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Review

Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

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Abstract

Background:
Vitamin D insufficiency has deleterious consequences on health outcomes. In elderly or postmenopausal women, it may exacerbate osteoporosis.

Scope:
There is currently no clear consensus on definitions of vitamin D insufficiency or minimal targets for vitamin D concentrations and proposed targets vary with the population. In view of the potential confusion for practitioners on when to treat and what to achieve, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) convened a meeting to provide recommendations for clinical practice, to ensure the optimal management of elderly and postmenopausal women with regard to vitamin D supplementation.

Findings:
Vitamin D has both skeletal and extra-skeletal benefits. Patients with serum 25-hydroxyvitamin D (25-(OH)D) levels <50 nmol/L have increased bone turnover, bone loss, and possibly mineralization defects compared with patients with levels >50 nmol/L. Similar relationships have been reported for frailty, nonvertebral and hip fracture, and all-cause mortality, with poorer outcomes at <50 nmol/L.

Conclusion:
The ESCEO recommends that 50 nmol/L (i.e. 20 ng/mL) should be the minimal serum 25-(OH)D concentration at the population level and in patients with osteoporosis to ensure optimal bone health. Below this threshold, supplementation is recommended at 800 to 1000 IU/day. Vitamin D supplementation is safe up to 10,000 IU/day (upper limit of safety) resulting in an upper limit of adequacy of 125 nmol/L 25-(OH)D. Daily consumption of calcium- and vitamin-D-fortified food products (e.g. yoghurt or milk) can help improve vitamin D intake. Above the threshold of 50 nmol/L, there is no clear evidence for additional benefits of supplementation. On the other hand, in fragile elderly subjects who are at elevated risk for falls and fracture, the ESCEO recommends a minimal serum 25-(OH)D level of 75 nmol/L (i.e. 30 ng/mL), for the greatest impact on fracture.

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Introduction

Few subjects have been the source of as much discussion in the medical community in recent years as vitamin D. Lack of vitamin D has well known direct effects on bone health. This occurs via the deregulation of calcium homeostasis and increased serum parathyroid hormone (PTH), which negatively affects bone remodeling by increasing bone resorption[1–3]. In elderly or postmenopausal women, this may exacerbate osteoporosis. Vitamin D insufficiency has a variety of causes (Table 1)[4,5], including reduced endogenous synthesis, decreased availability, and concomitant diseases. The risk factors for vitamin D insufficiency are related to race, latitude, exposure to sunlight and ability to tan, and cultural attitudes to supplementation and general health[6]. The indications for screening include bone diseases, old age (particularly in case of falls or fracture), malabsorption syndromes, and certain medications (Table 1)[4,5].

The deleterious consequences of vitamin D insufficiency increase with the degree of the lack of vitamin D. Despite this, there is currently no clear consensus on definitions of vitamin D deficiency and insufficiency[1]. For the purposes of this review, we propose the terms laid out in Table 2, and interpret them in terms of serum 25-hydroxyvitamin D (25-(OH)D), which is considered to be the best biomarker of vitamin D status[7,8]. Thus, we define individuals with serum 25-(OH)D levels below 25 nmol/L (i.e. <10 ng/mL) as having 'vitamin D deficiency'. Above this level, 'vitamin D insufficiency' identifies individuals with serum 25-(OH)D levels greater than 25 nmol/L, but less than 50 nmol/L (i.e. <20 ng/mL). Individuals with levels above 50 nmol/L (i.e. ≥20 ng/mL) are defined as 'vitamin D sufficient'. The upper limit of adequacy, i.e. the level above which adverse effects are possible, is defined as 125 nmol/L[9].

Vitamin D insufficiency is widespread[10–12], and is present in every region of the world. The rates of vitamin D deficiency are highest in the Middle East and South Asia[11]. In elderly populations in Europe, vitamin D insufficiency is more common in the south than in the north, and more likely in women than in men[13]. It may be present in as many as 50% of women with osteoporosis[14]. The frequency of vitamin D insufficiency increases with age due to reduction in exposure to sunlight, poor nutrition, and a decrease in the capacity to produce vitamin D_3 in the skin[15]. The prevalence of vitamin D insufficiency is increasing – despite current recommendations for supplementation[16] – and it is an emerging health problem[11].

