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EMAS position statement: Vitamin D and postmenopausal health

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ABSTRACT

Introduction: There is emerging evidence on the widespread tissue effects of vitamin D.
Aims: To formulate a position statement on the role of vitamin D in postmenopausal women.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: Epidemiological and prospective studies have related vitamin D deficiency with not only osteoporosis but also cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease. However the evidence is robust for skeletal but not nonskeletal outcomes where data from large prospective studies are lacking. The major natural source of vitamin D is cutaneous synthesis through exposure to sunlight with a small amount from the diet in animal-based foods such as fatty fish, eggs and milk. Vitamin D status is determined by measuring serum 25-hydroxyvitamin D [25(OH)D] levels. Optimal serum 25(OH)D levels are in the region of 30–90 ng/mL (75–225 nmol/L) though there is no international consensus. Levels vary according to time of the year (lower in the winter), latitude, altitude, air pollution, skin pigmentation, use of sunscreens and clothing coverage. Risk factors for low serum 25(OH)D levels include: obesity, malabsorption syndromes, medication use (e.g. anticonvulsants, antiretrovirals), skin aging, low sun exposure and those in residential care. Fortified foods do not necessarily provide sufficient amounts of vitamin D. Regular sunlight exposure (without sunscreens) for 15 min, 3–4 times a week, in the middle of the day in summer generate healthy levels. The recommended daily allowance is 600 IU/day increasing to 800 IU/day in those aged 71 years and older. Supplementation can be undertaken with either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) with monitoring depending on the dose used and the presence of concomitant medical conditions such as renal disease.

1. Introduction

Vitamin D comprises a group of lipophilic hormones that regulates calcium homeostasis through its actions on the kidney, gastrointestinal tract, skeleton and parathyroid. It plays a pivotal role in maintaining skeletal health. The two major forms are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is produced from ergosterol by several organisms: phytoplankton, invertebrates and fungi in response to ultraviolet (UV) irradiation. The major natural source of vitamin D3 is cutaneous synthesis from 7-dehydrocholesterol through exposure to sunlight with a small amount from the diet in animal-based foods such as fatty fish, eggs and milk. There are wide individual variations in both cutaneous synthesis and gastrointestinal absorption of vitamin D. Two hydroxylations are needed to obtain the bioactive hormone 1,25-dihydroxyvitamin D or calcitriol. In the liver, the first metabolizes vitamin D into 25-hydroxyvitamin D [25(OH)D]

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or calcidiol; and the second produces calcitriol in the kidneys and other tissues [1–5]. Both vitamin D3 and vitamin D2 are synthesized commercially and found in dietary supplements or fortified foods.

Calcitriol stimulates calcium and phosphate absorption and participates in regulating the transcription of a large number of genes. In humans, locally synthesized calcitriol has a wide range of non-calciotropic functions including among others: insulin production, myocardial contraction, immunomodulation, monocyte antimicrobial action, innate immunity, cell proliferation and apoptosis [2,4,6–10].

2. Assessment of vitamin D status

There are many forms of the vitamin D in blood. To identify these compounds liquid chromatography and mass spectrometry are needed to separate active forms from inactive related compounds [11]. Currently the best available indicator of vitamin D status is circulating serum 25(OH)D which is most closely linked to parathyroid function and calcium homeostasis, although biologically less potent than calcitriol. In addition, serum 25(OH)D is taken up by target cells and would determine the risk of age-related chronic diseases more directly than calcitriol. Adequate plasma 25(OH)D levels seem to be between 30 ng/mL and 90 ng/mL (1 ng/mL = 2.5 nmol/L) at which parathyroid hormone (PTH) secretion and calcium resorption from bone are minimized, and intestinal calcium absorption is stabilized though there is no international consensus [2,12].

