



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

Thierry Chevalley¹ · Maria Luisa Brandi² · Kevin D. Cashman³ · Etienne Cavalier⁴ · Nicholas C. Harvey^{5,6} · Stefania Maggi⁷ · Cyrus Cooper^{5,6,8} · Nasser Al-Daghri⁹ · Oliver Bock^{10,11} · Olivier Bruyère¹² · Mario Miguel Rosa¹³ · Bernard Cortet¹⁴ · Alfonso J. Cruz-Jentoft¹⁵ · Antonio Cherubini¹⁶ · Bess Dawson-Hughes¹⁷ · Roger Fielding¹⁷ · Nicholas Fuggle^{5,6} · Philippe Halbout¹¹ · John A. Kanis^{18,19} · Jean-Marc Kaufman²⁰ · Olivier Lamy²¹ · Andrea Laslop²² · Maria Concepción Prieto Yerro²³ · Régis Radermecker²⁴ · Jotheeswaran Amuthavalli Thiyagarajan²⁵ · Thierry Thomas²⁶ · Nicola Veronese²⁷ · Marten de Wit²⁸ · Jean-Yves Reginster²⁹ · René Rizzoli¹

Received: 14 September 2022 / Accepted: 10 October 2022
© The Author(s) 2022

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 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

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

✉ Thierry Chevalley
Thierry.chevalley@hcuge.ch

Extended author information available on the last page of the article

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); and (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 (i.e., 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, on 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 $\sim 35^{\circ}$ to $\sim 69^{\circ}$ N [29]. Significant differences in UVB availability between inland and coastal areas were 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 outdoor 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 4–8 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 μg /day of vitamin D intake (400 IU) based on European dietary surveys with a mean intake of 3.3 and 2.7 μg /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 range 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 μg /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 (anti-fungals, 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 fourfold 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 $\leq \pm 5\%$ and an imprecision $\leq 10\%$ 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 twofold 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, etc.), 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, 41–43]. 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 immunoassays, 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 deplete 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 women with 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 3440 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 2157 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 anti-fracture 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,

Table 1 Meta-analyses on vitamin D supplementation and fractures

Author, year, studies	Intervention tested	Target population and limitations	Results for fractures
Bischoff-Ferrari et al. (2009) [51] 12 RCTs (non-vertebral fractures) N = 42,279 8 RCTs (hip fractures) N = 40,886	Vit D ± calcium Vit D ≤ 400 IU/d in 3 trials whereas the other 9 RCTs had mean intakes of 482–770 IU/d Calcium 500–1200 mg/d in combination with vit D in 7 RCTs	Mean age of 78 years, 89% women Duration from 12 to 84 months	Pooled relative risk 0.86 (95% CI 0.77–0.96) for prevention of non-vertebral fracture and 0.91 (95% CI 0.78–1.05) for hip fracture For the higher dose (> 400 IU), pooled RR 0.80 (95% CI 0.72–0.89); n = 33,265, 9 trials for non-vertebral fractures and 0.82 (95% CI 0.69–0.97); n = 31,872, 5 trials for hip fractures RR 1.13 (95% CI 0.98–1.29) for hip fractures No significant variations found between results of studies randomizing participants to: < 800 IU/day 1.14 (95% CI 0.86–1.49) or ≥ 800 IU/day 1.12 (95% CI 0.96–1.32)
Lai et al. (2010) [52] 7 RCTs N = 12,762	Vit D alone 400–1100 IU/day in 6 RCTs Vit D 800 IU + calcium 1000 mg/day in 1 RCT	RCT including a minimum of 100 participants with at least one radiologically confirmed hip fracture in each group	Vit D3 + calcium compared to placebo: OR 0.77 (95% CI 0.6–0.93) for non-vertebral fracture and OR 0.70 (95% CI 0.53–0.90) for hip fracture Pooled relative risk 1.03 [95% CI 0.84 to 1.26], with high heterogeneity
Bergman et al. (2010) [53] 8 RCTs N = 12,658	Vit D ± calcium 8 RCTs N = 12,658	4 RCTs on non-vertebral fracture, n = 3510 5 RCTs on hip fracture, n = 7473	Pooled relative risk, 0.88 [95% CI 0.78–0.99], with moderate heterogeneity Significant risk reduction among institutionalized elderly persons (relative risk, 0.71 [95% CI 0.57–0.89]) OR 0.81 (95% CI 0.68–0.96) for hip fracture and OR 0.94 (95% CI 0.84–1.02) for non-vertebral fracture Vit D and calcium given separately were ineffective RR 1.12 (95% CI 0.98–1.29) for hip fracture RR 1.03 (95% CI 0.96–1.11) for any fracture
Chung et al. (2011) [54] 16 RCTs N = 19,878	Vit D (400–1370 IU/d) alone 5 RCTs—N = 14,583 Vit D (300–1000 IU/d) + calcium 500–1200 mg/d 11 RCTs—N = 52,915	Elderly men and women with follow-up ranging from 7 months to 5 years	RR 0.84 (95% CI 0.74–0.96) for hip fracture RR 0.95 (95% CI 0.90–0.99) for any fracture RR 0.75 (95% CI 0.62, 0.92) and RR 0.85 (95% CI 0.74, 0.98) for hip and any fracture, respectively in institutionalized-dwelling subjects 15% reduction of total fractures (RR = 0.85; 95% CI 0.73–0.98) 30% reduction of hip fractures (RR = 0.70; 95% CI 0.56–0.87)
Murad et al. (2012) [55] Network meta-analysis	Vit D ± calcium	Median age, 64 years; 86% females and 88% Caucasians; median follow-up, 24 months	
Avenell et al. (2014) [47] 31 RCTs N = 36,282	Vit D alone 11 RCTs, N = 27,693 15 RCTs, N = 28,272 Vit D + calcium 9 RCTs, N = 49,853 10 RCTs, N = 49,976 <i>Institutional (2 RCTs), N = 3853</i>	12/31 RCTs had participants with a mean or median age of 80 years or over Prevention of fractures in community, nursing home or hospital inpatient populations	
Weaver et al. (2016) [56] 8 RCTs N = 30,970	Vit D + calcium	Mostly adults aged 65+ years – Excluded studies that tested vit D without calcium – Included 40% of the literature that contributed to current guidelines on vit D	

Table 1 (continued)

