**Role of Vitamin D supplementation in the management of musculoskeletal diseases: update from an European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group**

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**Abstract**

Vitamin D is a key component for optimal growth and for calcium-phosphate homeostasis. Skin photosynthesis is the main source of vitamin D. Limited sun exposure and insufficient dietary vitamin D supply justify vitamin D supplementation in certain age groups. In older adults, recommended doses for vitamin D supplementation vary between 200 and 2000 IU/day, to achieve a goal of circulating 25-hydroxyvitamin D (calcifediol) of at least 50 nmol/L. The target level depends on the population being supplemented, the assessed system and the outcome. Several recent large randomized trials with oral vitamin D regimens varying between 2000 IU/ day and 100,000 IU/month and mostly conducted in vitamin D replete and healthy individuals have failed to detect any efficacy of these approaches for the prevention of fracture and falls. Considering the well-recognized major musculoskeletal disorders associated with severe vitamin D deficiency and taking into account a possible biphasic effects of vitamin D on fracture and fall risks, an European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group convened, carefully reviewed and analyzed the meta-analyses of randomized controlled trials on the effects of vitamin D on fracture risk, falls or osteoarthritis, and came to the conclusion that 1000 IU daily should be recommended in patients at increased risk of vitamin D deficiency. The group also addressed the identification of patients possibly benefitting from a vitamin D loading dose to achieve early 25-hydroxyvitamin D therapeutic level or from calcifediol administration.

**Keywords:** vitamin D; fragility fracture; falls, osteoarthritis

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| **Introduction** |

Vitamin D plays a major role in optimal growth and in calcium-phosphate homeostasis. In humans, skin photosynthesis is the main endogenous source of vitamin D. When sun exposure is limited and in case of insufficient vitamin D dietary supply, vitamin D supplementation is recommended particularly in certain age groups [1, 2]. A majority of guidelines consistently recommend 400 IU/day (10 µg) to prevent rickets during the first year of life [3]. Calcium intake of 200 and 260 mg/day before 6 months and before 12 months, respectively, is also advised [1]. For treatment of nutritional rickets, the dose of 2000 IU/day for at least 3 months is recommended, with a normalization of PTH levels. Whilst recommendations for rickets prevention and treatment in childhood and adolescence are widely accepted [3], the target for calcifediol (25-hydroxyvitamin D (25(OH)D)) levels is still discordant among the various guidelines [2]. Regarding the preventive effect of vitamin D on fracture, many meta-analyses of RCTs have shown contradictory results, some showing no effect at all, while others showed a beneficial anti-fracture effect of vitamin D supplementation particularly when combined with calcium [2, 4].

Although 50 nmol/L of serum of 25(OH)D is considered as a threshold value for optimal bone health by many guidelines [3], higher concentrations, and correspondingly higher intake of vitamin D, have been suggested by some experts for maintaining bone health [5-8]. However, recent large trials conducted in vitamin D-replete healthy subjects have reported no effects either on falls [9, 10], non-vertebral fractures [9, 11], bone health outcomes [10], chronic knee pain [12], various clinical outcomes [13] and body composition [14]. It should be noted that 70% of RCTs with clinical outcomes were performed in patients with baseline 25(OH)D above 40 nmol/L and out of twenty-five large RCTs only one was undertaken in a vitamin D deficient population (25(OH)D below 25 or 30 nmol/L) and two in vitamin D insufficient populations (25(OH)D below 50 nmol/L) [15]. Indeed, vitamin D deficiency has been shown to be a risk factor for various musculoskeletal disorders, including fractures and falls [16, 17]. To identify vitamin D regimens to correct vitamin D deficiency and prevent related musculoskeletal events, a European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group reviewed and analyzed meta-analyses of randomized controlled trials on the effects of vitamin D supplementation on fracture risk, falls or osteoarthritis. This paper, which updates the 2013 ESCEO recommendation paper [18], is a narrative review of the data used by the working group to reach the conclusion that 1000 IU vitamin D daily should be recommended in patients at increased risk of vitamin D deficiency.

**Methods**

An ESCEO expert working group, comprising expert clinicians of different medical specialties (physical rehabilitation medicine (PRM) specialists, laboratory medicine specialists, rheumatologists, endocrinologists and geriatricians) and researchers was convened in May 2022, under the auspices of the WHO Collaborating Center for Epidemiology of Musculoskeletal Health and Aging (University of Liège, Belgium). This group reviewed the literature and discussed the current state of the art on the followings topics : (1) Epidemiology of vitamin D deficiency ; (2) New perspectives in the assessment of vitamin D circulating levels ; (3) Vitamin D and fracture prevention (effects in depleted and replete populations); (4) Vitamin D and falls (effects in depleted and replete populations); (5) Vitamin D and osteoarthritis (effects in depleted and replete populations) ; (6) Metabolic conditions justifying the use of 25(OH)D (calcifediol); (7) Vitamin D treatment safety and therapeutic window.This paper reflects the presentations and the discussions of the working group based on an extensive narrative literature review focusing on the most robust evidence such as a series of recent meta-analyses*.* After discussion and deliberation amongst the experts regarding the quality, scope and context of the collected evidence, a first draft of the manuscript was prepared. This draft manuscript was circulated to all the members of the expert group for critical revision. Any additionally identified high-quality evidence was subsequently incorporated. The first author coordinated the preparation of the final version of the manuscript, which was circulated to the entire expert group for final approval and unanimous endorsement.