Hypovitaminosis D includes three categories according to cut-off values: insufficiency if serum 25(OH)D levels are between 20 and 29.99 ng/mL, deficiency below 20 ng/mL, and severe deficiency below 10 ng/mL [2,4,12,13] but again there is controversy about absolute levels. Even taking into account sunny regions nearly 70% of the European population displays suboptimal levels (35% had insufficient, 25% deficient and 10% severely deficient levels) [13–17].

Severe vitamin deficiency affects bone health and muscle function, leading to rickets, osteomalacia and myopathy [18,19]. Low vitamin D levels are also prevalent among osteoporotic postmenopausal women [20] and have been associated to other diseases which include among others cardiovascular disease (CVD), cancer, diabetes, infections and neurological diseases [2,4,9,10].

3. Risk factors for hypovitaminosis D

General risk factors for hypovitaminosis D include low UV-induced skin synthesis, dark skin, skin aging, poor dietary intake, obesity, malabsorption, and certain medications (e.g. anticonvulsant, antiretrovirals). Furthermore low plasma vitamin D levels are more common in women than in men [4,9,13].

Since vitamin D synthesis depends on UV action on the keratinocytes, its deficiency is common especially in individuals with poor sunlight exposure such as those living at higher latitudes or residential care homes. Thus, latitude, altitude, time of the year (winter), time of the day (early morning and late afternoon), amount of exposed skin, skin pigmentation, sun protection (shade, extensive clothing cover, sunscreen use), and air pollution may interference with vitamin D skin synthesis [1,2,21]. People with natural dark skin produce half to a fifth of vitamin D than those with fair (white) for a similar level of sun exposure [22]. The use of sunscreens may drastically reduce cutaneous synthesis. In addition, skin aging is associated with lower 7-dehydrocholesterol levels [2,4,16] which is the vitamin D precursor required for skin photosynthesis.

25(OH)D is stored in adipose tissue, and obesity is a risk factor for vitamin D deficiency [23]. Patients with malabsorption (e.g., coeliac disease, Crohn's disease, gastrointestinal bypass surgery, cystic fibrosis with pancreatic insufficiency) may have difficulties in absorbing vitamin D [24] whereas those with renal insufficiency may have an increased urinary loss of 25(OH)D and limited capacity for calcitriol synthesis [2,25]. Chronic use of certain drugs, such as anticonvulsants, may reduce 25(OH)D levels due to accelerated inactivation of calcitriol caused by increased expression of CYP24 [26]. Antiretroviral agents may increase the conversion of 25(OH)D to calcitriol and accelerate its catabolism [27].

4. Conditions associated to low vitamin D status

4.1. Vitamin D and mortality

A systematic review of prospective studies reported a two- to five-fold higher mortality risk among subjects with lower serum 25(OH)D levels [28]. A systematic review reported the effect of supplementation with vitamin D, calcium, or both on subsequent cardiovascular events. This review concluded that vitamin D supplementation may reduce cardiovascular risk while calcium supplementation has minimal cardiovascular effects [29].

The effect of vitamin D supplementation has been studied in 50 randomised trials which have compared vitamin D treatment (median of two years) versus placebo or no intervention. Vitamin D treatment decreased mortality, although only vitamin D3 decreased mortality significantly whereas other related compounds did not. It has been estimated that 161 individuals should be treated to prevent one death. Vitamin D3 associated with calcium treatment, increases the risk of nephrolithiasis [30]. A more recent systematic review and meta-analysis of randomised controlled trials related with bone health, reported that vitamin D was not significantly associated to outcomes such as death, myocardial infarction and stroke [31].

4.2. Vitamin D, bone metabolism and fractures

Osteoporotic fractures are common and a serious health problem among postmenopausal women. Adequate levels of vitamin D may contribute not only to skeletal conservation but also to neuromuscular function [20]. Fracture risk significantly increases across quartiles of serum 25(OH)D levels, and is independent of other factors. Thus, women with the lowest 25(OH)D concentrations (<47.6 nmol/L, 19 ng/mL) had higher fracture risk than do those with the highest levels (>70.6 nmol/L, 28.2 ng/mL) [32].