Author, year, studies	Intervention tested	Target population and limitations	Results for fractures
Zhao et al. (2017) [57] 33 RCTs ($n=51,145$)	Vit D, Calcium and Vit D + calcium	Community-dwelling participants aged 50+ years for primary prevention without a prior fracture; baseline 25(OH)D \approx 50 nmol/L Exclusion of older adults living in institutions, most vulnerable to low calcium intake, vitamin D deficiency and fracture risk 11 out of 33 with follow-up of \leq 12 months with little potential to show benefit on fracture reduction, 4 trials had an open study design without a treatment in the control group No adjustment for adherence For vit D alone 8 of the 12 trials gave vit D in bolus doses (orally or intramuscular administration), which has repeatedly raised concerns in the literature about promoting both falls and fractures	No significant effect of calcium, vit D or both on risk of hip fracture compared with placebo or no treatment: Calcium: RR = 1.53 (95% CI 0.97–2.42) Vit D: RR = 1.21 (95% CI 0.99–1.47) Vit D + calcium RR = 1.09 (95% CI 0.85–1.39) No significant benefit on any intervention on the incidence of non-vertebral, vertebral, or total fractures
Kahwati et al. (2018) [58] 11 RCTs ($N=51,419$)	Vit D, Calcium and Vit D + calcium	Community-dwelling adults aged 50+ years not at risk for osteoporosis or vit D deficiency Panel acknowledged limited trial data for primary prevention	For vit D doses greater than 400 IU (according to current recommendations), the panel concluded that there is insufficient evidence to assess a benefit from vit D
Bolland et al. (2018) [59] 81 unblinded and blinded randomized trials among ($n=44,790$)	Vit D compared to untreated controls, placebo or another dose of vit D	Adults aged 50+ years Authors excluded trials that combined vit D with calcium and thereby 40% of the literature that contributed to current guidelines Authors included large bolus doses that have consistently increased the risk of falls and fractures Biased reporting on low-dose vit D with 800 IU vit D trials	No benefit on fractures Re-analysis of 800–1000 IU vit D trials of this meta-analysis and excluding bolus trials suggests a significant 14% reduction in total fractures
Hu et al. (2019) [60] 25 RCTs $N=43,510$	Vit D, Calcium and Vit D + calcium	Adults aged older than 50 years and living in their communities and only studies that lasted more than a year	No reduction of the risk of total, hip and vertebral fractures using different concentrations of vit D, calcium or their combination compared with placebo or no treatment
Yao et al. (2019) [61] 11 RCTs $N=34,243$ 6 RCTs $N=49,282$	Vit D alone (daily or intermittent dose of 400–30 000 IU) 11 RCTs Vit D (400–800 IU daily) + calcium (1000–1200 mg daily) 6 RCTs	Mean age 65.9–85.0 years, baseline 25(OH)D 26.5–65.8 nmol/L, mean duration 3 yrs. Yielding a median difference in 25(OH)D concentration of 21 nmol/L Constrained by infrequent intermittent dosing, low daily doses of vit D, or an inadequate number of participants Yielding a median difference in 25(OH)D concentration of 23 nmol/L	Vit D alone: no reduction of risk of any fracture (RR 1.06; 95% CI 0.98–1.14) or hip fracture (RR 1.14; 95% CI 0.98–1.32) ↓ 6% of any fracture (RR 0.94; 95% CI 0.89–0.99) and ↓ 16% of hip fracture (RR 0.84; 95% CI 0.72–0.97)

Table 1 (continued)

Author, year, studies	Intervention tested	Target population and limitations	Results for fractures
Eleni et al. (2020) [62] 10 RCTs N = 74,325	Vit D + calcium	Patients aged 50 years or older Reported on fractures as a primary outcome	RR 0.74 (95% CI 0.58–0.94) for total fracture RR: 0.61 (95% CI 0.4–0.92) for hip fracture 8 RCTs, N = 68,957
Thanapluetiwong et al. (2020) [63] 26 RCTs N = 40,209	Vit D ± calcium	Major populations were elderly women with age less than 80 years	Vit D alone failed to show any fracture lowering benefit, RR 0.949 (95% CI 0.846–1.064) Vit D + calcium significantly lower fracture rates, RR 0.859 (95% CI 0.741–0.996)
Li et al. (2021) [64] 33 RCTs N = 83,083	Vit D ± calcium	No younger than 47 years old; Follow-up ranged from 3 to 84 months Fracture cases confirmed with hospital diagnosis, medical records, or World Health Organization diagnostic criteria; subjects not treated with any osteoporosis medications and did not have any special physical training; Mean age between 62 and 85 years	Vit D alone: no reduction of the risk of total fractures (RR 0.96 (95% CI 0.87–1.05)) Vit D3 (700–800 IU/d) + calcium: significant reduction of total (RR 0.85 (95% CI 0.77–0.95), hip (RR 0.81 (95% CI 0.68–0.97), and non-vertebral fractures (RR 0.84 (95% CI 0.74–0.95), in a pairwise meta-analysis Vit D + calcium: ↓ risk of hip fractures in 8/12 SRs/MAs (RR 0.61–0.84) ↓ risk of any fractures in 7/11 SRs/MAs (RR 0.74–0.95)
Chakhtoura et al. (2022) [65] Umbrella review of meta-Analyses 25 RCTs	Vit D + calcium—13 SR/MAs		
	Vit D alone—19 SR/MAs Vit D dose 400–800 IU/day	Trials extended from 1 to 7 years 5 SRs/MAs reported on baseline 25(OH)D (20.9–83.8 nmol/L)	
	6 SR/MAs included 1 trial providing a high dose of 300,000 IU once Calcium dose was 500–1200 mg/day		No fracture risk reduction in SRs/MAs exclusively evaluating community-dwelling individuals or in those on vit D alone compared to placebo/control
Kong et al. (2022) [66] 32 RCTs N = 104,363 16 RCTs N = 36,793 for fracture outcome	Vit D (median dose of 800 IU/d) ± calcium 8 studies reported < 800 IU/day	Most studies included women with 75% of participants (range 15–100%)	Vit D 800–1000 IU/d: Pooled relative risk 0.87 (95% CI 0.78–0.97) for osteoporotic fractures
	15 studies 800–1000 IU/day, and	Median age was 72 years (range 53–85)	No reduction of hip fractures RR 0.84 (95% CI 0.64–1.10)
	9 studies > 1000 IU/day 26 studies reported daily administration, while 6 reported intermittent administration	Median follow-up duration was 24 months (range 9–120)	Vit D 800 to 1000 IU/d + calcium: pooled RR 0.88 (95% CI 0.78–1.00) for osteoporotic fractures

RCT randomized controlled trial, 25(OH)D 25-hydroxyvitamin D, Vit D vitamin D, RR relative risk, OR odds ratio

Bold: statistically significant differences

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 1000 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, 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 700–800 IU/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- α -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

