can decrease the incidence of fractures in elderly vitamin D deficient subjects".[4] Despite this, there is a need for more specific evidence on the matter.

Another issue is determining the appropriate dosage of vitamin D supplementation and calcium in order to prevent fractures. Specific treatments for osteoporosis and fracture risk, with different mechanisms of action, have in general included vitamin D supplementation, mainly in older women. Overall, intervention has been recommended in women who are postmenopausal and have low BMD (T score < -2.5), a history of spine or hip fracture, or a score suggestive of increased fracture risk as assessed with the Fracture Risk Assessment Tool. Treatments for postmenopausal osteoporosis include a many heterogeneous and varied options.[25] However, it must be borne in mind that the aim of treating osteoporosis is to reduce facture risk. This means that pharmacological treatments should not be used in women with low BMD who have low fracture risk. The majority of postmenopausal women only require healthy lifestyle recommendations to reduce osteoporosis risk. Quality-of-life impairment will occur among elderly subjects in the event of a fracture. Specific drug treatments should be given in some women due to risk of fracture.

There is a large list of pharmacological options to prevent/reduce facture risk.[26,27] Many of these treatments include vitamin D supplementation. The Barrionuevo *et al.*[26] network meta-analysis of RCTs of postmenopausal women with primary osteoporosis demonstrated that calcium plus vitamin D supplementation combined with alendronate, zoledronate, risedronate, denosumab, estrogen with progesterone, and romosozumab significantly reduced the risk of hip fracture compared with placebo (RR = 0.81). In addition, abaloparatide, teriparatide, denosumab, and romosozumab were more effective than vitamin D and vitamin D plus calcium in the reduction of vertebral fracture risk. However, treatment with vitamin D and calcium alone is limited despite

available large trials.[26] The Hernandez *et al.*[27] meta-analysis of RCTs reported the effects of different bone anabolic therapies (BATs) in association with vitamin D supplementation on postmenopausal osteoporosis. They found that all BATs significantly reduced the risk of vertebral fractures, whereas no intervention significantly reduced the risk of non-vertebral fractures. In addition, all BATs significantly increased BMD at all locations compared with placebo, no treatment, or bisphosphonates.

Vitamin D and the metabolic syndrome

Low vitamin D status has been linked to the metabolic syndrome (MetS) in postmenopausal women. MetS is defined as the presence of at least three of the following findings: waist circumference >88 cm, serum triglycerides ⩾1.7 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.3 mmol/L, blood pressure ⩾130/85 mmHg, and a fasting plasma glucose of ⩾5.5 mmol/L. Its prevalence has been related to ethnicity, lifestyle, diet, physical activity, comorbidity, reproductive stage, and aging. Reports have indicated that the prevalence of MetS is higher in postmenopausal women with either deficient or insufficient serum 25(OH)D levels (both 57.8%) compared with those with normal vitamin D levels (39.8%).[28] MetS was significantly associated with serum 25(OH)D levels <30 ng/ml, high triglyceride (OR 1.55; 95% CI 1.13–2.35), and low HDL-C levels (OR 1.60; 95% CI 1.19–2.40) compared with women with sufficient 25(OH)D levels, after adjusting for age, time since menopause, BMI, smoking, and physical exercise.

In a double-blind RCT, a Brazilian research group reported the effect of vitamin D supplementation (1000 IU vitamin D_3/day) for 9 months on the metabolic risk profile of postmenopausal women aged 50–65 years.[29] The authors found a significant increase (+45.4%) of serum 25(OH)D levels in women receiving the supplement compared with a decrease (–18.5%) in the placebo group ($p = 0.049$). In addition, women receiving vitamin D displayed a significant reduction of serum triglycerides, insulin, and also homeostatic model assessment of insulin resistance (HOMA-IR) values. After adjustments for age, time since menopause, and BMI, women receiving vitamin D supplementation had a lower risk of presenting with MetS, hypertriglyceridemia, and hyperglycemia compared with the placebo group.

Among postmenopausal and older Chinese women who were not on estrogens, Huang *et al.*[30] reported a positive correlation between serum estradiol and 25(OH)D levels. Higher 25(OH)D levels were correlated with favorable lipid, blood pressure, and glucose levels, whereas serum estradiol levels were negatively correlated with cholesterol, triglyceride, and blood pressure values. When women were stratified by vitamin D status, the MetS risk was higher for vitamin D deficient women compared with those with sufficient levels (OR 2.19; 95% CI 1.19–4.01), and the association was not changed after further adjusting for estradiol levels (OR = 3.49; 95% CI 1.45–8.05, for the lowest *versus* the highest tertile). The authors concluded that among the studied female population vitamin D and estradiol deficiency may be related to a higher risk for MetS. A diet rich in vitamin D and an optimal vitamin D supplementation may be a way to prevent or reduce the risk of developing MetS.