Supplementation with vitamin D3 (>700 IU/day) and calcium produces benefits on bone mineral density (BMD) and reduces the risk of fractures as compared to placebo [33]. A meta-analysis including double blind randomised controlled trials studying individuals with a mean age of 65 years or older who received vitamin D (700–1000 IU/day) had a 19% reduction in the risk of falls. If serum 25(OH)D levels reached 60 nmol/L (24 ng/mL) or more there was a 23% fall reduction rate. However, daily vitamin D doses of less than 700 IU or serum 25(OH)D levels < 60 nmol/L did not reduce the risk of falls [34].

The effectiveness of 800 IU day of vitamin D3, with or without calcium, at increasing BMD and preventing fractures in postmenopausal women has been assessed in a meta-analysis. The results suggest that vitamin D reduces fracture incidence of osteoporotic non-vertebral, hip, and other locations. In addition, vitamin D treatment benefits related to fractures are greater than those obtained by calcium alone [35]. A more recent systematic review that included more than 45,000 subjects, mostly elderly and female, reported that vitamin D treatment significantly reduces the risk of falls. This effect is more important in individuals with low vitamin

D status and in studies in which vitamin D was complemented with calcium [36].

Vitamin D insufficiency may also be an important factor in the diminished response to bisphosphonates seen in clinical practice. Thus, postmenopausal women with 25(OH)D blood levels above 33 ng/mL (lower levels were considered as insufficient) were 7 times more likely to respond to osteoporosis therapy than those with lower levels. In this study, 16.8% of responders had insufficient serum 25(OH)D levels as compared to 54.9% among those non-responders to bisphosphonate treatment [37].

It seems that adequate amounts of calcium and vitamin D may prevent BMD loss, and increase muscle strength and reduce risk of falls. When osteoporosis is present, vitamin D supplements should be added to antiresorptives or other appropriate treatments.

4.3. Vitamin D, physical fitness and frailty

Muscle mass and strength declines in aged individuals and vitamin D status may contribute to this involution [13]. Reduced muscle strength increases the risk of falls in older women and is associated with low serum 25(OH)D levels [38,39]. Vitamin D deficiency predominantly affects the weight-bearing antigravity muscles of the lower limbs which are pivotal for postural balance and walking [12]. In healthy postmenopausal women, serum 25(OH)D levels have been related to physical fitness, and is a common factor in different indices such as android fat mass, lean mass, balance and handgrip strength [40]. In individuals aged 65 and older, vitamin D levels were inversely associated with poor physical performance [41].

The effect of vitamin D supplementation in adults, with or without calcium, on muscle strength has also been studied in a systematic review and meta-analysis of 17 randomised controlled trials. Pooled data showed a considerable effect of vitamin D supplementation over hip muscle strength only in subjects with serum 25(OH)D levels <25 nmol/L (10 ng/mL) [42]. Thus vitamin D may be involved in maintaining muscle strength.

4.4. Cardiovascular disease risk factors and vitamin D

Hypovitaminosis D has been associated with a series of risk factors, such as hypertension, glucose and lipid metabolism, obesity, peripheral artery disease, coronary artery disease, myocardial infarction, heart failure and stroke [43,44].

In young adult women baseline 25(OH)D insufficiency (<80 nmol/L, 32 ng/mL) was significantly associated to a higher risk of systolic hypertension [45]. A meta-analysis reported that serum 25(OH)D levels were inversely associated to hypertension risk. In a dose–response meta-analysis an increment of 16 ng/mL (40 nmol/L) in serum 25(OH)D levels was significantly associated with reduced blood pressure levels [46].

In adults, serum 25(OH)D levels are inversely associated with ultrasound measured intima–media and maximal carotid plaque thickness. Calcium, PTH and calcitriol were not associated with measures of carotid health [47].