Table 2 Meta-analyses of studies on vitamin D supplementation and falls

Author, year	Intervention	Target population, duration and baseline 25(OH)D	Outcome: falls
Bischoff-Ferrari et al. (2009) [92] 7 RCTs N = 1921	Vit D ± calcium	Individuals aged 65 years and older with a minimum follow-up of 3 months	Pooled RR 0.81 (95% CI 0.71–0.92) with Vit D 700 to 1000 IU daily ± calcium
Murad et al. (2011) [93] 26 RCTs N = 45,782	Vit D ± calcium	78% women, mean age 76 years, high risk of falling (15–69%, median 50%); duration: 3–62 months (median 12 months) Included both Vit D-deplete and -replete individuals, with info on Vit D status	Pooled RR 0.77 (95% CI 0.65–0.90) in those with achieved 25(OH)D ≥ 60 nmol/L OR 0.86 (95% CI 0.71–0.92) Effect more prominent in vit D-deficient patients at baseline and in studies in which calcium was co-administered with vit D
Gillepsie et al. (2012) [74]	Vit D	Most community-dwelling older people 7 RCTs; N = 9324 13 RCTs; N = 26,747	RR 1.00 (95% CI 0.90–1.11)—no reduction of the rate of falls RR 0.96 (95% CI 0.89–1.03)—no reduction of risk of falls
LeBlanc et al. (2015) [75] 11 RCTs N = 5682	Vit D	In those with low vit D level at baseline: 2 RCTs; N = 260 3 RCTs; N = 562 11 RCTs; N = 5682	RR 0.57 (95% CI 0.37–0.89) for rate of falls RR 0.65 (95% CI 0.46–0.91) for number of fallers RR 0.89 (95% CI 0.82–0.97)
Wu et al. (2017) [94] 26 RCTs N = 32,686	Vit D (ranged from 200 to 1000 IU/day in 11/26 RCTs dosage was 800 IU/day, 6 RCTs used a total dosage ranging from 300,000 IU/36 months to 600,000 IU/6 months) ± calcium	Low vit D levels (90% of population < 75 nmol/L); 7 RCTs; N = 2118 Not low vit D levels or not reported: 4 RCTs; N = 3564 Mean age ± SD of participants in these studies varied from 67 ± 2 to 92 ± 6 years Duration: 1–60 months	RR 0.85 (95% CI 0.73–0.98) in bold RR 0.89 (95% CI 0.83–1.04 not in bold since not significant) OR for experiencing at least one fall, 0.87 (95% CI 0.80–0.94) with combined vit D + calcium
Guirguis-Blake et al. (2018) [95] 7 RCTs n = 7531	Vit D ± calcium Vit D (700 IU or 800 IU daily, 150 000 IU every 3 months or 500 000 IU annually) 2 trials administered 1 µg of 1-hydroxycholecalciferol daily or 0.25 µg of calcitriol twice daily	Mean age: 71–77 years Vit D for 9 months up to 5 years Excluded studies on Vit D deplete Baseline mean serum 25(OH)D levels ranging from 65.9 to 79.4 nmol/L	Vit D did not prevent falls Annual high-dose cholecalciferol (500,000 IU) showed an increase in falls, people experiencing a fall, and injurious falls; Calcitriol showed a reduction in falls and people experiencing a fall
Bolland et al. (2018) [59] 37 RCTs N = 34,144	Vit D alone in the majority of RCTs with daily dose mostly < 1000 IU/day	Unselected populations of community-dwelling women aged 65 years or older Duration ≤ 1 year for the majority of studies	OR 0.97 (95% CI 0.93–1.02) Results were similar in RCTs of high-dose versus low-dose vit D and in sub-group analyses of RCTs using doses greater than 800 IU per day

Table 2 (continued)

Author, year	Intervention	Target population, duration and baseline 25(OH)D	Outcome: falls
Thanapluetiwong et al. (2020) [63] 47 RCTs N = 58,424	Vit D ± calcium 37 trials with vit D3 7 trials with vit D2 1 trial with vit D2 and vit D3 2 trials with vit D analogues	Only 6% (4 studies) 25OHD < 25 nmol/L Non standardized lab measurements Excluded trials with Vit D and calcium supplementation Populations were mainly elderly women with age less than 80 years	Comment by Bishoff-Ferrari (2019): considering 11 trials testing 800–1000 IU Vit D daily, with more than 50% adherence, and excluding large annual dosing trials, we see a significant falls' reduction (RR = 0.88) RR 0.948 (95% CI 0.914–0.984) By sub-group analyses, only Vit D with calcium supplement significantly reduce fall incidence, RR 0.881 (95% CI 0.821–0.945) Vit D3 supplement decreased incidence of fall but this occurred only when vit D3 was combined to calcium RR 1.00 (95% CI 0.95–1.05) Subgroup analyses showed that with baseline of serum 25OHD < 50 nmol/L fall risk was reduced RR 0.77 (95% CI 0.61–0.98) RR 0.88 (95% CI 0.80–0.97)
Ling et al. (2021) [96] 31 RCTs N = 57,867	Vit D alone, daily or intermittent doses of 400–60 000 IU 21 RCTs, n = 51,984	Only trials enrolling adults (age ≥ 18)	
Kong et al. (2022) [66] 32 RCTs N = 104,363	Vit D (daily doses of 700–1000 IU) plus calcium (daily doses of 1000–1200 mg) 10 RCTs, n = 5883 Median daily dose of Vit D: 800 IU	Most studies included women (75% of participant; range 15–100%) Median age was 72 years (range 53–85) Median follow-up duration: 24 months (range 9–120)	Pooled RR 0.91 (95% CI 0.85–0.98) with daily Vit D dose of 800–1000 IU No reduction in studies with < 800 or > 1000 IU/day Daily administration of Vit D associated with reduced risk of falls, while intermittent dose was not Patients with vit D deficiency showed a significant risk reduction of falls with Vit D supplementation
	21 RCTs, N = 36,793 with falls as outcomes 8 studies: < 800 IU/day 15 studies: 800–1000 IU/day, and 9 studies: > 1000 IU/day 26 studies reported daily administration, while 6 reported intermittent administration		

RCT randomized controlled trial, 25(OH)D 25-hydroxyvitamin D, Vit D vitamin D, RR relative risk, OR odds ratio

Bold: statistically significant differences

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 decreased 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,

Table 3 Meta-analyses of studies on vitamin D supplementation and knee osteoarthritis

Author	RCT number and sample size	Vit D intervention	Outcome
Gao et al. (2017) [107]	4 RCTs; <i>n</i> = 1136	800–2000 IU daily or 50,000–60,000 IU monthly	<p>↓ WOMAC pain: score – 1.65 (95% CI – 2.16 to – 1.14) with 2000 IU/day</p> <p>↑ WOMAC function: score -1.87 (95% CI – 2.58 to – 1.17) with 2000 IU/day</p> <p>No effect on WOMAC stiffness and tibia cartilage volume</p>
Diao et al. (2017) [108]	4 RCTs; <i>n</i> = 1136	800–2000 IU daily or 50,000–60,000 IU monthly	<p>↓ WOMAC pain: SDM -0.32 (95% CI – 0.63 to – 0.02)</p> <p>No effect on tibia cartilage volume or joint space width, regardless of baseline 25(OH)D levels</p>
Beaudart et al. (2020) [109]	4 RCTs; <i>n</i> = 1136	800–2000 IU daily or 50,000–60,000 IU monthly	<p>↓ WOMAC pain: SDM -0.31 (95% CI – 0.56 to – 0.06)</p> <p>↑ WOMAC function: SDM -0.30 (95% CI – 0.49 to – 0.11)</p>
Zhao et al. (2021) [110]	6 RCTs; <i>n</i> = 1599	800–2000 IU daily or 50,000–60,000 IU monthly	<p>↓ WOMAC pain: SDM -0.32 (95% CI – 0.63 to – 0.02)</p> <p>↑ WOMAC function: SDM -0.34 (95% CI – 0.60 to – 0.08)</p> <p>↑ WOMAC stiffness: SDM -0.13 (95% CI – 0.26 to – 0.01)</p> <p>No effect on tibia cartilage volume or joint space width</p>
Mathieu et al. (2022) [111]	3 RCTs; <i>n</i> = 662	2000 IU daily or 50,000–60,000 IU monthly	<p>↓ WOMAC pain: SDM -0.20 (95% CI – 0.35 to – 0.04)</p> <p>↑ WOMAC function: SDM – 0.44 (95% CI – 0.80 to – 0.09)</p>