**Epidemiology of Vitamin D deficiency**

Vitamin D deficiency varies depending on the thresholds used for serum 25(OH)D values [19]. Furthermore, serum 25(OH)D levels vary over the course of the year in relation to UVB exposure [20-22]. Low thresholds such as 25(OH)D below 25 or 30 nmol/L (ie deficiency or severe deficiency, depending on the experts society) have been suggested when the focus was more on the prevention of rickets/osteomalacia and a higher threshold below 50 nmol/L (insufficiency or deficiency, depending on the experts society) was chosen if the concern was suppression of PTH. Using a <30 nmol/L threshold, 5% of Americans and about 9% of Canadians have serum values of 25(OH)D below this level [22, 23]. Regarding vitamin D status in the United States, an American survey between 2011 and 2014 suggested that in average 5% of the population was at risk of deficiency as defined with 25(OH)D level below 30 nmol/L, but if the population was divided according to the ethnicity, then the risk of vitamin D deficiency of the Caucasian population was around 2% as compared to 17.5% of the black population [23]. In Europe, 1 out of 8 inhabitants (13% on average) are at risk of vitamin D deficiency (based on a 25(OH)D level below 30 nmol/L), but this percentage can increase up to 28-65% for ethnic minority groups within Northern European countries [24]. However, the prevalence of serum 25(OH)D below 30 nmol/L ranged from 4.6 to 30.7% and this range increased from 27.2 to 61.4% for 25(OH)D using a threshold of 50 nmol/L according to European standardized data [24]. Considering both continents, this represents 120 million of subjects who are vitamin D deficient using a 30 nmol/L threshold and 390 million of subjects with 25(OH)D below 50 nmol/L. Predictors for low 25(OH)D in all models were higher age, higher BMI, use of walking aid, limited time spent outdoors in Summer, smoking, no calcium supplementation, no use of multivitamins, no use of vitamin D on prescription or self-administered, and the season when serum 25(OH)D was tested [25]. There are other potential factors that contribute to increased risk of vitamin D deficiency such as inflammation [5, 26, 27], patients with fat malabsorption syndromes, bariatric surgery, nephrotic syndrome, as well as patients on a variety of medications which may interfere with vitamin D absorption or metabolism [5].

The major source of vitamin D in humans is ultraviolet B (UVB)-induced dermal synthesis of cholecalciferol, whereas food sources are believed to play a lesser role, although among white residents of the UK, meat eaters have 20 nmol/L higher 25(OH)D than vegans [28]. There is a clear trend of decreasing UVB exposure by moving from South to North within Europe, with an almost six-fold difference in mean yearly modeled UVB dose between these two latitudes from ~35○ N to ~69○ N [29]. Significant differences in UVB availability between inland and coastal areas was also reported at the same latitude within the UK, due to different cloud conditions [30]. Environmental and personal factors influence cutaneous vitamin D synthesis [31]:the main determinants are solar zenith angle, controlling the potential available UVB (latitude, season and time of day), skin type and age, clothing, sunscreen, and outdoors activities**.** Therefore, UVB availability and diet, as well as other lifestyle factors, must be considered in preventive and therapeutic approaches to vitamin D deficiency.In Europe, if the extreme North and South are excluded, dietary supply becomes especially important 4 to 8 months a year when vitamin D synthesis in the skin is very limited and 50-100% of Europeans have vitamin D intakes below the recommended level.Indeed, the vast majority of European countries consume below the estimated average requirement of 10 ug/day of vitamin D intake (400 IU) based on European dietary surveys with a mean intake of 3.3 and 2.7 ug/day in adult males and females, respectively [32]. The mean vitamin D intake varies between 1.5 and 5 μg/day in Western Europe and below 1 μg/day to about 3 μg/day in Southern Europe, while in Northern Europe it ranges between 4 and 14 μg/day [33]. According to WHO, the strategies for the control of micronutrient malnutrition are to increase the diversity of the foods consumed, food fortification and supplementation [34]. Nevertheless, increasing the diversity of foods consumed and improving intake of naturally occurring vitamin D‑rich foods is particularly challenging because there are very few food sources rich in vitamin D. For a serum 25(OH)D threshold of 25 nmol/L, a vitamin D intake ranges of 7.5 and 10 µg/day would allow 95% and 97.5% of individuals, respectively, to maintain their winter serum 25(OH)D above this threshold. On the other hand, for a serum 25(OH)D threshold of 50 nmol/L, the corresponding vitamin D intakes needed are 23.5 and 25 ug/day (≈ 1000 IU/day), respectively, intakes which are too difficult to reach with food fortification and may need a more active public health approach involving recommendations for lifestyle including sunshine exposure, healthy nutrition, food fortification and vitamin D supplementation [35].

*In summary, vitamin D deficiency (25(OH)D below 25 or 30 nmol/L)* *is evident throughout the European population at prevalence rates that are of concern and that require action both from a public health and a clinical perspective.*

**New perspectives in the assessment of vitamin D circulating levels**

Commonly cited indications where vitamin D testing is appropriate are : rickets, osteomalacia, osteoporosis, hyperparathyroidism, malabsorption syndromes, medications affecting absorption or metabolism of vitamin D (antifungals, HIV antiretroviral therapy, anticonvulsants, etc), chronic kidney disease, hypophosphatemia and hypo/hypercalcemia, deeply pigmented skin and isolated elevation of alkaline phosphatase [36].A major issue in the determination of a 25(OH)D threshold value is the absolute need for a standardized method. In 2010, the Vitamin D External Quality Assessment Scheme (DEQAS) for the determination of 25(OH)D included 13 different methods which displayed high coefficient of variation and a range of four-fold between the lowest and highest values for a given sample. To standardize 25(OH)D measurement in both clinical and research laboratories, the Vitamin D Standardization Program (VDSP) was agreed in 2010 by the Office of Dietary Supplements (ODS) of the National Institutes of Health (NIH) [37]. This collaboration involved the coordinated efforts of ODS, the National Institute for Standards and Technology (NIST), the Centers for Disease Control and Prevention (CDC), the Vitamin D External Quality Assessment Scheme (DEQAS), the College of American Pathologists (CAP), the American Association for Clinical Chemistry (AACC), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), along with national surveys and collaborators around the world. The VDSCP calibration-certification process conducted by CDC comprised 2 phases : Phase 1 assessed and readjusted current calibration based on 40 single donor samples with assigned target values. In Phase 2, four quarterly challenges with 10 unknown serum samples were performed to verify that calibration was stable over 1 year. If performance criteria of a mean bias ≤ ±5% and an imprecision ≤ 10% were reached, then the certified labs were listed on the CDC website <https://www.cdc.gov/labstandards/pdf/hs/CDC_Certified_Vitamin_D_Procedures-508.pdf>. In 2018, the DEQAS reported an explosion of the number of methods for 25(OH)D determination, but with lower coefficient of variation values as compared to 2010 and a narrowing distribution with a smaller range of two-fold between the lowest and highest values for a given sample. The impact of the VDSP re-standardization was an overall improvement in the bias observed between the reference method and the different commercially available assays. Liquid chromatography–mass spectrometry (LCMS/MS) methods performed globally better than immunoassays, but all LCMS/MS methods are not equivalent and there are still important issues with immunoassays and LCMS/MS.

All the standardization process was performed with samples from healthy individuals, but 25(OH)D should also be measured in patients with different diseases (CKD, osteoporosis, …), physiological status (pregnancy) or ethnicity. Vitamin D binding protein concentration and polymorphism have also an impact on the results. In addition serum matrix may be different in sick patients and in healthy individuals [38].

The vitamin D metabolite ratio (VMR) 24,25(OH)2D to 25(OH)D has been proposed as a new marker of vitamin D status and as being predictive of fracture risk [39]. Cavalier et al. suggested that in clinical practice the concentrations of 24,25(OH)2D and 25(OH)D should be reported together with the probability that a ratio value is found in healthy subjects [40]. This information would allow one to escape the concept of vitamin D deficiency solely on the basis of a 25(OH)D threshold [5, 41, 42 , 43 ]. For example, amongst individuals with a 25(OH)D concentration above 52 nmol/L, over 99% exhibit detectable amounts of 24,25(OH)2D and thus are probably vitamin D sufficient [44]. This finding supports the 50 nmol/L cut-off recommended by the IOF [45]. However, the ratio 24,25(OH)2D to 25(OH)D can only be measured after determination of both moieties by LCMS/MS.

*In summary, great improvements in 25(OH)D assays standardization have been achieved in recent years. LCMS/MS methods generally perform better than immuno-assays, but all LCMS/MS methods are not equivalent. 24,25(OH)2D and VMR are promising tools to evaluate vitamin D deficiency at the individual level, but are only available with LCMS/MS.*

**Vitamin D and fracture risk**

In a prospective observational study in 1662 community-dwelling elderly men followed over a period of 4 years, a U-shaped association was observed with an increased risk of fracture in men with either 25(OH)D values ​​below 36 nmol/L or above 75 nmol/L [46]. Whether vitamin D, calcium or both supplements together are effective for the primary prevention of fractures is still debated. The absence or the demonstration of a beneficial anti-fracture effect is linked not only to the vitamin D dose, addition or not of calcium and duration of vitamin D supplementation but also largely to the population studied and in particular if this population is vitamin D depleted or replete.