The use of calcium supplements, with and without vitamin D, has been associated to cardiovascular events in a reanalysis of the Women's Health Initiative cohort and a meta-analysis [48,49]. In this study calcium supplements, with or without vitamin D (400 IU/day), increased the risk of cardiovascular events, especially myocardial infarction, suggesting that the excess of calcium supplementation may have negative consequences on cardiovascular health. Therefore, there is now concern about giving calcium in women whose diet is replete as well as vitamin D.

4.5. Diabetes mellitus and vitamin D

Vitamin D is involved in the regulation of insulin secretion, as suggested by the presence of vitamin D receptors in pancreatic islets. In adults without diabetes mellitus, serum 25(OH)D levels are inversely associated to fasting glucose and insulin levels, and positively associated to insulin sensitivity index and high density lipoprotein cholesterol levels [50]. In a US cross-sectional multicenter cohort study, only diabetes was significantly associated with lower 25(OH)D and calcitriol levels [51].

Subjects who developed type 2 diabetes in a 5-year period, had lower serum 25(OH)D as compared to those who remained free of the disease. It was estimated that the diabetes risk would be reduced by 24% for each 25 nmol/L (10 ng/mL) increment in serum 25(OH) levels. In addition, serum 25(OH)D levels were positively associated to insulin sensitivity. High calcium diet content was not associated to diabetes risk [52].

4.6. Vitamin D, breast cancer and colon cancer

Vitamin D induces cell differentiation and inhibits proliferation and metastatic potential and hence may be considered as an antiapoptotic agent [53,54]. A meta-regression analysis found that a 10 ng/mL (25 nmol/L) increase in serum 25(OH) D was significantly associated to a lower risk for colorectal and breast cancer [55]. Therefore, it seems that 25(OH)D levels display a consistent inverse relationship with these two types of cancer.

A meta-analysis of observational studies reported an association between serum 25(OH)D levels and breast cancer. The summary of relative risks for a 20 ng/mL (50 nmol/L) increase of serum 25(OH)D levels and decreased breast cancer risk were significant for included case–control studies, nested case–control studies and both combined study designs [56]. Another meta-analysis reported a significant inverse relationship between vitamin D intake and breast cancer risk. In addition, the highest quartile of serum 25(OH)D levels was associated to a 45% decrease in breast cancer risk as compared to the lowest quartile. On the other hand, women in the highest quartile of calcium intake displayed a 19% reduction of breast cancer risk as compared to the lowest quartile [57].

Low serum 25(OH)D levels measured before chemotherapy were correlated to more deaths among postmenopausal women diagnosed with breast cancer and followed up for 5.8 years. Hence, a 10 nmol/L (4 ng/mL) decrement in serum 25(OH)D levels was associated with an 8% increase in death risk and a 14% increase in risk of distant metastasis [58]. These results are similar to those reported by Goodwin et al. [59] in women with early breast cancer followed up for a mean of 11.6 years.

In one study postmenopausal women were randomly assigned to receive 1400–1500 mg calcium/day alone, calcium plus 1100 IU vitamin D/day, or placebo. Cancer incidence was significantly lower in women receiving the combined treatment as compared to the placebo group. Multiple logistic regression analysis determined that treatment with either calcium or calcium/vitamin D were significantly independent predictors of cancer risk [60]. In a pooled analysis of case–control studies, the estimated risk in the highest versus the lowest quartile across all 11 studies was significant. In addition, serum 25(OH)D levels of 47 ng/mL (117.5 nmol/L) were associated to a 50% lower risk of breast cancer [61].