Bold value indicates statistically significant differences

Vit D vitamin D, *RCT* randomized controlled trial, *SDM* standardized mean difference

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 women with 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 25(OH)D. 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 (e.g., Vitamin D replete vs deficient, obese, comorbidities, etc.) [141]. In vitamin D intoxication, there

Table 4 Conditions in which the administration of calcifediol may be preferable to cholecalciferol

Inactivating mutations of genes encoding hepatic 25-hydroxylase
Iatrogenic inhibition of hepatic 25-hydroxylase [e.g., anticonvulsants, antiretroviral drugs, glucocorticoids and bisphenol A]
Hepatic insufficiency
Decreased bioavailability (adipose tissue sequestration)
Fat malabsorption
CKD—renal osteodystrophy
Nephrotic syndrome (proteinuria)
Male hypogonadism
Other conditions (e.g., diabetes mellitus I, transplant recipients)
Long-lasting osteomalacia
COVID-19

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–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 400–4800 IU) or placebo [144]. The maximum decrease in falls was obtained with serum 25(OH)D of 75–100 nmol/L and median doses 1600–3200 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 60° [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 µg 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 sub-group 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 3000–4000 compared to 400–1000 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 4000 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 4000 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 1500 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/L by 3–5 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

Table 5 Indications for vitamin D supplementation

Daily vitamin D (800–1000 IU)
Subjects at risk of osteoporosis
Patients on concurrent osteoporosis treatment
Patients with fragility fracture
Elderly people at risk of falling
Obese patients
Subjects with pigmented skin
Subjects with limited sun exposure
Subjects with insufficient vitamin D intake
Patients with malabsorption ^a
Patients after bariatric surgery ^a
Patients on anticonvulsants
Patients on glucocorticoids
Loading dose (25,000 or 50,000 IU/week for 4–6 weeks)
Low 25-hydroxyvitamin D levels
Need for a rapid correction of vitamin D deficiency
After bariatric surgery
Malabsorption
Severe obesity

In some countries, 25,000 IU monthly (corresponding thereby to 800 IU/day) is commonly prescribed, and might be acceptable if it meets patients' preference despite equivalence with the daily dose was not clearly established

^aHigher doses (2000 IU/daily) may be needed

of fracture healing [154]. These results call for some caution in using large loading doses [155].

In summary, daily doses of 800–1000 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.

Funding Open access funding provided by University of Geneva.

Declarations

Conflict of interest MLB has received consultancy, lecture fees and honoraria from Abiogen, Alexion, Amgen, Bruno Farmaceutici, Kyowa Kirin, Servier, and SPA. EC is consultant for DiaSorin, Fujirebio, IDS, Menarini, Nittobo and bioMérieux. NCH has received consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, UCB, Shire, Consilient Healthcare, Kyowa Kirin and Internis Pharma. SM reports grants from Sanofi, MSD, GSK, Pfizer, Takeda, Mylan through institution as organizer of meetings/congresses and as principal investigator of epidemiological studies, for taking part to advisory boards and expert meetings. CC has received consultancy, lecture fees and honoraria from AMGEN, GSK, Alliance for Better Bone Health, MSD, Eli Lilly, Pfizer, Novartis, Servier, Medtronic and Roche. OBR reports consulting or lecture fees for AMGEN, Aptissen, Biophytis, IBSA, MEDA, Mylan, Novartis, Sanofi, TRB Chemedica, UCB, Viatrix outside this manuscript subject. BC has received fees for lectures or scientific advisory boards from Alexion, AMGEN Aptissen, BMS, Expanscience, Ferring, Lilly, Kyowa-Kirin, MSD, Novartis, Roche diagnostics, Sublimed, Theramex, UCB, Viatrix. ACJ has received fees for performing educational activities from Abbott Nutrition, Nutricia/Danone, Nestlé Medical Nutrition and Fresenius Kabi and consulting fees from Rejuvenate Biomed, Reneo Pharmaceuticals and Akros Pharma. AC has received fees for lectures or scientific advisory boards from Bristol Myers Squibb and Nestle. BD-H has received grants through her institution for research from DSM and Pfizer, for Data Safety and Monitoring board membership from AgNovos, and a lecture fee from Grupo Italfarmaco. RAF reports stock options from Inside Tracker and Axcella Health and consultancy from Nestlé, Biophytis, Pfizer, Rejuvenate Biomed, and Chugai. TT has received consultancy/speaker's fees from AMGEN, Arrow, Biogen, Chugai, Expanscience, Grunenthal, Jansen, LCA, Lilly, MSD, Nordic, Novartis, Pfizer, Sanofi, Thuasne, Theramex, TEVA and UCB and financial support or fees for research activities from: Bone Therapeutics, Chugai, UCB. NV reports personal fees from IBSA, Mylan, Viatrix, Fidia, MSD outside of the submitted work. JYR reports consulting fees or advisory board participation for IBSA-Genevri, Mylan, Radius Health, Pierre Fabre, Faes Pharma, Rejuvenate Biomed, Samumed, TEVA, Theramex, Pfizer, Mithra Pharmaceuticals, lecturing fees for IBSA-Genevri, Mylan, Cniel, Dairy Research Council (DRC), Nutricia, Danone, Agnovos and grant support from IBSA-Genevri, Mylan, Cniel, Radius Health and TRB. RR has received fees for lectures or scientific advisory boards from Abiogen, Danone, Echolight, European Milk Forum, Nestlé, ObsEva, Pfizer Consumer Health and Theramex. TC, KDC, NAD, OB, MR, NF, JAK, PH, JMK, OL, AL, MPY, RPR, JAT, MW have no conflict of interest or disclosures with regard to this manuscript.

Ethical approval Approval from the institutional review board was not required for this study.

Statement of human and animal rights This article does not contain any studies with human participants or animals not previously published. All procedures performed in the previously published by the author were in accordance with ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent For this review, formal consent was not required.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long