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) last met on the subject of vitamin D in 2008, when it produced recommendations on the role of calcium and vitamin D in the management of osteoporosis[17]. The main conclusion of the consensus document was that there is a rationale to supplement patients with osteoporosis, and those at increased risk for the disease, to ensure that serum 25-(OH)D levels remain above 50 nmol/L. Oral supplementation (800 IU/day) was recommended in osteoporotic patients, ideally in combination with calcium 1000 mg/day to improve compliance and efficacy. The ESCEO also considered the upper limit for safety to be 10,000 IU/day vitamin D, though agreed that the level for intoxication is likely to be higher than this. The ESCEO 2008 recommendations are in line with the current joint recommendations of the ESCEO and International Osteoporosis Foundation (IOF) for the management of postmenopausal osteoporosis, which cite at least 1000 mg/day calcium and 800 IU/day vitamin D in men and women aged over 50 years[18].

The vitamin D field has moved considerably since the publication of the ESCEO 2008 recommendations. As regards minimal targets for vitamin D concentrations, there are currently two main categories of opinion. The Institute of Medicine (IOM) considers that the recommended daily allowance for vitamin D

Table 1. Vitamin D insufficiency: causes and indications for screening. Adapted, in part, from Holick *et al.* (2011)[4] and Bischoff-Ferrari *et al.* (2012)[5].

Causes of vitamin D insufficiency
- Reduced epidermal synthesis (e.g., due to use of sunscreen, aging, season, or skin pigment)
- Decreased availability (e.g., due to malabsorption or obesity)
- Increased catabolism/loss (e.g., due to use of anticonvulsants, presence of heart disease or nephrotic syndrome)
- Pregnancy or lactation
- Decreased 25-(OH)D synthesis (e.g., due to liver failure)
- Decreased 1,25-$(OH)_2$D synthesis (e.g., due to chronic renal failure, vitamin-D-dependent rickets, X-linked hypophosphatemia, autosomal dominant hypophosphatemia, or oncogenic osteomalacia)

Indications for vitamin D screening
- Bone diseases (e.g., rickets, osteomalacia, osteoporosis, nontraumatic fracture, or hyperparathyroidism)
- Old age
- (particularly in case of history of falls or nontraumatic fracture)
- Dark skin (e.g., Africans, African-Americans, Hispanics, or Asians)
- Obesity (e.g., adults with body mass index >30 kg/m^2 and obese children with other risk factors or symptoms)
- Pregnancy or lactation (with risk factors) (e.g., dark-skinned or overweight, gestational diabetes, or very low exposure to sunlight, and no vitamin D supplementation)
- Sports athletes (especially indoor sports)
- Chronic kidney disease
- Liver failure
- Malabsorption syndromes (e.g., cystic fibrosis, inflammatory bowel disease, Crohn's disease, bariatric surgery, or radiation enteritis)
- Medications (e.g., antiepileptic drugs, glucocorticoids, AIDS drugs, antifungals, or cholestyramine)
- Granuloma-forming diseases (e.g., sarcoidosis, tuberculosis, histoplasmosis, coccidiomycosis, or berylliosis)

Table 2. Vitamin D (25-(OH)D) levels and their impact on bone health.

Definition	Serum 25-(OH) D level*	Impact on bone health
Vitamin D deficiency	<25 nmol/L	Mineralization defect
Vitamin D insufficiency	<50 nmol/L	Increased bone turnover and/or PTH
Vitamin D sufficiency	50 to 75 nmol/L	Neutral effect (bone turnover and PTH normalized), desirable benefits on fracture, falls, and mortality
	≥75 nmol/L	Desirable target in the fragile elderly due to optimal benefits on fracture, falls, and mortality
Upper limit of adequacy	125 nmol/L	Possibility of adverse effects above this level

*25 nmol/L is equivalent to 10 ng/mL, 50 nmol/L to <20 ng/mL, and 75 nmol/L to 30 ng/mL.

should lead to serum 25-(OH)D levels of at least 50 nmol/L (i.e. ≥20 ng/mL) and that individuals below that level should receive vitamin D supplementation[8,9,19]. This report was published in January 2011 by a committee of 14 experts from a variety of fields in medicine, and the conclusions were reached on the basis of a rigorous and comprehensive review of the data. The IOM recommendations are in line with those of the IOF[20] and other bodies, such as the Standing Committee of European Doctors (CPME)[21] and the Swiss Federal Commission for Nutrition[22]. In parallel, the US Endocrine Society issued recommendations regarding vitamin D insufficiency in July 2011[4], which differ from those of the IOM on three main points: they recommend a higher treatment target (≥75 nmol/L) for health benefits; they state that individuals below 50 nmol/L should be considered as vitamin D deficient; and, as a consequence, they arrive at a substantially higher proportion of the population at risk for vitamin D insufficiency[23].