Excessive body weight and fat distribution

The menopausal transition is associated with changes in body composition and fat distribution, even in cases without body weight modifications.[31] Body fat accumulation can be demonstrated by increases in BMI, body weight, body fat percentage, waist circumference, hip circumference, visceral fat, and trunk fat percentage.[32] Excessive body weight (including both overweight and obesity) is a frequent complaint related to low circulating 25(OH)D levels in peri- and postmenopausal women. In fact, BMI is a good predictor of vitamin D status in women of all ages. Delle Monache *et al.*[33] reported that 80% of Italian women presented with serum 25(OH)D concentrations below 30 ng/ml, with the highest 25(OH)D mean value measured in September and the lowest mean value in March. This sinusoidal circannual rhythm, with high 25(OH)D levels during spring/summer, affected both obese and non-obese women, and has been reported in other regions of the world in relation to climatic and lifestyle conditions, reaching differences of 8–10 ng/ml between higher and lower levels depending on the period of the year.[34]

The inverse relation between fat mass and serum 25(OH)D has been described for all ages and in different scenarios. Therefore, fat distribution has relevant implications for maintaining endogenous 25(OH)D levels and concomitant metabolic

adjustments. For instance, in the previously cited VITAL study, a *post-hoc* analysis showed that after excluding 1 year and 2 years of follow up the death rate was significantly lower after vitamin D supplementation than with placebo, with a protective effect on breast cancer when the BMI was $<25\,kg/m^2$.[12] It is likely that fat tissue of overweight and obese women extracts a higher amount of the vitamin D supplementation, hence losing its protective factor against breast cancer. However, BMI directly correlates with vitamin D-binding proteins rather than with circulating 25(OH)D levels. Therefore, the link between low 25(OH)D and obesity is still to be elucidated. Furthermore, vitamin D supplementation dosage should be adjusted according to BMI in order to be effective and body weight reduction could be followed with increases in circulating 25(OH)D levels. Also, several trials have suggested that concomitant vitamin D and calcium supplementation potentially reduces central fat deposits, especially in subjects with low dietary calcium intake.[35]

A meta-analysis of RCTs[36] regarding adults supplemented with vitamin D_3 with doses ranging from 400 IU to 5714 IU showed that a dosage of 1000 IU best suppressed serum PTH levels, while 4000 IU showed the greatest increase in serum 25(OH)D levels in the overweight and normal obese population. Since postmenopausal women may also have some other component of MetS, the initial dose should be 1000–2000 IU/day with serum 25(OH)D required to be measured after 3–4 months to check if the dose is sufficient or should be increased. Some overweight and obese postmenopausal women probably need higher doses of vitamin D supplementation depending on their diet and exposure to sunlight in order to increase serum 25(OH)D levels. Another approach is to titrate the dose of vitamin D supplementation in cases of excessive body weight as recommended by Ekwaru *et al.*[37] They suggested that vitamin D supplementation should be 2–3 times higher for obese subjects and 1.5 times higher for overweight subjects compared with subjects of normal weight.

Glucose, insulin resistance, and diabetes risk

Vitamin D status has been related to glucose metabolism, and higher serum 25(OH)D levels are associated with better glycemic control, better pancreatic β-cell function, and insulin sensitivity. Valladares *et al.*[38] have studied fasting plasma glucose and 25(OH)D levels in women aged 35–74 years. This study reported that 65.4% had 25(OH)D <30 ng/ml and 25.6% <20 ng/ml and lower serum 25(OH)D levels were associated with higher glucose levels. A recent meta-analysis showed no association between serum 25(OH)D levels and prediabetes.[39] There were no significant differences in hemoglobin A1c, fasting plasma glucose, and HOMA-IR values between individuals with prediabetes treated with vitamin D and those taking placebo.

Niroomand *et al.*[40] in a double-blind RCT studied the effect of a high dose of vitamin D_3 (50,000 IU oral pearls weekly for 3 months, followed by one pearl per month for an additional period of 3 months) or placebo on insulin sensitivity in adults with prediabetes. As expected, at the end of the study period, 25(OH)D levels were significantly higher in the supplemented group (36 ng/ml *versus* 16 ng/ml), and there were no significant differences in fasting plasma glucose and the 2-h oral glucose tolerance test. However, the HOMA-IR score was significantly lower among patients given supplementation suggesting that treatment with a high vitamin D dose may improve insulin sensitivity and decrease the risk of progression toward diabetes. However, further studies are needed for a possible clinical recommendation.

The D2d study[41] randomized adult individuals (45% women with a mean age of 60 years and basal 25(OH)D of 28.0 ± 10.0 ng/ml) with two of three glycemic criteria for prediabetes (i.e. fasting plasma glucose level, 5.6–6.9 mmol/L, plasma glucose level 2 h after a 75-g oral glucose load, 7.8–11.0 mmol/L, and glycated hemoglobin level, 5.7–6.4%) and those with no diagnostic criteria for diabetes to receive 4000 IU/day of vitamin D_3 or placebo, regardless of the baseline serum 25(OH)D level. After a median follow up of 2.5 years, vitamin D supplementation was not associated with a significantly lower risk of diabetes when compared with placebo. Nevertheless, in a subgroup of prediabetic individuals with severe vitamin D deficiency, i.e. 25(OH)D <12 ng/ml, vitamin D supplementation aimed to reach normal 25(OH)D levels and reduce the risk of progression from prediabetes to diabetes. This suggests that the benefits (reduction in progression from prediabetes to diabetes) may be achieved in individuals with low basal circulating 25(OH)D, whereas subjects with higher pretreatment

serum 25(OH)D levels do not obtain this preventive benefit. It seems that there is no straight relationship between higher serum 25(OH)D (beyond 30 ng/ml) and the reduction of diabetes risk.

Vitamin D and muscle function

Skeletal muscle function is under the direct influence of vitamin D, vitamin D receptors, and the 1-α-hydroxylase enzyme (CYP27B1). Indeed, the bioactive hormone $1,25(OH)_2D_3$ is produced and is present in the skeletal muscle.[42] Low muscle strength rises from 7.1% in women in their 40s to 79.4% in their 80s, and sarcopenia increases from 6.7% to 58.1% for the same ages. Frailty increases from <1% under age 60 years to 39.5% in women in their 80s.[43]

Muscle strength was measured in postmenopausal women aged <65 years (mean age 57.3 ± 3.7 years) who had normal 25(OH)D levels (≥30 ng/ml) and no physical disabilities, with a mean age at menopause of 50.5 ± 2.2 years and a mean BMI of 24.9 ± 3.8.[44] A total of 12.2% of women were diagnosed with dynapenia using a cut-off value of <20 kg in the hand-grip strength (HGS) test. There was a weak inverse correlation between grip strength and age, and an earlier age at menopause onset was associated with an increased risk for dynapenia.[44] In addition, HGS is associated with increased femoral neck and total lumbar spine BMD in premenopausal and postmenopausal women.[45]

Subjects aged 65 years or older with 25(OH)D deficiency, i.e. serum 25(OH)D <20 ng/ml, were about two times more likely to be frail compared with individuals with serum 25(OH)D status ≥20 ng/ml, whereas there were no associations between the pre-frail state and serum 25(OH)D status.[46] Using different tests, there are other studies that confirmed a correlation between low serum 25(OH)D and low muscle function.[47] In addition, older women with insufficient 25(OH)D were more frail than women with sufficient 25(OH)D.[48] Therefore, it seems reasonable to supplement women with vitamin D in order to prevent such a negative clinical condition. However, evidence that such intervention can be preventive is still lacking.

There are conflicting results concerning the effect of vitamin D supplementation on muscle strength. The Beaudart *et al.*[49] meta-analysis reported in 2014 a small significant positive effect of vitamin D supplementation on muscle strength without effect on muscle mass or muscle power. The use of low-dose vitamin D supplementation in subjects at high risk of having knee osteoarthritis free from frailty (followed up for 8 years) was not associated with any decreased risk of frailty during the follow up.[50] However, another later meta-analysis[51] reported that serum 25(OH)D levels were lower in fallers compared with non-fallers, and the risk of falls was inversely associated with serum 25(OH)D levels.

Osteoporosis and sarcopenia are closely related and both probably increase fall and fracture risk. In community-dwelling older adults (69.6% women) with a median age of 76 years (interquartile range 70–81 years), osteoporosis prevalence increased from 47.6% in non-sarcopenic individuals to 65.5% in those with probable sarcopenia, and 78.1% in those with confirmed sarcopenia ($p < 0.05$).[52] After adjusting for age, sex, and vitamin D status in multivariate models, osteoporosis was significantly associated with a greater risk of confirmed sarcopenia. The number of fragility fractures was also significantly higher in those with confirmed sarcopenia *versus* those without, but this finding did not remain significant in the adjusted models.[52]

Iolascon *et al.*[53] reported the results of a multicenter retrospective study regarding the influence of vitamin D deficiency on muscle performance in older postmenopausal women (mean age 66.9 ± 8.5 years). A cut-off value of 30 ng/ml for serum 25(OH)D was used to define sufficient and insufficient vitamin D levels. There were significant differences in terms of appendicular lean mass/BMI ratio, total fat mass, visceral adipose tissue, HGS, knee isometric extension strength (KES), short physical performance battery (SPPB), and percentage of people with a 4-m gait speed (4MGS) (all $p < 0.01$). In addition, there were significant correlations between serum 25(OH)D status and HGS, KES, and SPPB sit to stand.

Iolascon *et al.*[54] also reported in a prospective study the effectiveness of calcifediol (800 IU as 4 oral drops/day) for a 6-month period on serum 25(OH)D levels, appendicular muscle strength, physical performance, and prevention of falls in women of similar age with osteoporosis and/or serum 25(OH)D <30 ng/ml. After 6 months,

calcifediol treatment produced a significant increase in 25(OH)D serum levels ($p < 0.001$), appendicular muscle strength ($p < 0.001$), and physical performance at SPPB and 4MGS ($p < 0.01$). Equally at 6 months, the percentage of fallers was lower, although not significant, whereas there was a significant reduction both in the percentage of recurrent fallers and the mean number of falls ($p < 0.001$ and $p = 0.020$, respectively).

Pain and lumbar disc degeneration

Chronic low back pain has been associated with vitamin D deficiency and related to osteomalacia.[55,56] The relationship between low back pain in postmenopausal women and lumbar pain with disc degeneration has recently been studied.[57] Postmenopausal women (mean age 65.6 ± 10.1 years) with severe low serum 25(OH)D levels (<10 ng/ml) have higher pain scores, as assessed on a visual analog scale, lower BMD, and more severe lumbar disc degeneration in the lumbosacral region (although less in the upper lumbar region). In addition, after adjusting for different confounding factors, low BMD was associated with a higher incidence of moderate to severe back pain.

Vitamin D supplementation in midlife and older women

A wide variety of vitamin D supplements (dosages/frequencies) is used among mid-aged and older women. Many scientific societies have given recommendations for midlife and older women. The majority suggest supplementation if serum 25(OH)D is <20 ng/ml following the US Institute of Medicine[58] criteria, whereas other organizations recommend supplementation for women with lower levels (12 ng/ml).[59,60] Dietary recommendations are not always correctly followed, adequate foods are few and sometimes expensive, or simply compliance is difficult when the daily diet is monotonous.[61] Therefore, surveillance results have indicated that a vitamin D diet is not sufficient to maintain adequate vitamin D status. On the other hand, food fortification needs national or regional approval by political authorities, which is debatable and not unanimously accepted.[62] The current Western lifestyle is associated with a low vitamin D diet, low sunlight exposure, and spending a great deal of time indoors. Therefore the standard recommended vitamin D supplementation is not enough or borderline in the recommendations.[63]

In the majority of recommendations both vitamin D_3 (cholecalciferol) and D_2 (ergocalciferol) are considered equivalent in terms of clinical and metabolic effects. However, the area under the curve indicates that it is some 28% higher for cholecalciferol and with a longer half-life than for ergosterol.[64] Supplementation with calcifediol 25(OH)D is another alternative having better advantages.[65,66] Calcifediol is more soluble than cholecalciferol and has good intestinal absorption and high affinity for the vitamin D-binding protein. The balance for oral administration is more effective for calcifediol (3–5 times more intestinal absorption), however, there are fewer available studies than for cholecalciferol.[67] A recent RCT comparing vitamin D_3 (400 IU/day) and calcifediol (200 IU/day, 400 IU/day, or 600 IU/day) for a period of 24 weeks demonstrated that vitamin D_3 increased 25(OH)D levels to 28 ng/ml within 16 weeks, while supplementation with 400 IU/day or 600 IU/day calcifediol caused 25(OH)D levels to surpass >30 ng/ml in 8 weeks and 4 weeks, respectively. During the study period, this trial did not report cases of hypercalcemia.[65] Hence, it seems that this treatment was well accepted by elderly subjects and there were no significant risks of hypercalcemia or other health aspects.

Despite the high prevalence of low vitamin D status, it seems that in some countries in the last 10–15 years there has been an increase in global mean vitamin D levels. For instance, in the Study of Women's Health Across the Nation there was an increase in mean vitamin D values and a reduction in the prevalence of low vitamin D status.[68]

The long-term effects of vitamin D supplementation are a major clinical concern. The RCT Calgary Vitamin D study recently reported the effects of vitamin D_3 supplementation of 400 UI/day, 4000 UI/day, or 10,000 UI/day on healthy adults aged 55–70 years (mean age 64 ± 4 years) of which 51% were women.[69] Calcium supplementation was initiated when dietary calcium intake was less than 1200 mg/day. The safety profile of vitamin D supplementation was similar for the three doses. Hypercalcemia occurred more frequently with higher doses of vitamin D, but

was rare, mild, and transient.[69] Also, the three proposed dosages produced the same changes in bone strength at either the radius or tibia, suggesting that vitamin D supplementation at high doses does not have additional benefits for bone health.[70]

Malihi *et al.*[71] reported the results of a double-blind RCT regarding the effects of high doses of vitamin D supplementation (monthly doses of 100,000 IU of vitamin D_3 or placebo) in adults (50–84 years) for a median of 3.3 years (range 2.5–4.2 years). Despite a slightly higher incidence of recurrent adverse events in the vitamin D exposed group, this increase was not significant when compared with placebo after adjustment for age, gender, and ethnicity. In addition, in this cohort the incidence of kidney stone events or hypercalcemia was similar to that observed in the placebo group.[72] Despite these RCTs, the available evidence suggests that excessive (very high) circulating levels of 25(OH)D are not always associated with better health outcomes. Vitamin D supplementation should be individualized according to the characteristics of each patient and the aimed clinical outcome.

Healthy women without specific risks may regularly expose themselves to sunlight, without sunscreen for 15 min, 3–4 times per week in the middle of the day to generate healthy endogenous vitamin D levels. Other women may prefer to use the recommended daily dose of 600 IU of cholecalciferol for those aged up to 70 years, and 800 IU for those aged 71 years or more.[1]

Conclusion

There are several prevalent conditions in postmenopausal women associated with low serum 25(OH)D; hence, normalization of 25(OH)D levels may improve those conditions. Despite this, an excessive increase of 25(OH)D levels is not associated with better clinical results. In postmenopausal women low vitamin D levels are associated with hypersecretion of PTH and vitamin D supplementation reduces serum PTH and increases 25(OH)D levels. Increased PTH is associated with increased cortical bone porosity. Women who are not vitamin D deficient would not obtain benefit from vitamin D supplementation. However, elderly women that do not receive active bone- forming treatments and have osteoporosis and low serum vitamin D should receive vitamin D supplementation as an anti-fracture agent. Meta-analysis of RCTs indicates that vitamin D and calcium supplementation produce a significant reduction of fracture risk (any and hip).

Insufficient and deficient 25(OH)D levels are associated with an increased risk of MetS in postmenopausal women and vitamin D supplementation significantly reduces triglyceride, insulin, and HOMA-IR values. BMI is a good predictor of low 25(OH)D status in women and the vitamin D supplementation dose should be adjusted according to BMI. In addition, concomitant vitamin D and calcium supplementation may reduce central fat deposits. Obese women may need higher vitamin D supplementation doses to normalize their circulating levels. In women with prediabetes and low 25(OH)D levels, vitamin D supplementation may improve insulin sensitivity. However, those with normal 25(OH)D levels do not obtain this preventive effect. It seems that there is no direct relationship between higher 25(OH)D levels beyond 30 ng/ml and the reduction of diabetes risk.

Subjects aged 65 years who have low serum 25(OH)D levels have low muscle function and are more frail. The number of fragility fractures is higher among those with confirmed sarcopenia. Calcifediol treatment increases 25(OH)D levels and physical performance while reducing the risks of falls.

Vitamin D supplementation can be performed with cholecalciferol or calcifediol. In postmenopausal women, cholecalciferol (vitamin D_3) and calcifediol supplementation should be used at different and sufficient doses and in accordance with the particular individual needs, body weight, health issues, or risks to be prevented. Calcifediol dosage should be adjusted to approximately one third of the cholecalciferol dose.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Faustino R. Pérez-López https://orcid.org/0000-0002-2801-416X

Author contribution(s)

Faustino Perez-Lopez: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Supervision; Writing-original draft.

Peter Chedraui: Formal analysis; Methodology; Writing-review & editing.

Stefan Pilz: Formal analysis; Methodology; Supervision; Validation; Writing-review & editing.

References

1. Pérez-López FR, Brincat M, Erel CT, *et al*. European menopause and andropause society position statement: vitamin D and postmenopausal health. *Maturitas* 2012; 71: 83–88.
2. Pérez-López FR, Chedraui P and Fernández-Alonso AM. Vitamin D and aging: beyond calcium and bone metabolism. *Maturitas* 2011; 69: 27–36.
3. Altieri B, Cavalier E, Bhattoa HP, *et al*. Vitamin D testing: advantages and limits of the current assays. *Eur J Clin Nutr* 2020; 74: 231–247.
4. Giustina A, Adler RA, Binkley N, *et al*. Consensus statement from 2nd international conference on controversies in vitamin D. *Rev Endocr Metab Disord* 2020; 21: 89–116.
5. Nahas-Neto J, Cangussu LM, Orsatti CL, *et al*. Effect of isolated vitamin D supplementation on bone turnover markers in younger postmenopausal women: a randomized, double-blind, placebo-controlled trial. *Osteoporos Int* 2018; 29: 1125–1133.
6. Bislev LS, Langagergaard Rødbro L, Rolighed L, *et al*. Bone microstructure in response to vitamin D3 supplementation: a randomized placebo-controlled trial. *Calcif Tissue Int* 2019; 104: 160–170.
7. Osima M, Borgen TT, Lukic M, *et al*. Serum parathyroid hormone is associated with increased cortical porosity of the inner transitional zone at the proximal femur in postmenopausal women: the Tromsø study. *Osteoporos Int* 2018; 29: 421–431.
8. Reid IR. Vitamin D effect on bone mineral density and fractures. *Endocrinol Metab Clin N Am* 2017; 46: 935–945.
9. Jorde R and Grimnes G. Vitamin D and health: the need for more randomized controlled trials. *J Steroid Biochem Mol Biol* 2015; 148; 269–274.
10. Jorde R, Stunes AK, Kubiak J, *et al*. Effects of vitamin D supplementation on bone turnover markers and other bone-related substances in subjects with vitamin D deficiency. *Bone* 2019; 124: 7–13.
11. LeBoff MS, Chou SH, Murata EM, *et al*. Effects of supplemental vitamin D on bone health outcomes in women and men in the VITamin D and omegA-3 triaL (VITAL). *J Bone Miner Res*. Epub ahead of print 30 January 2020. DOI: 10.1002/jbmr.3958.
12. Manson JE, Cook NR, Lee IM, *et al*. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019; 380: 33–44.
13. Weaver CM. Calcium supplementation: is protecting against osteoporosis counter to protecting against cardiovascular disease? *Curr Osteoporos Rep* 2014; 12: 211–218.
14. Bolland MJ, Grey A and Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol* 2018; 6: 847–858.
15. Gallagher JC. Vitamin D and bone density, fractures, and falls: the end of the story? *Lancet Diabetes Endocrinol* 2018; 6: 834–835.
16. Binkley NC and Wiebe DA. It's time to stop prescribing ergocalciferol. *Endocr Pract* 2018; 24: 1099–1102.
17. Binkley N. *Clinical evaluation of vitamin D (and metabolite) assay results*. Presented at The AAAC/The Endocrine Society Joint Symposium, 6 August 2019, Anaheim, CA.
18. Pérez-López FR, Chedraui P, Pérez-Roncero GR, *et al*.; Health Outcomes and Systematic Analyses (HOUSSAY) Project. Effectiveness of the cervical pessary for the prevention of preterm birth in singleton pregnancies with a short cervix: a meta-analysis of randomized trials. *Arch Gynecol Obstet* 2019; 299: 1215–1231.
19. Fassio A, Rossini M and Gatti D. Vitamin D: no efficacy without deficiency. What's new?. *Reumatismo* 2019; 71: 57–61.
20. Mosali P, Bernard L, Wajed J, *et al*. Vitamin D status and parathyroid hormone concentrations influence the skeletal response to zoledronate and denosumab. *Calcif Tissue Int* 2014; 94: 553–559.
21. Prieto-Alhambra D, Pages-Castell A, Wallace G, *et al*. Predictors of fracture while on treatment with oral bisphosphonates: a population-based cohort study. *J Bone Miner Res* 2014; 29: 268–274.

22. Kahwati LC, Weber RP, Pan H, *et al*. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: evidence report and systematic review for the US preventive services task force. *JAMA* 2018; 319: 1600–1612.

23. Yao P, Bennett D, Mafham M, *et al*. Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. *JAMA Netw Open* 2019; 2: e1917789.

24. Zhuang HF, Wang PW, Li YZ, *et al*. Analysis of related factors of brittle hip fracture in postmenopausal women with osteoporosis. *Orthop Surg* 2020; 12: 194–198.

25. Black DM and Rosen CJ. Clinical practice. Postmenopausal osteoporosis. *N Engl J Med* 2016; 374: 254–262.

26. Barrionuevo P, Kapoor E, Asi N, *et al*. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab* 2019; 104: 1623–1630.

27. Hernandez AV, Pérez-López FR, Piscoya A, *et al*. Comparative efficacy of bone anabolic therapies in women with postmenopausal osteoporosis: a systematic review and network meta-analysis of randomized controlled trials. *Maturitas* 2019; 129: 12–22.

28. Schmitt EB, Nahas-Neto J, Bueloni-Dias F, *et al*. Vitamin D deficiency is associated with metabolic syndrome in postmenopausal women. *Maturitas* 2018; 107: 97–102.

29. Ferreira PP, Cangussu L, Bueloni-Dias FN, *et al*. Vitamin D supplementation improves the metabolic syndrome risk profile in postmenopausal women. *Climacteric* 2020; 23: 24–31.

30. Huang H, Guo J, Chen Q, *et al*. The synergistic effects of vitamin D and estradiol deficiency on metabolic syndrome in Chinese postmenopausal women. *Menopause* 2019; 26: 1171–1177.

31. Razmjou S, Abdulnour J, Bastard JP, *et al*. Body composition, cardiometabolic risk factors, physical activity, and inflammatory markers in premenopausal women after a 10-year follow-up: a MONET study. *Menopause* 2018; 25: 89–97.

32. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, *et al*. Fat mass changes during menopause: a metaanalysis. *Am J Obstet Gynecol* 2019; 221: 393–409.e50.

33. Delle Monache S, Di Fulvio P, Iannetti E, *et al*. Body mass index represents a good predictor of vitamin D status in women independently from age. *Clin Nutr* 2019; 38: 829–834.

34. Kroll MH, Bi C, Garber CC, *et al*. Temporal relationship between vitamin D status and parathyroid hormone in the United States. *PLoS One* 2015; 10: e0118108.

35. Hyppönen E and Boucher BJ. Adiposity, vitamin D requirements, and clinical implications for obesity-related metabolic abnormalities. *Nutr Rev* 2018; 76: 678–692.

36. Lotito A, Teramoto M, Cheung M, *et al*. Serum parathyroid hormone responses to vitamin D supplementation in overweight/obese adults: a systematic review and meta-analysis of randomized clinical trials. *Nutrients* 2017; 9: pii: E241.

37. Ekwaru JP, Zwicker JD, Holick MF, *et al*. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. *PLoS One* 2014; 9: e111265.

38. Valladares T, Cardoso MR and Aldrighi JM. Higher serum levels of vitamin D are associated with lower blood glucose levels. *Menopause* 2019; 26: 781–784.

39. Yu L, Zhai Y and Shen S. Association between vitamin D and prediabetes: a PRISMA-compliant meta-analysis. *Medicine (Baltimore)* 2020; 99: e19034.

40. Niroomand M, Fotouhi A, Irannejad N, *et al*. Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. *Diabetes Res Clin Pract* 2019; 148: 1–9.

41. Pittas AG, Dawson-Hughes B, Sheehan P, *et al*.; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* 2019; 381: 520–530.

42. Pojednic RM and Ceglia L. The emerging biomolecular role of vitamin D in skeletal muscle. *Exerc Sport Sci Rev* 2014; 42: 76–81.

43. Blümel JE, Salinas C, Danckers L, *et al*. Muscle health in hispanic women. REDLINC VIII. *Climacteric* 2020; 23: 184–191.

44. Garcia-Alfaro P, Garcia S, Rodríguez I, *et al*. Factors related to muscle strength in postmenopausal women aged younger than 65 years with normal vitamin D status. *Climacteric* 2019; 22: 390–394.

45. Luo Y, Jiang K and He M. Association between grip strength and bone mineral density in general

US population of NHANES 2013-2014. *Arch Osteoporos* 2020; 15: 47.

46. Vaes AMM, Brouwer-Brolsma EM, Toussaint N, *et al*. The association between 25-hydroxyvitamin D concentration, physical performance and frailty status in older adults. *Eur J Nutr* 2019; 58: 1173–1181.

47. Kitsu T, Kabasawa K, Ito Y, *et al*. Low serum 25-hydroxyvitamin D is associated with low grip strength in an older Japanese population. *J Bone Miner Metab* 2020; 38: 198–204.

48. Buchebner D, Bartosch P, Malmgren L, *et al*. Association between vitamin D, frailty, and progression of frailty in community-dwelling older women. *J Clin Endocrinol Metab* 2019; 104: 6139–6147.

49. Beaudart C, Buckinx F, Rabenda V, *et al*. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014; 99: 4336–4345.

50. Bolzetta F, Stubbs B, Noale M, *et al*. Low-dose vitamin D supplementation and incident frailty in older people: an eight year longitudinal study. *Exp Gerontol* 2018; 101: 1–6.

51. Annweiler C and Beauchet O. Questioning vitamin D status of elderly fallers and nonfallers: a meta-analysis to address a 'forgotten step'. *J Intern Med* 2015; 277: 16–44.

52. Kirk B, Phu S, Brennan-Olsen SL, *et al*. Associations between osteoporosis, the severity of sarcopenia and fragility fractures in community-dwelling older adults. Eur Geriatr Med. *Epub ahead of print* 11 March 2020. DOI: 10.1007/s41999-020-00301-6.

53. Iolascon G, Mauro GL, Fiore P, *et al*. Can vitamin D deficiency influence muscle performance in postmenopausal women? A multicenter retrospective study. *Eur J Phys Rehabil Med* 2018; 54: 676–682.

54. Iolascon G, Moretti A, de Sire A, *et al*. Effectiveness of calcifediol in improving muscle function in post-menopausal women: a prospective cohort study. *Adv Ther* 2017; 34: 744–752.

55. Al Faraj S and Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine* 2003; 28: 177–179.

56. Rkain H, Bouaddi I, Ibrahimi A, *et al*. Relationship between vitamin D deficiency and chronic low back pain in postmenopausal women. *Curr Rheumatol Rev* 2013; 9: 63–67.

57. Xu HW, Yi YY, Zhang SB, *et al*. Does vitamin D status influence lumbar disc degeneration and low back pain in postmenopausal women? A retrospective single-center study. *Menopause*. Epub ahead of print 10 February 2020. DOI: 10.1097/GME.0000000000001499.

58. Institute of Medicine. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press, 2011.

59. Reid IR, Horne AM, Mihov B, *et al*. Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial. *J Intern Med* 2017; 282: 452–460.

60. Macdonald HM, Reid IR, Gamble GD, *et al*. 25-hydroxyvitamin D threshold for the effects of vitamin D supplements on bone density: secondary analysis of a randomized controlled trial. *J Bone Miner Res* 2018; 33: 1464–1469.

61. Cashman KD. Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. *Calcif Tissue Int* 2020; 106: 14–29.

62. Pilz S, März W, Cashman KD, *et al*. Rationale and plan for vitamin D food fortification: a review and guidance paper. *Front Endocrinol (Lausanne)* 2018; 9: 373.

63. Mitchell DM, Henao MP, Finkelstein JS, *et al*. Prevalence and predictors of vitamin D deficiency in healthy adults. *Endocr Pract* 2012; 18: 914–923.

64. Oliveri B, Mastaglia SR, Brito GM, *et al*. Vitamin D3 seems more appropriate than D2 to sustain adequate levels of 25OHD: a pharmacokinetic approach. *Eur J Clin Nutr* 2015; 69: 697–702.

65. Vaes AMM, Tieland M, de Regt MF, *et al*. Dose-response effects of supplementation with calcifediol on serum 25-hydroxyvitamin D status and its metabolites: a randomized controlled trial in older adults. *Clin Nutr* 2018; 37: 808–814.

66. López-Baena MT, Pérez-Roncero GR, Pérez-López FR, *et al*. Vitamin D, menopause, and aging: Quo vadis? *Climacteric* 2020; 23: 123–129.

67. Cesareo R, Falchetti A, Attanasio R, *et al*. Hypovitaminosis D: is it time to consider the use of calcifediol? *Nutrients* 2019; 11: pii: E1016.

68. Mitchell DM, Ruppert K, Udupa N, *et al*. Temporal increases in 25-hydroxyvitamin D in midlife women: longitudinal results from the study of women's health across the nation. *Clin Endocrinol (Oxf)* 2019; 91: 48–57.

69. Billington EO, Burt LA, Rose MS, *et al*. Safety of high-dose vitamin D supplementation: secondary analysis of a randomized controlled trial. *J Clin Endocrinol Metab* 2020; 105: dgz212.

70. Burt LA, Billington EO, Rose MS, *et al*. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA* 2019; 322: 736–745. *Erratum* in *JAMA* 2019; 322: 1925.

71. Malihi Z, Lawes CMM, Wu Z, *et al*. Monthly high-dose vitamin D3 supplementation and self-reported adverse events in a 4-year randomized controlled trial. *Clin Nutr* 2019; 38: 1581–1587.

72. Malihi Z, Lawes CMM, Wu Z, *et al*. Monthly high-dose vitamin D supplementation does not increase kidney stone risk or serum calcium: results from a randomized controlled trial. *Am J Clin Nutr* 2019; 109: 1578–1587.