as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Munns CF, Shaw N, Kiely M et al (2016) Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab* 101:394–415
- Bouillon R, Marcocci C, Carmeliet G et al (2019) Skeletal and Extraskelatal Actions of Vitamin D: Current Evidence and Outstanding Questions. *Endocr Rev* 40:1109–1151
- Bouillon R (2017) Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol* 13:466–479
- Harvey NC, Biver E, Kaufman JM et al (2017) The role of calcium supplementation in healthy musculoskeletal ageing : An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF). *Osteoporos Int* 28:447–462
- Holick MF, Binkley NC, Bischoff-Ferrari HA et al (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96:1911–1930
- Dawson-Hughes B, Mithal A, Bonjour JP et al (2010) IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 21:1151–1154
- American Geriatrics Society Workgroup on Vitamin DSfOA (2014) Recommendations abstracted from the American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and Their Consequences. *J Am Geriatr Soc* 62:147–152
- Barnsley J, Buckland G, Chan PE et al (2021) Pathophysiology and treatment of osteoporosis: challenges for clinical practice in older people. *Aging Clin Exp Res* 33:759–773
- Khaw KT, Stewart AW, Waayer D et al (2017) Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. *Lancet Diabetes Endocrinol* 5:438–447
- LeBoff MS, Murata EM, Cook NR et al (2020) VITamin D and Omega-3 TriAL (VITAL): effects of vitamin D supplements on risk of falls in the US population. *J Clin Endocrinol Metab* 105:2929–2938
- LeBoff MS, Chou SH, Ratliff KA et al (2022) Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. *N Engl J Med* 387:299–309
- MacFarlane LA, Cook NR, Kim E et al (2020) The effects of vitamin D and marine omega-3 fatty acid supplementation on chronic knee pain in older US adults: results from a randomized trial. *Arthritis Rheumatol* 72:1836–1844
- Bischoff-Ferrari HA, Vellas B, Rizzoli R et al (2020) Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH Randomized Clinical Trial. *JAMA* 324:1855–1868
- Chou SH, Murata EM, Yu C et al (2021) Effects of Vitamin D3 Supplementation on Body Composition in the VITamin D and Omega-3 TriAL (VITAL). *J Clin Endocrinol Metab* 106:1377–1388
- Bolland MJ, Grey A, Avenell A (2018) Assessment of research waste part 2: wrong study populations- an exemplar of baseline vitamin D status of participants in trials of vitamin D supplementation. *BMC Med Res Methodol* 18:101
- Cauley JA, Greendale GA, Ruppert K et al (2015) Serum 25 hydroxyvitamin D, bone mineral density and fracture risk across the menopause. *J Clin Endocrinol Metab* 100:2046–2054
- Visser M, Deeg DJ, Lips P et al (2003) Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 88:5766–5772
- Rizzoli R, Boonen S, Brandi ML et al (2013) 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). *Curr Med Res Opin* 29:305–313
- Cashman KD (2020) Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. *Calcif Tissue Int* 106:14–29
- Kroll MH, Bi C, Garber CC et al (2015) Temporal relationship between vitamin D status and parathyroid hormone in the United States. *PLoS ONE* 10:e0118108
- Hypponen E, Power C (2007) Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* 85:860–868
- Brooks SPJ, Greene-Finestone L, Whiting S et al (2017) An analysis of factors associated with 25-hydroxyvitamin D levels in white and non-white Canadians. *J AOAC Int* 100:1345–1354
- Herrick KA, Storandt RJ, Afful J et al (2019) Vitamin D status in the United States, 2011–2014. *Am J Clin Nutr* 110:150–157
- Cashman KD, Dowling KG, Skrabakova Z et al (2016) Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* 103:1033–1044
- Merlijn T, Swart KMA, Lips P et al (2018) Prediction of insufficient serum vitamin D status in older women: a validated model. *Osteoporos Int* 29:1539–1547
- Reid D, Toole BJ, Knox S et al (2011) The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. *Am J Clin Nutr* 93:1006–1011
- Vimaleswaran KS, Berry DJ, Lu C et al (2013) Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med* 10:e1001383
- Crowe FL, Steur M, Allen NE et al (2011) Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. *Public Health Nutr* 14:340–346
- O'Neill CM, Kazantzidis A, Ryan MJ et al (2016) Seasonal Changes in Vitamin D-Effective UVB Availability in Europe and Associations with Population Serum 25-Hydroxyvitamin D. *Nutrients* 8:533
- Kazantzidis A, Smedley A, Kift R et al (2015) A modeling approach to determine how much UV radiation is available across the UK and Ireland for health risk and benefit studies. *Photochem Photobiol Sci* 14:1073–1081
- Webb AR (2006) Who, what, where and when-influences on cutaneous vitamin D synthesis. *Prog Biophys Mol Biol* 92:17–25
- Cashman KD (2022) Global differences in vitamin D status and dietary intake: a review of the data. *Endocr Connect* 11:e210282
- Lips P, Cashman KD, Lamberg-Allardt C et al (2019) Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* 180:P23–P54

34. Allen LdBB, Dary O, Hurrell R (2006) Guidelines on food fortification with micronutrients. World Health Organization and Food and Agriculture Organization of the United Nations. Geneva. http://apps.who.int/iris/bitstream/handle/10665/43412/9241594012_eng.pdf. Accessed 5 Sept 2022
35. Gallagher JC, Sai A, Templin T 2nd et al (2012) Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. *Ann Intern Med* 156:425–437
36. McChesney C, Singer A, Duquette D et al (2022) Do not routinely test for vitamin D. *BMJ* 378:e070270
37. Sempos CT, Vesper HW, Phinney KW et al (2012) Vitamin D status as an international issue: national surveys and the problem of standardization. *Scand J Clin Lab Invest Suppl* 243:32–40
38. Cavalier E, Lukas P, Bekaert AC et al (2016) Analytical and clinical evaluation of the new Fujirebio Lumipulse(R)G non-competitive assay for 25(OH)-vitamin D and three immunoassays for 25(OH)D in healthy subjects, osteoporotic patients, third trimester pregnant women, healthy African subjects, hemodialyzed and intensive care patients. *Clin Chem Lab Med* 54:1347–1355
39. Ginsberg C, Hoofnagle AN, Katz R et al (2021) The Vitamin D metabolite ratio is associated with changes in bone density and fracture risk in older adults. *J Bone Miner Res* 36:2343–2350
40. Herrmann M (2020) Towards a personalized assessment of vitamin D status. *Clin Chem Lab Med* 58:149–151
41. Cesareo R, Attanasio R, Caputo M et al (2018) Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. *Nutrients* 10:546
42. Schramm S, Lahner H, Jockel KH et al (2017) Impact of season and different vitamin D thresholds on prevalence of vitamin D deficiency in epidemiological cohorts—a note of caution. *Endocrine* 56:658–666
43. Okazaki R, Ozono K, Fukumoto S et al (2017) Assessment criteria for vitamin D deficiency/insufficiency in Japan: proposal by an expert panel supported by the Research Program of Intractable Diseases, Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral Research and the Japan Endocrine Society [Opinion]. *J Bone Miner Metab* 35:1–5
44. Cavalier E, Huyghebaert L, Rousselle O et al (2020) Simultaneous measurement of 25(OH)-vitamin D and 24,25(OH)₂-vitamin D to define cut-offs for CYP24A1 mutation and vitamin D deficiency in a population of 1200 young subjects. *Clin Chem Lab Med* 58:197–201
45. IOM (2011) Dietary reference intakes for calcium and vitamin D. National Institute of Medicine, Academies Press, Washington DC
46. Bleicher K, Cumming RG, Naganathan V et al (2014) U-shaped association between serum 25-hydroxyvitamin D and fracture risk in older men: results from the prospective population-based CHAMP study. *J Bone Miner Res* 29:2024–2031
47. Avenell A, Mak JC, O'Connell D (2014) Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev* 4:227
48. Chapuy MC, Arlot ME, Duboeuf F et al (1992) Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 327:1637–1642
49. Lyons RA, Johansen A, Brophy S et al (2007) Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporos Int* 18:811–818
50. Sanders KM, Stuart AL, Williamson EJ et al (2010) Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 303:1815–1822
51. Bischoff-Ferrari HA, Willett WC, Wong JB et al (2009) Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 169:551–561
52. Lai JK, Lucas RM, Clements MS et al (2010) Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies. *BMC Public Health* 10:331
53. Bergman GJ, Fan T, McFetridge JT et al (2010) Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. *Curr Med Res Opin* 26:1193–1201
54. Chung M, Lee J, Terasawa T et al (2011) Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 155:827–838
55. Murad MH, Drake MT, Mullan RJ et al (2012) Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab* 97:1871–1880
56. Weaver CM, Alexander DD, Boushey CJ et al (2016) Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int* 27:367–376
57. Zhao JG, Zeng XT, Wang J et al (2017) association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA* 318:2466–2482
58. Kahwati LC, Weber RP, Pan H et al (2018) Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 319:1600–1612
59. Bolland MJ, Grey A, Avenell A (2018) Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol* 6:847–858
60. Hu ZC, Tang Q, Sang CM et al (2019) Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomised controlled trials. *BMJ Open* 9:e024595
61. Yao P, Bennett D, Mafham M et al (2019) Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. *JAMA Netw Open* 2:e1917789
62. Eleni A, Panagiotis P (2020) A systematic review and meta-analysis of vitamin D and calcium in preventing osteoporotic fractures. *Clin Rheumatol* 39:3571–3579
63. Thanapluetiwong S, Chewcharat A, Takkavatakarn K et al (2020) Vitamin D supplement on prevention of fall and fracture: a Meta-analysis of Randomized Controlled Trials. *Medicine (Baltimore)* 99:e21506
64. Li S, Xi C, Li L et al (2021) Comparisons of different vitamin D supplementation for prevention of osteoporotic fractures: a Bayesian network meta-analysis and meta-regression of randomised controlled trials. *Int J Food Sci Nutr* 72:518–528
65. Chakhtoura M, Bacha DS, Gharios C et al (2022) Vitamin D supplementation and fractures in adults: a systematic umbrella review of meta-analyses of controlled trials. *J Clin Endocrinol Metab* 107:882–898
66. Kong SH, Jang HN, Kim JH et al (2022) Effect of vitamin D supplementation on risk of fractures and falls according to dosage and interval: a meta-analysis. *Endocrinol Metab (Seoul)* 37:344–358
67. Smith H, Anderson F, Raphael H et al (2007) Effect of annual intramuscular vitamin D on fracture risk in elderly men and women—a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology (Oxford)* 46:1852–1857