In view of the potential confusion for practitioners on when to treat and what to achieve, the ESCEO convened a meeting in November 2012 in an attempt to clarify the situation. The aim of this document is to provide recommendations for the practitioner, to ensure the optimal management of patients with regard to vitamin D for bone health.

Impact of serum vitamin D level on bone health and mortality

The relationship between serum 25-(OH)D levels and bone health has been explored from a variety of different perspectives. A number of studies have examined the relationship between serum 25-(OH)D and indices of skeletal metabolism[24–26]. One study investigated serum 25-(OH)D and PTH in blood samples collected from 387 men and women aged 65 to 87 years[24]. PTH values were markedly lower at 25-(OH)D levels between 25 and 50 nmol/L, but reached a plateau at values between 50 and 75 nmol/L (Figure 1A). Similar results were found in a study in 488 Caucasian women (mean age 71 years), in which there was an association between 25-(OH)D values and serum osteocalcin and urinary N-telopeptides. Bone turnover markers were highest at 25-(OH)D values less than 25 nmol/L, were lower up to 50 nmol/L and then formed a clear plateau at values greater than 50 nmol/L[25]. Further evidence for a plateauing of the effect above 50 nmol/L comes from studies in bone microarchitecture. Iliac crest bone biopsies were collected at autopsy from 675 men and women, and analyzed by bone histomorphometry[26]. In this postmortem study, individuals with the lower serum 25-(OH)D levels (<25 nmol/L) had greater osteoid volume, surface, and thickness than those with higher