In a Cochrane review [47], taking into account 11 studies involving more than 27,000 patients, vitamin D alone did not prevent hip fractures or any fractures (the latter based on 15 studies including more than 28,000 patients) (**Table 1**). On the other hand, the combination of vitamin D and calcium reduced the incidence of hip fractures by 16% based on 9 studies in almost 50,000 patients and the risk of any fractures by 5% taking into account 10 studies involving nearly 50,000 patients. In addition, fracture risk reduction was shown to be more important in institutionalized patients both for hip and for any fractures [47]. Nevertheless, even in institutionalized patients, the reduction of fracture incidence seems to be dependent on baseline serum 25(OH)D levels. Indeed, in 3,270 French institutionalized womenwith a mean age of 85 years and a baseline serum 25(OH)D of 35 nmol/L, a supplementation of 800 IU of vitamin D and 1200 mg of calcium for 18 months reduced the incidence of hip and of non-vertebral fractures [48]. In contrast, in an English study among 3,440 institutionalized men and women with a mean age of 85 years, but with a baseline 25(OH)D above 54 nmol/L, a supplementation of 100,000 units of vitamin D every 4 months for 3 years did not show a significant decrease in the incidence of fractures at the hip or at other sites [49]. More recently the Do-Health study involving 2,157 elderly subjects with a baseline 25(OH)D of 56 nmol/L, a daily supplementation of 2000 IU of vitamin D for 3 years did not reduce the incidence of non-vertebral fractures [13]. In the VITAL trial performed in more than 25,000 vitamin D replete subjects, there was no antifracture effect of 2000 IU/day of vitamin D [11]. With only 7 against 8 fractures in patients with 25(OH)D below a not prespecified 30 nmol/L threshold, a conclusion as to whether a response to supplementation is detectable in vitamin D deficient patients cannot be drawn.

In the ViDA trial in New Zealand, a monthly administration of 100,000 IU of vitamin D over about 3 years, after a loading dose of 200,000 IU, did not prevent fractures with even a non-significant trend for a higher fracture risk observed among healthy volunteers aged between 50 and 84 years and with a baseline 25(OH)D of 63 nmol/L [9]. Furthermore, an increase in falls and fractures was also previously observed with an annual high bolus of 500,000 IU of vitamin D in community-dwelling elderly Australian women at high risk of fracture, but with a baseline 25(OH)D considered as sufficient at around 50 nmol/L [50].

Many meta-analyses including various numbers of trials, hence of subjects, were recently published [47, 51-66] (**Table 1**). In that of Bolland et al [59], which included 81 studies but with only 6% of vitamin D deficient subjects at baseline, supplementation of vitamin D alone was not associated with a reduction of the incidence of total and hip fractures as well as of falls. Moreover this systematic review not only excluded trials combining vitamin D and calcium but included studies either with low doses of vitamin D or conversely high doses, especially bolus, which are known to increase falls and fractures [50, 67]. In another meta-analysis including 11 randomized trials enrolling at least 500 participants with the occurrence of at least 10 fractures representing more than 30,000 elderly subjects with baseline levels of 25(OH)D between 26 and 65 nmol/L, vitamin D supplementation alone did not decrease the risk of any or hip fracture [61]. In the meta-analysis of Yao et al [61] involving 6 RCTs representing 49,282 participants including institutionalized subjects, the combination of vitamin D allowing a median increase of 23 nmol/L in 25(OH)D level and of 1,000 to 1,200 mg/day of calcium supplementation, led to a 6% reduction in the risk of any fracture and a 16% reduction of hip fractures.

Regarding the effect of the combination of vitamin D and calcium on fracture prevention, a meta-analysis of 33 randomized trials involving more than 50,000 community-dwelling adults above 50 years of age and with an average baseline level of 25(OH)D at around 50 nmol/L did not show that vitamin D or calcium alone or the combination of vitamin D and calcium reduced the risk of fractures [57]. These negative results can be attributed to the exclusion of institutionalized subjects, to a very short follow-up for one-third of the studies and for the effect of vitamin D alone, and two-third of the trials concerned vitamin D given as a bolus.

In a network meta-analysis which tested the effect of different doses of vitamin D, calcium and their combination in randomized controlled trials lasting more than one year in community-dwelling subjects aged over 50 years, vitamin D, calcium or both were not better than placebo or no treatment for the reduction of the risk of any or hip fractures [60]. Very recently, a systematic umbrella review of meta-analyses of controlled trials showed that the combined supplementation of vitamin D and calcium was associated with a reduction in the risk of hip fracture in two-third of 12 meta-analyses (RR 0.61-0.84) and a reduction in the incidence of any fracture in 7 of 11 meta-analyses (RR 0.74-0.95) with greater effect among institutionalized subjects [65]. It should be noted that the baseline levels of vitamin D available in 5 of these meta-analyses were between 21 and 83 nmol/L and that no fracture risk reduction was observed in meta-analyses exclusively evaluating community-dwelling individuals or in those on vitamin D alone [65]. Finally, the review of Li et al [64] included not only pairwise meta-analysis of 35 trials, but also a bayesian network meta-analysis.Oral vitamin D3 supplementation did not significantly reduce the risk of any fractures, but vitamin D3 alone at a dose of 700–800IU/day and vitamin D3 plus calcium reduced by 9% and 15%, respectively, the incidence of any fractures in the pairwise meta-analysis. Similar results were obtained for hip fractures. However, no significant results were observed using Bayesian network meta-analyses [64]. Finally, in the most recent meta-analysis [66], 800-1000 IU/day of vitamin D and vitamin D together with calcium were associated with a 13% reduction in osteoporotic fracture risk.

*In summary, intervention studies in elderly subjects with vitamin D deficiency, as demonstrated by low serum 25(OH)D, have shown a beneficial effect of vitamin D (800-1000 IU/day) and calcium supplementation on any and hip fractures. Vitamin D deficient adults with 25(OH)D levels below 50 nmol/L could benefit from vitamin D and calcium supplementation that brings them into a 25(OH)D range of 50-100 nmol/L. On the other hand, vitamin D replete adults with 25(OH)D levels in the range of 50-100 nmol/L are unlikely to benefit from vitamin D supplementation. Furthermore, vitamin D supplementation resulting in 25(OH)D levels above 100 nmol/L probably increases the risk of fractures.*

**Vitamin D and falls**

According to some falls prevention guidelines, vitamin D supplementation is one of the components of multifactorial interventions, together with strategies aimed at minimizing medications, initiating individually tailored exercise program, treating vision impairment, managing postural hypotension, heart rate and rhythm abnormalities, curing foot and footwear problems and modifying the house environment [68, 69].

Vitamin D deficiency is associated with a higher risk of falls but vitamin D supplementation trials have produced discordant results, probably due to different doses and dosing intervals, calcium co-administration, observation duration and disregard of 25(OH)D at baseline and follow-up. Indeed, many randomized controlled trials with vitamin D and calcium supplementation contain substantial, and sometimes fatal design flaws [70]. To be informative as well as to be included in a systematic review, a randomized controlled trial should include features such as: use of a single form of vitamin D and not either 1-a-hydroxyvitamin D or calcitriol as recently reviewed [71, 72]; use of a low exposure control group, and the intervention must be large enough to produce a meaningful change in nutrient status; adequacy of dose in the treatment group and compliance to the treatment; demonstration/documentation of the depleted status at baseline and adequate status with a “therapeutic” blood level during follow-up; use of a uniform response measure and optimization of co-nutrient status such as calcium intake [70]. Overall, baseline 25(OH)D level is a key issue as an inclusion criteria and a cut-off has still to be identified as well as the serum 25(OH)D to be reached to obtain the beneficial effect [73].

If the effect of vitamin D supplementation is considered in the general population, no fall prevention can be detected as reported in a Cochrane systematic review [74] **Table 2**. On the other hand, a highly significant decrease of 43% of the risk of falls was observed in the two studies with lower baseline levels of 25(OH)D [74]. This observation has been confirmed in another meta-analysis in which a 15% decrease in the risk of falls was obtained when 90% of the population had a baseline vitamin D level below 75 nmol/L whereas there was no preventive effect of vitamin D in the replete population [75] (**Table 2**).

Regarding randomized controlled trials assessing the effect of vitamin D on falls, several studies showed a significant decrease of the risk of falls in participants who are vitamin D depleted at baseline and/or reached appropriate serum levels of 25(OH)D during the intervention [76-80]**.** There are also some interesting data from the DEX Trial showing no differences in fall risk in 409 home-dwelling women over 70 years of age with baseline vitamin D levels superior to 65 nmol/L [81-83], but when the same population was stratified for the levels of serum 25(OH)D reached during the 2-year follow-up, the highest quartile was associated with an about 37% lower risk of falls as compared to the lowest quartile[84]. Vitamin D supplementation doses higher than 1000 IU/day among community-dwelling older adults with an elevated fall risk and baseline 25(OH)D of 25 to 72.5 nmol/L might have differential effects on fall risk, with an increased risk of first time fall with fracture, but a decrease risk of outdoor falls [85].

Many randomized controlled trials have also not shown any reduction of falls with vitamin D supplementation. This lack of reduction in falls was probably either due to the populations studied which were already vitamin D replete at baseline [10, 86-89] or when high doses of vitamin D supplementation were administered [9, 90, 91].

Systematic reviews confirm that the reduction of falls with vitamin D supplementation is essentially observed in vitamin D deplete individuals [59, 63, 66, 74, 75, 92-96] (**Table 2)**. Indeed, in the review by Bolland et al. [59] which concluded that vitamin D did not prevent falls based on 81 trials, 44 of these trials were with daily doses less than 1000 IU and only 6% of participants had baseline 25(OH)D below 25 nmol/L. A comment by Bischoff-Ferrari et al. [97] reported that by considering only the 11 trials testing 800-1000 IU daily with more than 50% adherence and excluding large annual dosing trials (which have been shown to be associated with higher rates of falls), a significant fall reduction of 12% was observed. Another systematic review including 7 trials on vitamin D supplementation focused on community-dwelling vitamin D replete populations showed no prevention of falls [95]. More recent megatrials suggested that vitamin D supplementation in vitamin D replete individuals does not provide any benefit and it was also clearly indicated that large bolus doses of vitamin D increased the risk of falls [98, 99]. Indeed there is evidence that high dose vitamin D stimulates release of FGF-23 from osteocytes which impairs the 1-alpha hydroxylation of 25(OH)D to 1,25(OH)2D and also promotes 24-hydroxylation of 25(OH)D to the inactive form of 24, 25(OH)2D, and therefore excessive vitamin D may cause insufficiency of the active metabolite 1,25(OH)2D [100-102]

*In summary, vitamin D3 supplementation with doses less than 800 IU/day does not seem to reduce falls while doses between 800 and 1000 IU/day reduce falls and large bolus doses increase falls. In vitamin D deplete patients and as part of a multicomponent intervention, vitamin D supplementation may be effective in reducing fall risk. Unfortunately the recent 2017-2020 megatrials did not address the question of vitamin D and falls in vitamin D deplete populations.*

**Vitamin D and osteoarthritis**

The older adult population at risk of osteoporosis and falls is also at risk of osteoarthritis (OA). The effect of vitamin D on OA is unclear at least on the epidemiological point of view, but also at the intervention level, and may differ according to the severity of OA. The relationship between vitamin D and OA during OA development and progression is still debated. Observational studies have not shown any relationship between vitamin D status and OA development in patients with mean 25(OH)D above 50 nmol/L for pain, radiologic OA and cartilage volume loss [103]. A recent meta-analysis taking into account a series of confounders did not show significant associations between serum levels of 25(OH)D and the prevalence, incidence or progression of knee radiographic OA and joint space narrowing [104]. However, a sub-group analysis showed a significant associations between low vitamin D levels and progression of knee OA. A recent Mendelian randomization study involving 455,221 participants and taking into account the role of genetic background, indicated an inverse causal relationship between serum PTH concentrations and development of OA [105]. Moreover, a site-specific association was also observed between serum PTH levels and knee OA. The potential mechanisms by which serum PTH affects OA need to be further investigated. However, there was no evidence of a causal effect of serum 25(OH)D levels on OA [105]. In a large cross-sectional Italian study involving 2756 men and women with a mean age of 74.2 years, the relationship between 25(OH)D levels and any presence of OA and pain was examined [106]. Considering the subjects in the highest 25(OH)D quartile as a reference, those in the lowest quartile had significantly higher odds of OA and OA-related pain, particularly when the hand and hip were involved.

Randomized controlled trials on the effects of vitamin D supplementation on the progression of knee OA and related symptoms were recently summarized in several meta-analysis [103, 107-111] and are presented in **Table 3** including various studies[112-118]. Vitamin D supplementation to patients with 25(OH)D below 50 nmol/L, but not higher, may alleviate pain and improve joint function. In the review of Mathieu et al. [111], 3 studies assessing the effects of 2000 to 3000 IU of vitamin D per day for 1 or 2 years on OA symptoms in more than 500 patients demonstrated that VAS evaluated pain and WOMAC function were significantly improved, albeit with a modest effect size.

*In summary, observational and intervention studies provide little evidence for a protective effect of vitamin D on cartilage volume loss or radiologic OA worsening, although it may have a favorable effect on joint pain. Indeed, subset analyses and one pilot randomized controlled trial suggest that patients with 25(OH)D below 50 nmol/L may experience less joint pain with vitamin D supplementation. Trials assessing radiologic OA and cartilage loss did not demonstrate an effect of vitamin D supplementation in patients with* *25(OH)D levels above 50 nmol/L. No trials have been performed in patients with low 25(OH)D levels.*

**Metabolic conditions and treatment with calcifediol (25-hydroxyvitamin D (25(OH)D))**

The synthesis of calcifediol depends on the individual synthetic potential of CYP2R1, CYP24A1, CYP3A4, CYP2D25 enzymes [119, 120]. The mechanisms of control of CYP2R1 are unknown, even if there are some data on the effects of calcitriol, phenobarbital, glucocorticoids and antiretroviral drugs. Calcifediol administration produces rapid (within hours) increases in plasma 25(OH)D levels [121]. Calcifediol given daily, weekly, or as a single bolus is about two to three times more potent and more rapid in increasing plasma 25(OH)D concentrations than vitamin D in a double-blind randomized controlled trial in 35 Caucasian postmenopausal women aged between 50 and 70 years of age [122]. In another randomized controlled trial, 20 healthy postmenopausal women with an average 25(OH)D level of 33 nmol/L (13.2 ng/ml) and a mean age of 61.5 years were randomized to 20 μg of calcifediol or to 20 μg (800 IU) of vitamin D3 daily [123]. At 4 months, mean 25(OH)D levels increased to 173 nmol/L (69.3 ng/ml) in the calcifediol group and to 76 nmol/L (30.5 ng/ml) in the vitamin D group (p<0.0001). Calcifediol improved gait speed by 18% compared with vitamin D [123]. In another randomized controlled trial, 303 postmenopausal womenwith baseline levels of serum 25(OH)D below 50 nmol/L (20 ng/ml) were randomized 1:1:1 to calcifediol 0.266 mg/month for 12 months, calcifediol 0.266 mg/month for 4 months followed by placebo for 8 months, and cholecalciferol 25,000 IU/month for 12 months [124]. At month 4, 35% of postmenopausal women treated with calcifediol and 8.2% of those treated with cholecalciferol reached serum 25(OH)D levels above 75 nmol/L (30 ng/ml) (p < 0.0001). This difference was already observed after the first month of treatment and confirms that calcifediol is effective, faster, and more potent than cholecalciferol in increasing serum 25(OH)D levels [124].

Calcifediol may be an option for managing vitamin D deficiency in obese or malabsorptive patients who have difficulty increasing serum 25(OH)D with vitamin D supplementation. Indeed, in a pharmacokinetic study of a randomized, double-blind crossover trial, AUCs of 900 ug calcifediol were not significantly different between either malabsorptive patients and healthy participants, and between participants with higher BMI and those with lower BMI whereas AUCs of 900 ug vitamin D3 were significantly lower by 64% and 53%, respectively[102].

Calcifediol in an extended-release formulation (ERC) could be a novel approach to manage secondary hyperparathyroidism linked to 25(OH)D insufficiency in non-dialysis CKD [125]. Indeed, ERC has been shown to increase 25(OH)D gradually and provide a physiologically-regulated increase in 1,25(OH)2D that can reliably lower PTH in CKD stage G3–G4 without clinically meaningful increases in serum calcium and phosphate levels [126]. Patients with nephrotic syndrome have low blood levels of 25OHD. Oral therapy with 200 ug calcifediol normalized plasma levels of 25(OH)D within 48 h in patients with nephrotic syndrome though intestinal calcifediol absorption was delayed and its elimination rate was enhanced as compared to control subjects [127].

In men with hypogonadism characterized by low levels of 25(OH)D, supplementation with calcifediol (4000 IU or 100 ug per week) for 3 months, but not the administration of cholecalciferol(5000 IU per week), increased 25(OH)D and decreased PTH levels [128]. Among renal transplant recipients, insufficient or deficient 25(OH)D levels are highly prevalent, and these deficits improved with moderate doses of oral calcifediol without side effects [129].

Another condition in which a rapid correction of inadequate vitamin D levels has been advocated is COVID-19. While the available evidence based largely on poor-quality observational studies may show a trend for an association between low serum 25(OH)D levels and COVID-19 related health outcomes, this relationship was not found to be always statistically significant [130-132]. Calcifediol supplementation may have a protective effect on COVID-19 related ICU admissions in an observational cohort study [133] and in a pilot randomized clinical study [134] and was also associated with lower in-hospital mortality during the first 30 days [135] as well as a lower mortality in patients achieving serum 25(OH)D levels ≥ 75 nmol/L [136], as compared with those not receiving calcifediol. Even moderate doses of 5000 IU daily for 2 weeks was associated with faster resolution of Covid-19 symptoms [137]. The current use of high doses of vitamin D in COVID-19 patients is not based on solid evidence. Very recently in a randomized controlled trial with 50 subjects hospitalized for COVID-19 with a mean age of 65 years and a baseline 25(OH)D level at 55 nmol/L, 25,000 IU cholecalciferol/day over 4 consecutive days followed by 25,000 IU/week up to 6 weeks reduced the hospitalization duration (4 days vs 8 days) and the need for supplemental oxygen [138].

*In summary the administration of calcifediol is superior to cholecalciferol in conditions requiring a rapid increase in 25(OH)D and in conditions of liver insufficiency (****Table 4****, adapted from [139]).*

**Vitamin D safety and therapeutic window**

The upper limit of safety for vitamin D intake is suggested to be 4000 IU/day according to the Institute of Medicine [45]. For serum total 25(OH)D levels, the Institute of Medicine and the US Endocrine Society used different cut-points to define deficiency, insufficiency and sufficiency as well as for a threshold of possible harm (125 and 250 nmol/L, respectively) [140]. Issues in vitamin D supplementation safety concern the dose of vitamin D, the outcomes such as serum levels and urinary excretion of calcium, falls and bone, the schedule of administration and the target population (eg. Vitamin D replete vs deficient, obese, comorbidities, etc) [141]. In vitamin D intoxication, there is persistence of abnormally elevated fasting urinary calcium and of serum 25(OH)D concentrations, long after normalization of plasma calcium, indicating that calcemia may be not sensitive enough to detect vitamin D overdosing [142]. A dose-response relationship based on randomized controlled trials’ results was observed between higher dose and higher achieved 25(OH)D serum values and fall and fracture prevention with optimal benefits with 700 IU to 1000 IU vitamin D3/day or mean serum 25(OH)D levels between 75 and 110 nmol/L [143]. In a 12-month double blind randomized controlled trial, elderly women with a mean age of 66 years and a relatively low baseline 25(OH)D of 38 nmol/L were randomized to one of seven daily oral doses of vitamin D3 (range 400 to 4800 IU) or placebo [144]. The maximum decrease in falls was obtained with serum 25(OH)D of 75-100 nmol/L and median doses 1600 to 3200 IU while fall rates increase as serum 25(OH)D exceeded 100 to 112.5 nmol/L suggesting a biphasic effect (U-shape curve) of vitamin D effect [144]. Likewise, in healthy community-dwelling postmenopausal women with vitamin D insufficiency (25(OH)D < 50 nmol/L), a relatively high dose of vitamin D3 (2800 IU/day) had no beneficial effects on muscle strength and physical performance with even some deleterious effect on handgrip and knee flexion 60o [145]. Furthermore, in a one-year double blind randomized controlled trial, community-dwelling men and women aged 70 years and older amongst whom 58% were vitamin D insufficient (< 50 nmol/L), received 24,000 IU vs 60,000 IU vitamin D3 vs 24,000 IU vitamin D3 and 300 ug calcifediol [146]. Although higher monthly doses of vitamin D were effective in reaching a 25(OH)D threshold of at least 75 nmol/L, participants had no benefit on lower extremity function, but an increased risk of falls was even observed in the highest quartile of achieved 25(OH)D of 125 nmol/L as compared to the lowest quartile with 25(OH)D at 67 nmol/L [146]. Finally, in the Australian D-Health trial, a monthly dose of 60,000 IU of cholecalciferol given to 21,315 participants aged 60–84 years for a maximum of 5 years with mean achieved serum 25(OH)D concentrations of 114.8 nmol/L did not reduce the risk of falling, but even was associated with a higher risk in a subgroup with BMI < 25 kg/m2 [91].

The importance of the outcome and of the target population in evaluating vitamin D dosing and efficacy was well illustrated in a randomized controlled trial among older long-term care residents in whom high-dose vitamin D3 supplementation of 3,000-4,000 compared to 400-1,000 IU/day for 12 months reduced the incidence of acute respiratory infection but increased the rate of falls [147]. Another prospective observational study in older community-dwelling men followed for 4.3 years highlighted a safe target range for serum 25(OH)D concentrations since the risk for fracture was greatest in men with 25(OH)D levels in the lowest quintile (< 36 nmol/L) as well as in men in the highest quintile (> 72 nmol/L) [46]. Regarding bone microstructure, vitamin D given for 3 years at a dose of 4,000 IU or 10,000 IU compared with 400 IU/day in healthy men and women with a mean age of 62 years and a baseline 25(OH)D level of 79 nmol/L resulted in statistically significant lower volumetric bone density at the distal radius and tibia with the 10,000 IU/day dose [148]. These deleterious effects of high-dose vitamin D supplementation with 4,000 or 10,000 IU, compared with 400 IU daily, resulted in greater losses of total volumetric BMD in healthy vitamin D-sufficient females, but not in males [149].

Regarding intermittent regimens of vitamin D supplementation, similar serum 25(OH)D concentration were achieved by 2 months with vitamin D3-supplementation of 1,500 IU daily, 10,500 IU once weekly, or 45,000 IU once monthly in elderly women randomized after hip fracture surgery [150]. In some European countries, 25,000 IU monthly (corresponding thereby to 800 IU/day) is commonly prescribed. There is no evidence to recommend or to discourage this regimen. The choice may be left to the patient’s preference for ensuring optimal adherence to vitamin D supplementation

In a large randomized controlled trial in UK among community-dwelling men and women, 100,000 IU oral vitamin D3 given every four month over five years, corresponding to about 800 IU daily, prevented fractures in this non-depleted vitamin D population with serum 25(OH)D measured in a small sub-group of 74.3 vs 53.4 nmol/L in the placebo group after four years [151]. On the other hand, among older community-dwelling women considered to be at high risk of fracture, annual oral dose of 500,000 IU of cholecalciferol for three years resulted in an increased risk of falls and fractures which was already observed within 3 months after dosing [50].

Is a vitamin D loading dose useful and/or safe? In a randomized controlled trial in vitamin D, non-depleted elderly participants with baseline 25(OH)D of 58 nmol/L, a loading dose of 500,000 IU showed a rapid increase in 25(OH)D up to 120 nmol/L by one month and then reached a plateau of about 80 nmol/ by 3 to 5 months whereas it took 3-5 months to obtain a similar plateau with 50,000 IU monthly of vitamin D supplementation [152]. A loading dose of 600,000 IU in elderly subjects increased sCTX already by day 1, which remained sustained for two months, whereas sCTX changes with 300,000 and 100,000 IU were considerably lower and reached statistical significance only within the first 3 days with the 300,000 IU dose [153]. Finally, a single bolus dose equivalent to 700 IU/day of vitamin D3 supplementation in postmenopausal women with a mean age of 65 years, did not improve distal radius fracture healing over a 6 week observation while a bolus equivalent to 1800 IU/day may be detrimental in restoring bone stiffness during the first 12 weeks of fracture healing [154]. These results call for some caution in using large loading doses [155].

*In summary, daily doses of 800-1’000 IU of vitamin D are safe while intermittent regimens with doses higher than those equivalent to this daily dosing* *are not recommended. The risk of overdosing expression is related to the outcome evaluated. The upper limit of safety for clinical outcomes (both for dose and circulating levels) should be better evaluated and defined.*

**Conclusion**

Considering the well-recognized major musculoskeletal disorders associated with severe vitamin D deficiency and taking into account a possible biphasic effect of vitamin D, the results of various meta-analyses of randomized controlled trials on the effects of vitamin D on fracture risk, falls or osteoarthritis, indicate that 1000 IU daily should be recommended in patients at increased risk of vitamin D deficiency (**Table 5**). This regimen is safe. Some groups of patients may benefit from a vitamin D loading dose or from calcifediol treatment to early achieve 25-hydroxyvitamin D therapeutic levels.

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