68. WHO (2021) Step safely :strategies for preventing and managing falls across the life-course. Licence :CC BY-NC_SA 30 IGO
69. Bussell ME (2021) Improving bone health: addressing the burden through an integrated approach. *Aging Clin Exp Res* 33:2777–2786
70. Lappe JM, Heaney RP (2012) Why randomized controlled trials of calcium and vitamin D sometimes fail. *Dermatoendocrinol* 4:95–100
71. Papadimitropoulos E, Wells G, Shea B et al (2002) Meta-analyses of therapies for postmenopausal osteoporosis. VIII: meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev* 23:560–569
72. Wang TJ, Pencina MJ, Booth SL et al (2008) Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 117:503–511
73. Shardell M, Cappola AR, Guralnik JM et al (2021) Sex-specific 25-hydroxyvitamin D threshold concentrations for functional outcomes in older adults: PROject on Optimal Vitamin D in Older adults (PROVIDO). *Am J Clin Nutr* 114:16–28
74. Gillespie LD, Robertson MC, Gillespie WJ et al (2012) Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 9:CD007146
75. LeBlanc ES, Chou R (2015) Vitamin D and falls-fitting new data with current guidelines. *JAMA Intern Med* 175:712–713
76. Pfeifer M, Begerow B, Minne HW et al (2000) Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res* 15:1113–1118
77. Cangussu LM, Nahas-Neto J, Orsatti CL et al (2016) Effect of isolated vitamin D supplementation on the rate of falls and postural balance in postmenopausal women fallers: a randomized, double-blind, placebo-controlled trial. *Menopause* 23:267–274
78. Ozsoy-Unubol T, Candan Z, Atar E et al (2021) The effect of vitamin D and exercise on balance and fall risk in postmenopausal women: a randomised controlled study. *Int J Clin Pract* 75:e14851
79. Prince RL, Austin N, Devine A et al (2008) Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med* 168:103–108
80. Pfeifer M, Begerow B, Minne HW et al (2009) Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int* 20:315–322
81. Uusi-Rasi K, Patil R, Karinkanta S et al (2015) Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA Intern Med* 175:703–711
82. Uusi-Rasi K, Patil R, Karinkanta S et al (2017) A 2-year follow-up after a 2-year RCT with vitamin D and exercise: effects on falls, injurious falls and physical functioning among older women. *J Gerontol A Biol Sci Med Sci* 72:1239–1245
83. Patil R, Kolu P, Raitanen J et al (2016) Cost-effectiveness of vitamin D supplementation and exercise in preventing injurious falls among older home-dwelling women: findings from an RCT. *Osteoporos Int* 27:193–201
84. Uusi-Rasi K, Patil R, Karinkanta S et al (2019) Serum 25-hydroxyvitamin D levels and incident falls in older women. *Osteoporos Int* 30:93–101
85. Wanigatunga AA, Sternberg AL, Blackford AL et al (2021) The effects of vitamin D supplementation on types of falls. *J Am Geriatr Soc* 69:2851–2864
86. Karkkainen MK, Tuppurainen M, Salovaara K et al (2010) Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65–71 years? A 3-year randomized population-based trial (OSTPRE-FPS). *Maturitas* 65:359–365
87. Hansen KE, Johnson RE, Chambers KR et al (2015) Treatment of vitamin D insufficiency in postmenopausal women: a randomized clinical trial. *JAMA Intern Med* 175:1612–1621
88. Bischoff-Ferrari HA, Freystatter G, Vellas B et al (2022) Effects of vitamin D, omega-3 fatty acids, and a simple home strength exercise program on fall prevention: the DO-HEALTH randomized clinical trial. *Am J Clin Nutr* 115:1311–1321
89. Appel LJ, Michos ED, Mitchell CM et al (2021) The effects of four doses of vitamin D supplements on falls in older adults: a response-adaptive, randomized clinical trial. *Ann Intern Med* 174:145–156
90. Dhesi JK, Jackson SH, Bearne LM et al (2004) Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing* 33:589–595
91. Waterhouse M, Sanguineti E, Baxter C et al (2021) Vitamin D supplementation and risk of falling: outcomes from the randomized, placebo-controlled D-Health Trial. *J Cachexia Sarcopenia Muscle* 12:1428–1439
92. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB et al (2009) Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 339:b3692
93. Murad MH, Elamin KB, Abu Elnour NO et al (2011) Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 96:2997–3006
94. Wu H, Pang Q (2017) The effect of vitamin D and calcium supplementation on falls in older adults: a systematic review and meta-analysis. *Orthopade* 46:729–736
95. Guirguis-Blake JM, Michael YL, Perdue LA et al (2018) Interventions to prevent falls in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 319:1705–1716
96. Ling Y, Xu F, Xia X et al (2021) Vitamin D supplementation reduces the risk of fall in the vitamin D deficient elderly: An updated meta-analysis. *Clin Nutr* 40:5531–5537
97. Bischoff-Ferrari HA, Orav EJ, Abderhalden L et al (2019) Vitamin D supplementation and musculoskeletal health. *Lancet Diabetes Endocrinol* 7:85
98. Dawson-Hughes B, Wang J, Barger K et al (2022) Intra-trial mean 25(OH)D and PTH levels and risk of falling in older men and women in the Boston STOP IT Trial. *J Clin Endocrinol Metab* 107:e1932–e1937
99. Bouillon R, Manousaki D, Rosen C et al (2022) The health effects of vitamin D supplementation: evidence from human studies. *Nat Rev Endocrinol* 18:96–110
100. Zittermann A, Berthold HK, Pilz S (2021) The effect of vitamin D on fibroblast growth factor 23: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr* 75:980–987
101. Zittermann A, Berthold HK, PilzSReply to Meshkini, et al (2021) *Eur J Clin Nutr* 75:990–991
102. Charoenngam N, Kalajian TA, Shirvani A et al (2021) A pilot-randomized, double-blind crossover trial to evaluate the pharmacokinetics of orally administered 25-hydroxyvitamin D3 and vitamin D3 in healthy adults with differing BMI and in adults with intestinal malabsorption. *Am J Clin Nutr* 114:1189–1199
103. Park CY (2019) Vitamin D in the prevention and treatment of osteoarthritis: from clinical interventions to cellular evidence. *Nutrients* 11:243
104. Yu Y, Liu D, Feng D et al (2021) Association between Vitamin D and knee osteoarthritis: a PRISMA-compliant meta-analysis. *Z Orthop Unfall* 159:281–287
105. Qu Z, Yang F, Yan Y et al (2021) A Mendelian randomization study on the role of serum parathyroid hormone and 25-hydroxyvitamin D in osteoarthritis. *Osteoarthritis Cartilage* 29:1282–1290