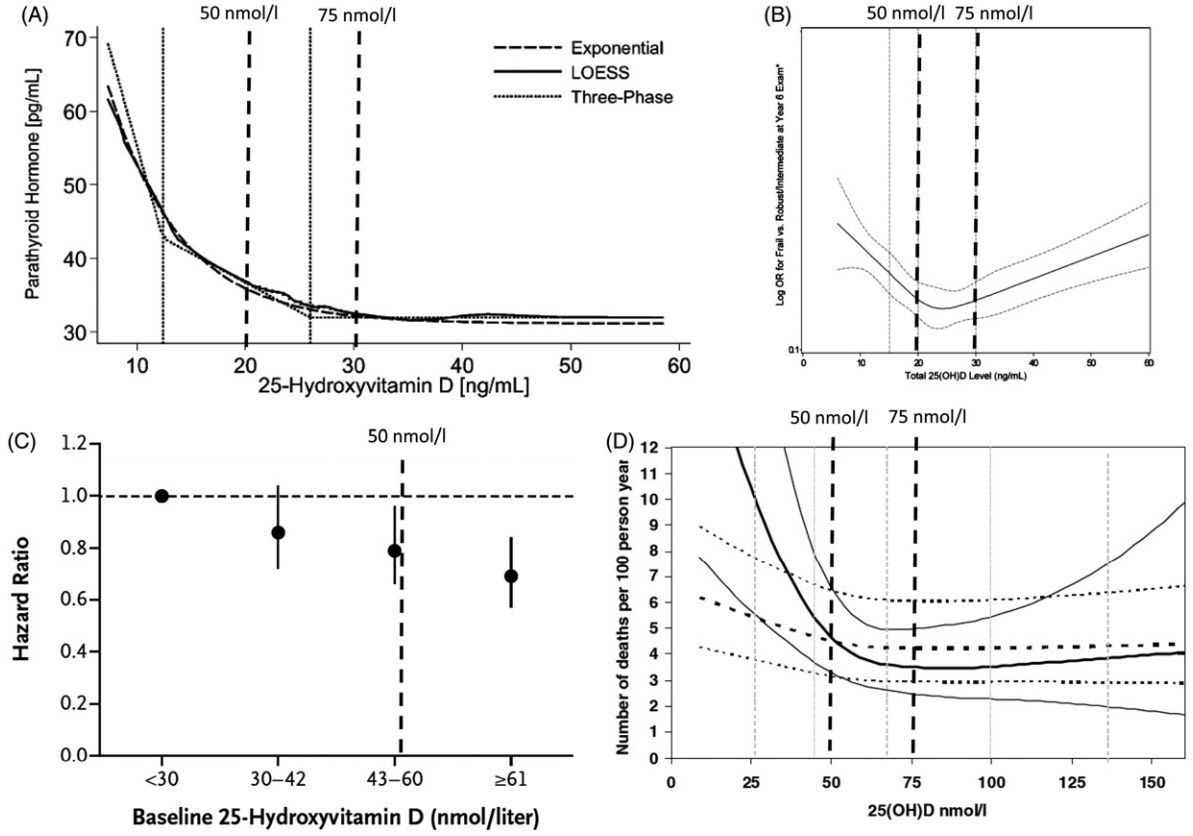

Figure 1. Relationship between serum 25-hydroxy vitamin D and parameters of bone health: parathyroid hormone (PTH) levels in blood samples from 387 men and women aged 65 to 87 years (A)[24]; frailty status in 6307 women aged ≥69 years (B)[28]; nonvertebral fracture in 4383 men and women aged 76 years (C)[39]; and mortality in 2878 men aged 76 years (D)[45]. Reproduced and adapted from references 24, 28, 39, and 45.

25-(OH)D levels. There appeared to be little additional difference in osteoid measurements at serum 25-(OH)D levels higher than 50 nmol/L[26]. Although this study may be limited due to the histological definition of osteomalacia, it suggests that 25-(OH)D levels below 25 nmol/L are associated with mineralization defects, and that these can be improved by increasing serum 25-(OH)D levels to above 50 nmol/L.

The impact of vitamin D on frailty and falls is related to a beneficial impact on muscle, with improved muscle strength and balance. Serum 25-(OH)D levels between 40 and 94 nmol/L have been associated with better musculoskeletal function in the lower extremities, as measured by the 8-foot walk test and the repeated sit to stand test[27]. The association between serum 25-(OH)D levels and frailty status (measured in terms of weakness, exhaustion, slowness, and level of physical activity) has been explored in both women and men[28–30]. For women, a U-shaped curve was found with optimal serum 25-(OH)D levels between 50 and 75 nmol/L (Figure 1B)[28,29]. Women with levels lower than 37.5 nmol/L were 47% more likely to be frail than the women between 50 and 75 nmol/L (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.19 to 1.82); those between 37.5 and 50 nmol/L were 24% more likely to be frail (OR 1.24, 95% CI 0.99 to 1.54); and those at 75 nmol/L or above were 32% more likely (OR 1.32, 95% CI 1.06 to 1.63)[28]. A similar study in men indicated a plateau between 50 and 75 nmol/L, though frailty appeared to be even less likely at higher serum 25-(OH)D levels, albeit with very large confidence intervals[30]. Neither of these studies found a very convincing relation between higher serum 25-(OH)D levels and a lower risk of future frailty or death.

The impact of vitamin D in reducing falls has been explored in meta-analyses[31,32]. A meta-analysis in 2426 patients participating in eight trials evaluated the relationship between falls and serum 25-(OH)D levels and demonstrated that levels of 60 nmol/L or higher were associated with a 23% reduction in falls (pooled relative risk [RR] 0.77, 95% CI 0.65 to 0.90)[32]. The authors interpreted this as a linear effect of vitamin D up to 95 nmol/L. This conclusion is controversial since a re-analysis of the same data by the IOM found no significant dose–response relationship for falls, possibly due to internal inconsistencies and selectivity of dose–response analyses[33].

There have been as many as 45 randomized controlled studies of the effect of vitamin D with and without calcium on fracture over the last 20 years, and a host of

observational and epidemiological studies, pooled analyses and meta-analyses[34–38]. Although the conclusions are sometimes limited, due to insufficient vitamin D dosage and the confounding influence of concomitant calcium supplements the relationship between vitamin D dosage and nonvertebral and hip fracture was clearly established with a substantial reduction of the fracture risk with daily supplementation of 800 IU/day or more. There are fewer trials exploring the relationship between serum 25-(OH)D levels and risk of fracture. A pooled analysis of 11 trials including 31,000 patients indicated that those with baseline serum 25-(OH)D levels of at least 60 nmol/L were at lower risk than those with less than 30 nmol/L, with a 31% reduction in risk for nonvertebral fracture (hazard ratio [HR] 0.69, 95% CI 0.57 to 0.84) and a 37% reduction in hip fracture (HR 0.63, 95% CI 0.46 to 0.87)[39]. Moving from lower to higher categories of serum 25-(OH)D levels, there was a dose-dependent decrease in nonvertebral fracture risk with no threshold effect (Figure 1C). We have some evidence, therefore, that the reduction in risk for fracture by vitamin D is dose dependent[37,39], and that levels above 60 nmol/L would be the most beneficial in terms of reduction in fracture[39,40].

An observational study performed in 2005 in 222 consecutive hip fracture patients reported that 60% had serum 25-(OH)D levels below 30 nmol/L and 80% were below 50 nmol/L[41]. Of note, only 10% of patients admitted for acute care after hip fracture had any form of supplementation for vitamin D. This illustrates the importance of public health efforts to implement supplementation in the elderly, particularly those living in nursing homes or assisted living. It also supports the administration of vitamin D supplementation in elderly and postmenopausal women.

The first evidence that supplementation with vitamin D could have an effect on survival came in 2007, with a meta-analysis of 18 randomized controlled trials and a 7% reduction of total mortality (RR 0.93, 95% CI 0.87 to 0.99) versus individuals receiving no vitamin D supplementation[42,43]. This has since been confirmed by other workers[44–47]. A recent analysis in 2878 elderly men showed that low serum 25-(OH)D levels was associated with an excess risk for total mortality versus values greater than 50 to 75 nmol/L (Figure 1D)[45]. There was a nonlinear relationship such that low serum values were associated with increased short-term mortality up to a value of about 60 nmol/L, but serum values above this were not associated with improved survival.

The evidence for an effect on mortality with vitamin D should be considered in the light of other analyses of the impact of concomitant calcium intake[48]. A recent meta-analysis[49] suggested that it is the combination of vitamin D and calcium that reduces mortality in the elderly, rather than vitamin D alone. The same authors also concluded that vitamin supplementation in the elderly is by no means harmful to survival and clearly also had other beneficial effects on health[49]. In this context, current recommendations in postmenopausal osteoporosis include supplementation with both calcium and vitamin D in addition to bone-protective therapy for maximum benefits on bone[18,50].

Discussion

Vitamin D supplementation: treatment threshold and targets for bone health

Vitamin D has both skeletal and extra-skeletal benefits. Cross-sectional studies suggest that patients with serum 25-(OH)D levels lower than 50 nmol/L have increased bone turnover with an increase in PTH, and possibly mineralization defects at levels below 25 nmol/L, compared with levels between 50 and 75 nmol/L[24–26]. Similar relationships have been reported for frailty[28–30], for nonvertebral and hip fracture[34,37,39], and for all-cause mortality[42–46], with poorer outcomes in patients with levels lower than 50 nmol/L and evidence for a plateauing of the effect above that value. There is also some evidence for falls, in the same direction, though this is less clear.

On the basis of our review and discussions, the definitions of vitamin D deficiency, insufficiency, and sufficiency, and their equivalents in terms of serum 25-(OH)D levels, can be related to their consequences on bone health (Table 2). Thus, the presence of vitamin D deficiency (<25 nmol/L) can be expected to be related to mineralization defects, increased bone turnover and PTH levels, and increased rates of frailty, fracture and all-cause mortality. Vitamin D insufficiency (<50 nmol/L) is associated with increased bone turnover and PTH, and poorer outcomes also in terms of frailty, fracture and all-cause mortality. Vitamin D sufficiency (above 50 nmol/L) represents the minimal levels to be achieved in the general population, since it is the level at which bone turnover and PTH are normalized and there are some benefits in terms of outcomes, with the best effect achieved above 60 nmol/L. Thus, a level of 75 nmol/L (which corresponds to 30 ng/mL) or above should be considered in fragile populations who are at increased risk of falls and fracture (i.e. those with a history of previous low-trauma fracture, those at advanced age, and those with muscle weakness).

This leads naturally to the ESCEO recommendation that 50 nmol/L should be the minimal serum 25-(OH)D concentration at the population level. Individuals below this threshold should receive vitamin D supplementation. The ESCEO consensus is also that osteoporotic patients with serum 25-(OH)D levels less than 50 nmol/L should receive vitamin D supplementation. As regards fragile elderly subjects who are at elevated risk for falls and fracture,

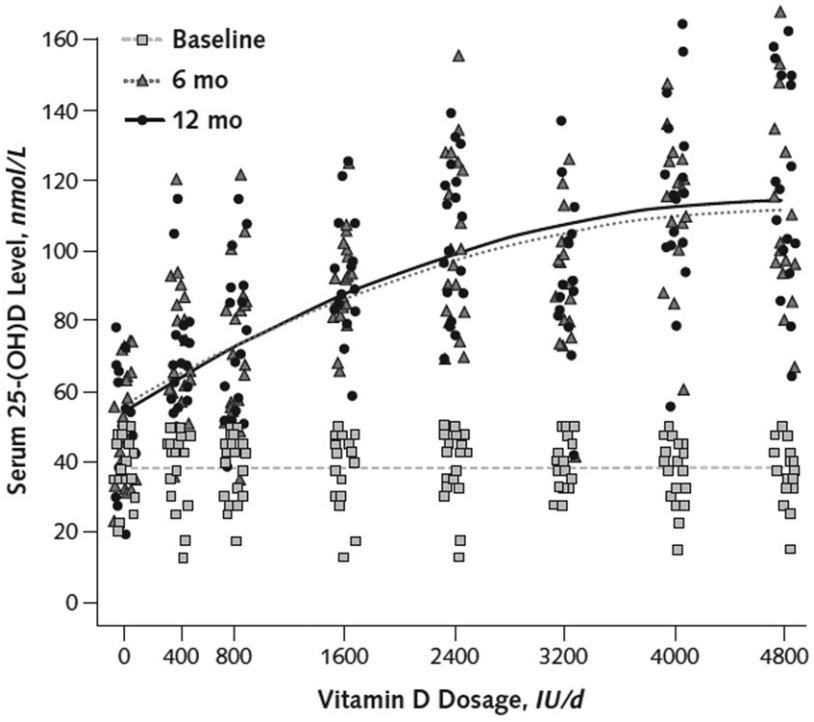

Figure 2. Relationship between dosage of vitamin D3 and serum 25-hydroxy vitamin D. Reproduced and adapted from reference 54.

the ESCEO recommends a serum 25-(OH)D level at least above 60 nmol/L, ideally 75 nmol/L.

These thresholds have been selected on the basis of the evidence outlined above, as well as considerations for real clinical practice, since the 50 nmol/L is where the physician would treat (i.e. a clinically relevant limit). The ESCEO considers that, at levels less than 50 nmol/L, there is a risk of adverse outcomes; above that threshold, there is no clear evidence for additional benefits of supplementation. Decisions to supplement should be made on an individual basis, notably, patients with serum 25-(OH)D levels between 50 and 75 nmol/L should be treated according to physician preference, as determined by age (very elderly in nursing homes may need higher dosages), severity of disease (more severe patients may need higher dosages), and kidney function. It should be recalled that osteoporosis treatments have been tested in patients receiving vitamin D and calcium supplements[51], irrespective of baseline 25(OH)D levels. This threshold is in line with the recommendations of the IOM[8,9,19], and would well fit with clinical practice where a serum 25-(OH)D is measured at diagnosis but not as part of the routine follow-up. Targeting a threshold of 75 nmol/L, as cited by the US Endocrine Society and by other authors[4,52,53], may be beneficial in patients at elevated risk, but would require a higher daily supplementation as well as monitoring of serum 25-(OH)D levels. In this context, a randomized, placebo-controlled trial in 163 healthy postmenopausal women who were vitamin D insufficient demonstrated that an oral dose of 1600 IU/day would be needed to increase levels to above 75 nmol/L in 97.5% of patients (Figure 2)[54]. The dosage selected will obviously also depend on pretreatment values. In daily practice, treatment decisions should also be made on the basis of the cost-effectiveness of higher vitamin D supplementation and follow-up dosages to achieve the 75 nmol/L threshold.

Implementation of vitamin D supplementation in elderly or postmenopausal women

In order to prevent vitamin D insufficiency and preserve bone health and associated consequences, elderly or postmenopausal women should be encouraged to increase their vitamin D levels if they are too low. Vitamin D is acquired both through cutaneous synthesis after sunlight exposure (80% to 90%) and nutrition (10% to 20%)[10]. There are three main routes to increase vitamin D levels: encourage increased intake of natural sources, fortification, and supplementation[55]. Vitamin D is found naturally in some foods, including oily fish, mushrooms and some dairy products (Table 3)[5]. However, given the low number of foods containing large amounts of vitamin D, and the variations in exposure to sunlight, a number of countries recommend fortification of certain foods with vitamin D, most often milk, margarine, butter, yoghurt, and other foods that are widely consumed in the population to maximize the impact of fortification[56]. In this context, dairy products

are a good choice in Europe since they bring an average 35% to 40% of total calcium intake from food and drink[57,58]. It is also logical to have calcium and vitamin D together in the same product or food matrix for bone health, since both are key elements. A recent analysis demonstrated that consuming fortified foods in vitamin D, including dairy products, can increase serum 25-(OH)D levels in adults and may also improve long-term adherence[59]. Calcium- and vitamin-D-fortified products (e.g. yoghurt or milk) that provide 400 mg calcium and 200 IU vitamin D per portion are considered valuable options in the management of postmenopausal osteoporosis[18,59].

Despite the promise of fortification of food, it is not sufficient to reach the required levels of vitamin D[55], especially in at-risk individuals or in those with osteoporosis. In that case, supplementation is required, in addition to fortified food, in order to ensure at least the intake of 800 IU/day. An intervention study in 113 elderly institutionalized female patients showed that supplementation with the dose of 880 IU/day takes serum 25-(OH)D levels above 50 nmol/L and was accompanied by significantly improved muscle strength and hip bone mineral density (both $P < 0.001$)[60]. Daily supplementation of 1600 IU brought no additional benefits in terms of muscle strength or bone mineral density[60]. In view of this study and previous recommendations, the ESCEO maintains its recommendation for supplementation at dosages between 800 and 1000 IU/day[17]. Such a threshold is in line with the majority of current vitamin D recommendations in Europe for patients aged over 60 to 70 years (Table 4), as well as those of the IOM and IOF[8,20].

As regards dosing schedule, supplementation with vitamin D can be achieved equally well with daily, weekly, or monthly dosing frequencies[61]. This implies that the choice of dose frequency should be made on the basis of optimal adherence to long-term supplementation. On the other hand, annual vitamin D (intramuscular or oral) is not recommended[62,63]. A randomized controlled trial of a single annual intramuscular dose of 300,000 IU vitamin D_2 in 9440 elderly men and women failed to find a significant impact in preventing nonvertebral fracture or falls[62]. Annual dosing may even be deleterious, since a more recent randomized controlled trial reported that a single annual dose of 500,000 IU vitamin D_3 in 2256 elderly women resulted in increased rates of fracture and falls[63].

Vitamin D supplementation is safe in patients above both 50 and 75 nmol/L, in terms of mortality and musculoskeletal health[17,64]. The adverse effects of hypercalcemia/hypercalciuria and nephrolithiasis may occur at much higher serum 25-(OH)D levels (>125 nmol/L), which has been set as the potential upper limit of adequacy (Table 2)[9]. According to the ESCEO 2008 recommendations, the upper limit for safety in terms of intake is 10,000 IU/day, though adverse effects are believed to occur at levels about four times higher than this[17].

Table 3. Natural sources of vitamin D. Adapted from Bischoff-Ferrari *et al.* (2012)[5].

Source	Content in vitamin D*
Wild salmon	600–1000 IU
Farmed salmon	100–250 IU
Sardines (canned)	300–600 IU
Mackerel (canned)	250 IU
Tuna (canned)	236 IU
Cod liver oil	400–1000 IU per tablespoon
Shiitake mushrooms (fresh)	100 IU
Shiitake mushrooms (dried)	1600 IU
Egg yolk	20 IU per yolk
Fresh mushrooms	76 IU
Butter	52 IU
Cheese (e.g., Emmental)	44 IU

*Per 100 grams, unless otherwise specified.

Conclusion

Serum 25-(OH)D levels below 50 nmol/L are harmful for bone health. The ESCEO recommends that elderly or

Table 4. Vitamin D recommendations for adults.

	Recommended vitamin D level (IU/day)				
	Age 19–50 years	Age 51–60 years	Age 61–70 years	Age >70 years	Pregnancy/ lactation
Nordic Dietary Recommendations	300	300	400	400	300
Dutch Health Council	400	400	400	800	400
Belgian Health Council (RDA)	400–600	400–600	400–600	600	800
Institute of Medicine (RDA)	600	600	600	800	600
US Endocrine Society*	600	600	600	800	800
Swiss Federal Nutrition Council*	600	600	800	800	600
DACH countries (Germany, Austria, and Switzerland)	800	800	800	800	800

*1500–2000 IU/day for patients with severe vitamin D deficiency (<25 nmol/L).
400 IU = 10 μg.
RDA = recommended daily allowance.

postmenopausal women with values less than 50 nmol/L should receive supplementation with between 800 and 1000 IU/day vitamin D in order to achieve levels above this threshold. Osteoporotic patients with levels less than 50 nmol/L should also receive supplementation at between 800 and 1000 IU/day. A serum 25-(OH)D level of 75 nmol/L is the ESCEO treatment threshold in fragile elderly patients who are at particular risk of falls and fracture since this is the level at which there may be the greatest impact on fracture. The ESCEO aligns with two august international bodies who have selected these thresholds (IOM and IOF)[8,9,19,20].

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Declaration of financial/other relationships
R.R. has disclosed receiving consulting and lecture fees for Merck Sharp and Dohme, Eli Lilly, Amgen, Novartis, Servier, Nycomed, Nestlé, and Danone. S.B. has disclosed receiving consulting and lecture fees, fees for advisory boards, and/or grant support from Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Ono, Roche, Sanofi-Aventis, Servier, and Warner Chilcott. M.-L.B. has disclosed receiving support from Fondazione F.I.R.M.O. (Fondazione Italiana Ricerca Malattie Ossee) and grants from Merck Sharpe & Dohme, Nycomed, Roche, Glaxo, Eli Lilly, and Wyeth, as well as speaker fees from Procter and Gamble, Merck Sharpe & Dohme, Nycomed, and Wyeth. O.B. has disclosed receiving grants for research from GlaxoSmithKline, IBSA, Merck Sharp & Dohme, Theramex, Novartis, Pfizer, Rottapharm, and Servier; consulting or lecture fees from IBSA, Rottapharm, and Servier; and reimbursement for attending meetings from IBSA, Merck Sharp & Dohme, Novartis, Pfizer, Rottapharm, Theramex, Servier. C.C. has disclosed receiving consulting fees and fees for advisory boards for Alliance for Better Bone Health, Glaxo Smith Kline, Roche, Merck Sharp and Dohme, Lilly, Amgen, Wyeth, Novartis, Servier, and Nycomed. J.A.K. has disclosed receiving consulting fees, fees for advisory boards, lecture fees, and/or grant support from the majority of companies concerned with skeletal metabolism. J.-M.K. has disclosed receiving speaker and/or consultant fees and/or research support from Amgen, Daiichi-Sankyo, Glaxo SmithKline, Merck Sharp & Dohme, Novartis, Nycomed, Servier, and Roche. J.D.R. has disclosed receiving consulting fees or fees for advisory boards for Amgen, Madaus, Merck, Servier; Lecture fees for Leo, Lilly, Novartis, Servier, and Teva. G.W. has disclosed receiving consulting fees or fees for advisory boards for Novartis and Lilly, as well as lecture fees from Lilly, Servier, Theramex, and Daiichi Sankyo and clinical trial investigator fees from Servier, Lilly, MSD, Amgen, Nycomed, and Roche. J.-Y.R. has disclosed receiving consulting fees, paid advisory boards, lecture fees, and/or grant support from Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB, Merck Sharp and Dohme, Rottapharm, IBSA, Genevrier, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Novo-Nordisk, and Bristol Myers Squibb.

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