Among colorectal cancer patients, serum 25(OH)D postdiagnosis levels are predictive of mortality. Thus, individuals with the highest serum 25(OH)D levels had a significant reduction in both cancer-related and overall mortality as compared to those with the lowest levels [62]. Serum 25(OH)D concentrations have a strong and significant inverse linear dose–response association with risk of colorectal cancer. Thus, patients in the highest 25(OH)D quintile had a 40% lower risk of colorectal cancer than those in the lowest

quintile [63]. A meta-analysis of eight prospective studies of circulating levels of 25(OH)D and colon and rectal cancers, including the Physicians' Health Study, found an inverse association between circulating 25(OH)D levels and colorectal cancer, with a stronger association for rectal cancer [64]. Another recent systematic review and meta-analysis of prospective studies, reported that vitamin D intake and serum 25(OH)D levels had inverse associations with colorectal cancer. Thus, both supplemental and total vitamin D intake and 25(OH)D status were inversely associated with colon cancer risk [65].

4.7. Vitamin D and infection

Susceptibility to infection has been related to vitamin D status, including upper respiratory tract viral infections. A secondary analysis of the Third National Health and Nutrition Examination Survey found that serum 25(OH)D levels were inversely associated with recent upper respiratory tract infection and that the association may be stronger in those with respiratory tract diseases such as asthma and chronic obstructive pulmonary disease [66]. A three year randomised clinical trial of vitamin D supplementation performed among postmenopausal women at great risk for vitamin D deficiency found a significant protective effect against respiratory infections [67].

A recent prospective study in patients with pneumonia reported that severe 25(OH)D deficiency was related to higher mortality rates when compared to those with sufficient levels. Increased mortality was not related to co-morbid conditions, age or severity of the acute illness [68].

4.8. Vitamin D and the brain function

Receptors for vitamin D, 1-α-hydroxylase and PTH are widely distributed in the human brain, and there are clinical data suggesting that vitamin D may affect cerebral function [69,70]. Vitamin D may have neuroprotective effects by different mechanisms, including antioxidative effects, neuronal calcium regulation, immunomodulation and vascular protection [71]. Observational and small randomised studies, with some methodological limitations, have suggested a positive effect of sunlight and/or adequate vitamin D levels on memory, cognition, all-cause dementia and Parkinson disease risk [71–74].

5. Maintaining vitamin D levels

There is a growing body of evidence suggesting an important role for sufficient serum vitamin D levels which may increase longevity and improve quality of life by reducing mortality and the risk of several age-related diseases [2,4,9]. Thus, it seems reasonable to maintain sufficient serum 25(OH)D levels (>30 ng/mL, 75 nmol/L) throughout life. However data on non skeletal outcomes are inconsistent and RCTs are sparse [4,10,75].

5.1. Diet and fortified food

Vitamin D is present in oil-rich fish, sunlight-exposed mushrooms, eggs, and milk. Cod liver oil is a rich natural source of vitamin D; although there is concern regarding its use at high doses due to its vitamin A content and the related adverse effects. Fortification of food with vitamin D varies worldwide. In some countries milk, bread and margarine are fortified with vitamin D. As their vitamin D content is quite variable, they do not necessarily provide sufficient amounts.

5.2. Sunlight exposure

Sunlight-induced vitamin D3 skin synthesis is influenced by season, latitude, time of day, cloud cover, smog, altitude, skin pigmentation, sunscreen use, clothing coverage and age. To produce vitamin D, sunlight UV radiation should act directly on the skin without the interference of sunscreens or glass (receiving sunlight indoors through a window does not induce vitamin D synthesis). Also, aging negatively influences vitamin D acquisition through sunlight photosynthesis [4–6,76].

A lifestyle with small doses of sunlight (15 min of sun exposure, 3–4 times a week) over the face and arms is recommended during the spring, summer and autumn months. Longer unprotected sunlight exposures are not recommended due to the increased risk of skin cancer [77]. It seems that sun UV radiation or an unidentified associated factor may reduce all-cause, cardiovascular- and cancer-related mortality in women. However, artificial UV exposure is associated to increased overall and cancer-related mortality [76,78].

5.3. Vitamin D supplementation

Different North American organizations, the International Osteoporosis Foundation and professional or scientific societies have published recommendations for vitamin D supplements [79–82].The recommended daily allowance is 600 IU/day increasing to 800 IU/day in those aged 71 years and older [75,80]. Vitamin D supplements should be used when diet and lifestyle (sunlight) recommendations cannot be implemented. Increasing fortified food intake or sunlight exposure is not recommended. It seems that up to 4000 IU of vitamin D3/day are devoid of any significant adverse effects, and effectively increases serum 25(OH)D levels to high-normal physiological concentrations [80–82]. Note that availability of different supplement preparations varies worldwide. Monitoring vitamin D levels depends on the dose of supplement used and the presence of concomitant medical conditions such as renal disease.

It could be recommended that healthy postmenopausal women over the age of 65 years should receive 800–1000 IU/day of vitamin D to maintain sufficient serum 25(OH)D levels [82].

Postmenopausal women with risk factors for low vitamin D status should be screened for serum 25(OH)D status and adequately treated. This marker should be measured at 2–3 months intervals until its level is stabilized in the normal range. Women with serum 25(OH)D levels below 20 ng/mL (50 nmol/L) may need treatment with 4000–10,000 IU/day to achieve adequate levels. If individual risk factors are not modifiable, the appropriate dose should be maintained with an annual serum 25(OH)D measurement. Women with morbid obesity (pre- and post gastrointestinal bypass surgery), malabsorption syndromes, and hepatic or renal diseases require specific tailored doses of vitamin D supplements.

Women with vitamin D deficiency related to osteoporosis and/or previous incidental fractures should receive adequate amounts of vitamin D (800–1200 IU/day if there are no risk factors for low serum vitamin D) and specific bone conserving therapies [82].

5.4. Vitamin D toxicity

Vitamin D toxicity is associated with hypercalcemia, hypercalciuria, vascular and soft tissue calcification and nephrolithiasis [30,83,84]. Vitamin D toxicity has never been reported from sunlight alone. There is no evidence supporting toxicity for serum 25(OH)D levels above 150 ng/mL (375 nmol/L) or indefinite supplementation with 10,000 IU/day [85,86]. On the other hand, the toxic effects may be related to excessive calcium supplementation and daily doses of vitamin D above 50,000 IU for several months.

A high vitamin D intake was not associated with nephrolithiasis in a large cohort [87], while calcium supplementation was associated with a 20% increased risk of nephrolithiasis [88]. Thus, patients with hypercalciuria and nephrolithiasis should be assessed to determine the risk of vitamin D therapy.

Of note postmenopausal women with sarcoidosis have considerably higher conversion rates of 25(OH)D to calcitriol [89]. Therefore, vitamin D dosage should be reduced to 200–400 IU/day and the response monitored with serum 25(OH)D measurements.

6. Summary recommendations

- Health professionals should be aware that vitamin D deficiency and insufficiency are common and may affect up to 70% of European populations (including those living in sunny regions).
- In healthy postmenopausal women, adequate serum concentrations can be achieved through sun exposure (15 min per day, 3–4 times a week) or vitamin D supplementation with 800–1000 IU/day.
- Women with low serum 25(OH)D levels should use doses ranging from 4000 to 10,000 IU/day to achieve adequate levels.
- Women with morbid obesity (pre and post gastrointestinal bypass surgery), malabsorption syndromes, hepatic or renal diseases, require specific tailored doses of vitamin D supplements.
- Women with vitamin D deficiency related to osteoporosis and/or previous incidental fractures should receive adequate amounts of vitamin D (800–1200 IU/day if there are no associated risk factors for low serum vitamin D levels) and specific bone conserving therapies.

Contributors

Faustino R. Pérez-López prepared the initial draft, contributed significantly to the intellectual input and writing of the final version. The draft was circulated to all EMAS board members for comment and approval. Production was coordinated by Margaret Rees.

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