106. Veronese N, Maggi S, Noale M et al (2015) Serum 25-hydroxyvitamin D and osteoarthritis in older people: the Progetto Veneto Anziani Study. *Rejuvenation Res* 18:543–553
107. Gao XR, Chen YS, Deng W (2017) The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials. *Int J Surg* 46:14–20
108. Diao N, Yang B, Yu F (2017) Effect of vitamin D supplementation on knee osteoarthritis: a systematic review and meta-analysis of randomized clinical trials. *Clin Biochem* 50:1312–1316
109. Beaudart C, Lengele L, Leclercq V et al (2020) Symptomatic efficacy of pharmacological treatments for knee osteoarthritis: a systematic review and a network meta-analysis with a 6-month time horizon. *Drugs* 80:1947–1959
110. Zhao ZX, He Y, Peng LH et al (2021) Does vitamin D improve symptomatic and structural outcomes in knee osteoarthritis? A systematic review and meta-analysis. *Aging Clin Exp Res* 33:2393–2403
111. Mathieu S, Soubrier M, Peirs C et al (2022) A meta-analysis of the impact of nutritional supplementation on osteoarthritis symptoms. *Nutrients* 14:1607
112. Sanghi D, Mishra A, Sharma AC et al (2013) Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. *Clin Orthop Relat Res* 471:3556–3562
113. Arden NK, Cro S, Sheard S et al (2016) The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. *Osteoarthritis Cartilage* 24:1858–1866
114. Chlebowski RT, Pettinger M, Johnson KC et al (2013) Calcium plus vitamin D supplementation and joint symptoms in postmenopausal women in the women's health initiative randomized trial. *J Acad Nutr Diet* 113:1302–1310
115. McAlindon T, LaValley M, Schneider E et al (2013) Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA* 309:155–162
116. Jin X, Jones G, Cicuttini F et al (2016) Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. *JAMA* 315:1005–1013
117. Wang X, Cicuttini F, Jin X et al (2017) Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis. *Osteoarthr Cartil* 25:1304–1312
118. Perry TA, Parkes MJ, Hodgson R et al (2019) Effect of Vitamin D supplementation on synovial tissue volume and subchondral bone marrow lesion volume in symptomatic knee osteoarthritis. *BMC Musculoskelet Disord* 20:76
119. Ellfolk M, Norlin M, Gyllensten K et al (2009) Regulation of human vitamin D(3) 25-hydroxylases in dermal fibroblasts and prostate cancer LNCaP cells. *Mol Pharmacol* 75:1392–1399
120. Haddad JG, Stamp TC (1974) Circulating 25-hydroxyvitamin D in man. *Am J Med* 57:57–62
121. Norlin M, Lundqvist J, Ellfolk M et al (2017) Drug-mediated gene regulation of vitamin D3 metabolism in primary human dermal fibroblasts. *Basic Clin Pharmacol Toxicol* 120:59–63
122. Jetter A, Egli A, Dawson-Hughes B et al (2014) Pharmacokinetics of oral vitamin D(3) and calcifediol. *Bone* 59:14–19
123. Meyer O, Dawson-Hughes B, Sidelnikov E et al (2015) Calcifediol versus vitamin D3 effects on gait speed and trunk sway in young postmenopausal women: a double-blind randomized controlled trial. *Osteoporos Int* 26:373–381
124. Perez-Castrillon JL, Duenas-Laita A, Brandi ML et al (2021) Calcifediol is superior to cholecalciferol in improving vitamin D status in postmenopausal women: a randomized trial. *J Bone Miner Res* 36:1967–1978
125. Ketteler M, Ambuhl P (2021) Where are we now? Emerging opportunities and challenges in the management of secondary hyperparathyroidism in patients with non-dialysis chronic kidney disease. *J Nephrol* 34:1405–1418
126. Cozzolino M, Minghetti P, Navarra P (2022) Extended-release calcifediol in stage 3–4 chronic kidney disease: a new therapy for the treatment of secondary hyperparathyroidism associated with hypovitaminosis D. *J Nephrol* 35:863–873
127. Haldimann B, Healy M, Jelliffe R et al (1980) Effect of an oral dose of 25-hydroxyvitamin D3 on its blood levels in patients with the nephrotic syndrome. *J Clin Endocrinol Metab* 50:470–474
128. Foresta C, Calogero AE, Lombardo F et al (2015) Late-onset hypogonadism: beyond testosterone. *Asian J Androl* 17:236–238
129. Kanter Berga J, Crespo Albiach J, Beltran Catalan S et al (2010) Vitamin D deficiency in a renal transplant population: safe repletion with moderate doses of calcidiol. *Transplant Proc* 42:2917–2920
130. Bassatne A, Basbous M, Chakhtoura M et al (2021) The link between COVID-19 and Vitamin D (VIVID): a systematic review and meta-analysis. *Metabolism* 119:154753
131. Rhein H (2021) Vitamin D-let common sense prevail-on the balance of probabilities. *Aging Clin Exp Res* 33:2633
132. Dissanayake HA, de Silva NL, Sumanatilleke M et al (2022) Prognostic and Therapeutic Role of Vitamin D in COVID-19: Systematic Review and Meta-analysis. *J Clin Endocrinol Metab* 107:1484–1502
133. Noguez X, Ovejero D, Pineda-Moncusi M et al (2021) Calcifediol treatment and COVID-19-related outcomes. *J Clin Endocrinol Metab* 106:e4017–e4027
134. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM et al (2020) Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. *J Steroid Biochem Mol Biol* 203:105751
135. Alcalá-Díaz JF, Limia-Pérez L, Gómez-Huelgas R et al (2021) Calcifediol treatment and hospital mortality due to COVID-19: a cohort study. *Nutrients* 13:1760
136. Oristrell J, Oliva JC, Casado E et al (2022) Vitamin D supplementation and COVID-19 risk: a population-based, cohort study. *J Endocrinol Invest* 45:167–179
137. Sabico S, Enani MA, Sheshah E et al (2021) Effects of a 2-week 5000 IU versus 1000 IU vitamin D3 supplementation on recovery of symptoms in patients with mild to moderate covid-19: a randomized clinical trial. *Nutrients* 13:2170
138. De Niet S, Tremege M, Coffiner M et al (2022) Positive effects of vitamin D supplementation in patients hospitalized for COVID-19: a randomized, double-blind, placebo-controlled trial. *Nutrients* 14:3048
139. Cianferotti L, Cricelli C, Kanis JA et al (2015) The clinical use of vitamin D metabolites and their potential developments: a position statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). *Endocrine* 50:12–26
140. Sempos CT, Binkley N (2020) 25-Hydroxyvitamin D assay standardisation and vitamin D guidelines paralysis. *Public Health Nutr* 23:1153–1164
141. Rizzoli R (2021) Vitamin D supplementation: upper limit for safety revisited? *Aging Clin Exp Res* 33:19–24
142. Rizzoli R, Stoermann C, Ammann P et al (1994) Hypercalcemia and hyperosteolysis in vitamin D intoxication: effects of clodronate therapy. *Bone* 15:193–198
143. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B et al (2010) Benefit-risk assessment of vitamin D supplementation. *Osteoporos Int* 21:1121–1132

144. Smith LM, Gallagher JC, Suiter C (2017) Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: a randomized clinical trial. *J Steroid Biochem Mol Biol* 173:317–322
145. Bislev LS, LangagergaardRodbro L, Rolighed L et al (2018) Effects of vitamin D3 supplementation on muscle strength, mass, and physical performance in women with vitamin D insufficiency: a randomized placebo-controlled trial. *Calcif Tissue Int* 103:483–493
146. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B (2016) Estimating vitamin D status and the choice of supplementation dose-reply. *JAMA Intern Med* 176:865–866
147. Ginde AA, Blatchford P, Breese K et al (2017) High-dose monthly vitamin D for prevention of acute respiratory infection in older long-term care residents: a randomized clinical trial. *J Am Geriatr Soc* 65:496–503
148. Burt LA, Billington EO, Rose MS et al (2019) Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA* 322:736–745
149. Burt LA, Billington EO, Rose MS et al (2020) Adverse effects of high-dose vitamin D supplementation on volumetric bone density are greater in females than males. *J Bone Miner Res* 35:2404–2414
150. Ish-Shalom S, Segal E, Salganik T et al (2008) Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J Clin Endocrinol Metab* 93:3430–3435
151. Trivedi DP, Doll R, Khaw KT (2003) Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 326:469
152. Bacon CJ, Gamble GD, Horne AM et al (2009) High-dose oral vitamin D3 supplementation in the elderly. *Osteoporos Int* 20:1407–1415
153. Rossini M, Adami S, Viapiana O et al (2012) Dose-dependent short-term effects of single high doses of oral vitamin D(3) on bone turnover markers. *Calcif Tissue Int* 91:365–369
154. Heyer FL, de Jong JJ, Willems PC et al (2021) The effect of bolus vitamin D3 supplementation on distal radius fracture healing: a randomized controlled trial using HR-pQCT. *J Bone Miner Res* 36:1492–1501
155. Mazess RB, Bischoff-Ferrari HA, Dawson-Hughes B (2021) Vitamin D: bolus is bogus—a narrative review. *JBM Plus* 5:e10567

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Thierry Chevalley¹  · Maria Luisa Brandi² · Kevin D. Cashman³ · Etienne Cavalier⁴ · Nicholas C. Harvey^{5,6} · Stefania Maggi⁷ · Cyrus Cooper^{5,6,8} · Nasser Al-Daghri⁹ · Oliver Bock^{10,11} · Olivier Bruyère¹² · Mario Miguel Rosa¹³ · Bernard Cortet¹⁴ · Alfonso J. Cruz-Jentoft¹⁵ · Antonio Cherubini¹⁶ · Bess Dawson-Hughes¹⁷ · Roger Fielding¹⁷ · Nicholas Fuggle^{5,6} · Philippe Halbout¹¹ · John A. Kanis^{18,19} · Jean-Marc Kaufman²⁰ · Olivier Lamy²¹  · Andrea Laslop²² · Maria Concepción Prieto Yerro²³ · Régis Radermecker²⁴ · Jotheeswaran Amuthavalli Thiyagarajan²⁵ · Thierry Thomas²⁶ · Nicola Veronese²⁷ · Marten de Wit²⁸ · Jean-Yves Reginster²⁹ · René Rizzoli¹

¹ Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

² Metabolic Bone Diseases Unit, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

³ Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences, University College Cork, Cork, Ireland

⁴ Department of Clinical Chemistry, University of Liege, CHU de Liege, Liege, Belgium

⁵ MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

⁶ NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

⁷ CNR Aging Branch-IN, Padua, Italy

⁸ UKNIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

⁹ Chair for Biomarkers of Chronic Diseases, Biochemistry Department, College of Science King Saud University, Riyadh 11451, Saudi Arabia

¹⁰ Department of Osteoporosis, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

¹¹ International Osteoporosis Foundation, Nyon, Switzerland

¹² Division of Public Health, Epidemiology and Health Economics, WHO Collaborating Center for Public Health Aspects of Musculo-Skeletal Health and Ageing, University of Liège, Liège, Belgium

¹³ Centro de Estudos Egas Moniz Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

¹⁴ Department of Rheumatology, University of Lille, CHU Lille, MABlab ULR 4490, Lille, France

¹⁵ Servicio de Geriátria, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

¹⁶ Dipartimento dei percorsi geriatrici della fragilità, Geriatria, Accettazione geriatrica e Centro di ricerca per l'invecchiamento della continuità di cura e riabilitativi, IRCCS INRCA, Ancona, Italy

¹⁷ Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA

¹⁸ Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK

- ¹⁹ Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia
- ²⁰ Department of Endocrinology, Ghent University Hospital, Ghent, Belgium
- ²¹ Bone Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
- ²² Scientific Office, Federal Office for Safety in Health Care, Austrian Medicines and Medical Devices Agency, Vienna, Austria
- ²³ Spanish Agency for Medicines and Medical Devices, Madrid, Spain
- ²⁴ Department of Clinical Pharmacology Diabetes, Nutrition and Metabolic Disorders, CHU Liege, Liège, Belgium
- ²⁵ Ageing and Health Unit, Department of Maternal, Newborn, Child and Adolescent Health & Ageing, WHO HQ, Geneva, Switzerland
- ²⁶ Department of Rheumatology, North Hospital, CHU Saint-Etienne and INSERM U1059, University of Lyon-University Jean Monnet, Saint-Etienne, France
- ²⁷ Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy
- ²⁸ Department of Medical Humanities, Amsterdam University Medical Centre, Amsterdam, The Netherlands
- ²⁹ Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium