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Review**Vitamin D supplementation and fracture risk: evidence for a U-shaped effect**

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Highlights

- Vitamin D monotherapy does not seem to reduce the risk of fractures.
- On the other hand, high vitamin D doses (60,000–100,000 IU/month or >4,000 IU/day) appear to be harmful in relation to falls, fracture risk and bone mineral density.
- Vitamin D supplementation could be of benefit for institutionalized elderly people with severe vitamin D deficiency, at doses of 800 IU/day or more, combined with calcium (1000–1200 mg/day).

Abstract

During the last decade, a cascade of evidence has questioned the anti-fracture efficacy of vitamin D supplementation. In general, vitamin D status, reflected by serum 25-hydroxy-vitamin D [25(OH)D] concentrations, seems to predict fracture risk and bone mineral density (BMD). Despite the well-documented detrimental effect of vitamin D deficiency on bones, vitamin D monotherapy does not seem to reduce the risk of fractures. On the other hand, high vitamin D doses, either at monthly (60,000–100,000 IU) or daily intervals (>4,000 IU), appear to be harmful with regard to falls, fracture risk and BMD, especially for people without vitamin D deficiency and at low fracture

risk. Therefore, a U-shaped effect of vitamin D on the musculoskeletal system may be supported by the current evidence. Vitamin D supplementation could be of value, at daily doses of at least 800 IU, co-supplemented with calcium (1000–1200 mg/day), in elderly populations, especially those with severe vitamin D deficiency [25(OH)D <25–30 nmol/L (<10–12 ng/mL)], although its anti-fracture and anti-fall efficacy is modest. Good compliance and at least 3-5 years of therapy are required.

Keywords

Vitamin D; 25(OH)D; Fracture risk; U-shaped effect

1. Introduction

Vitamin D is an essential nutrient for obtaining and maintaining optimal bone health [1]. Its status is reflected by serum concentrations of 25-hydroxy-vitamin D [25(OH)D], an interim molecule, prior to transformation of its precursors, cholecalciferol (D₃) or ergocalciferol (D₂), into their active metabolite, 1,25-dihydroxyvitamin-D₃ (calcitriol) [1]. Specific anthropometric (age, gender), lifestyle [nutrition, body mass index (BMI)], environmental (season, latitude), behavioural (sun exposure, clothing) and genetic factors (race, ethnicity, gene polymorphisms) account for variations in 25(OH)D concentrations across different individuals and populations [1-3].

With respect to vitamin D deficiency, there is no universal consensus regarding its definition. According to Endocrine Society's guidelines, published in 2011, a threshold of <50 nmol/L (<20 ng/mL) for 25(OH)D has been adopted for this purpose [1]. This is also adopted by other societies, such as the International Osteoporosis Foundation (IOF) [4]. These two societies have set a cut-off value of >75 nmol/L (>30 ng/mL) for vitamin D sufficiency [1, 4]. In contrast, the Institute of Medicine (IOM) has set a threshold of >50 nmol/L (>20 ng/mL) as optimal for musculoskeletal health, with concerns raised for concentrations <40 nmol/L (<16 ng/mL), which require intervention [5].

Vitamin D deficiency leads to decreased intestinal calcium and phosphorus absorption and to an increase in parathyroid hormone concentrations [especially for 25(OH)D <75 nmol/L (<30 ng/mL)] [6], which may compromise the acquisition of peak bone mass since childhood [7]. In adults, this may lead to decreased bone mineralization. In cases of severe vitamin D deficiency [<15 - 25 nmol/L (<6 - 10 ng/mL)], osteomalacia may be observed, which is associated with increased risk of fractures [1, 8]. Vitamin D deficiency is also associated with increased risk of sarcopenia, a condition of deterioration of muscle mass, strength and/or performance, which further augments fracture risk [9]. Current guidelines [10, 11] recommend vitamin D and calcium (preferably by diet or by, alternatively, supplements) at daily doses of 400–800 IU and 800–1200 mg, respectively, in patients with low bone mineral density (BMD) and at high risk of fractures. This recommendation is mostly based on the concept of that the anti-fracture efficacy of major anti-osteoporotic medications has arisen in combination with vitamin D plus calcium supplementation [10, 11]. Notwithstanding these recommendations, a mounting body of evidence during the last decade has questioned the anti-fracture benefit of vitamin D supplementation (alone or in concert with

calcium) [12, 13]. Potential risks have also emerged with high doses [14, 15], indicating, therefore, a U-shaped effect.

The purpose of this narrative review was to appraise current evidence regarding the dose-dependent effect of vitamin D supplementation on the musculoskeletal system, with regard to BMD, falls and fracture risk.

2. Is vitamin D associated with fracture risk?

2.1 Observational data

2.1.1 Effects on falls

An inverse association between 25(OH)D concentrations and the risk of falls seems to exist, with the most advantageous serum concentrations of 25(OH)D being 90-100 nmol/L (36–40 ng/mL) [16]. In detail, analysis of data from the National Health and Nutrition Examination Survey III (NHANES III) has shown that lower-extremity function is positively associated with 25(OH)D concentrations throughout the reference range of 22.5–94 nmol/L (9–39 ng/mL). The most abrupt association was seen for 25(OH)D concentrations 22.5–40 nmol/L (9–16 ng/mL), which was blunted in the range of 40–94 nmol/L (16–39 ng/mL). This was independent of gender, race, ethnicity and calcium intake [16]. Furthermore, a meta-analysis has shown that achieving 25(OH)D concentrations ≥ 60 nmol/L (≥ 24 ng/mL) is associated with a 23% reduction in the risk of falls compared with concentrations < 60 nmol/L (< 24 ng/mL) [pooled relative risk (RR) 0.77, 95% confidence interval (CI) 0.65–0.90] [17].

2.1.2 Effects on BMD

In addition, observational data have shown that 25(OH)D concentrations may predict BMD. In particular, a stepwise increase in BMD with serum 25(OH)D concentrations has been reported in both genders [18]. Interestingly, data from the NHANES III have shown a continuously positive association in individuals at 20-49 years of age, even out of the range of 22.5–94 nmol/L (9–37.6 ng/mL), with increases in BMD even for 25(OH)D >100 nmol/L (>40 ng/mL). However, in individuals aged >50 years, a plateau is observed for 25(OH)D concentrations of 90-100 nmol/L (36-40) and an inverse association for concentrations >100 nmol/L (>40 ng/mL), suggesting a U-shaped association in this population [16]. In white populations, subjects in the highest 25(OH)D quintile [>98.1 nmol/L (39.2 ng/mL)] compared with in the lowest quintile [<53 nmol/L (21.2 ng/mL)] had a 4.1% and 4.8% higher BMD in younger and older ages. Similar differences, although to a lesser extent, were observed in Mexican Americans and blacks [16].

2.1.3 Effects on fractures

In general, there is evidence for an inverse association between serum 25(OH)D concentrations and fracture risk. Individuals at the lowest 25(OH)D quartile [9.2–47 nmol/L (3.7–19 ng/mL)] exert an almost two-fold increased risk of hip fracture compared with those at the highest quartile [70–121 nmol/L (28–48 ng/mL)] [adjusted odds ratio (OR) 1.71, 95% CI 1.05–2.79] [19]. Furthermore, a recent meta-analysis (11 observational studies; $n=39,141$) showed that each 25 nmol/L (10 ng/mL) increase in 25 (OH)D concentrations is associated with an adjusted RR 0.93 (95% CI 0.89–0.96) for any fracture of and 0.80 (95% CI 0.75–0.86) for hip fracture [20].

Therefore, vitamin D status, assessed by 25(OH)D concentrations, seems to be inversely associated both with the risk of falls and fractures and positively with BMD,

although this may be reversed for 25(OH)D concentrations >100 nmol/L (40 ng/mL) in individuals >50 years of age, suggesting a U-shaped association in this population.

2.2 Data from interventional studies

2.2.1 Effects on BMD

A cascade of randomized controlled trials (RCTs) has been published heretofore regarding the effect of vitamin D supplementation on BMD. One of the most representative meta-analyses, published in 2014 (23 RCTs, $n=4,082$, 92% women, average age 59 years) showed only a small benefit of vitamin D supplementation on femoral neck BMD compared with placebo [weighted mean difference: 0.8% (95% CI 0.2%–1.4%); $p=0.005$]. However, no effect on other skeletal sites (lumbar spine, total hip, forearm) was observed. The reported dietary calcium dosage was 390–1340 mg/day. No differences according to 25(OH)D concentrations (<50 nmol/L vs ≥ 50 nmol/L), vitamin D dose (<800 IU vs ≥ 800 IU), study duration (≤ 12 vs >12 months) or calcium supplementation, were noticed between subgroups [21]. However, in a *post-hoc* examination of their results, the same authors reported a benefit only in studies with baseline 25(OH)D concentrations <40 nmol/L (16 ng/mL) [22].

Moreover, a recent *post-hoc* analysis of the VITamin D and OmegA-3 Trial (VITAL) study compared the effect of vitamin D 2,000 IU/day ($n=388$) with placebo ($n=383$) on BMD, in otherwise healthy men (≥ 55 years old) and women (≥ 50 years old). After two years, no effect on areal BMD at all skeletal sites, assessed with dual-energy X-ray absorptiometry (DXA), or volumetric BMD and cortical thickness at the radius and tibia, assessed by peripheral quantitative computed tomography, was observed in either group. It must be underlined that participants were in general good health, with

normal/osteopenic BMD, with similar mean baseline 25(OH)D concentrations [69.1 nmol/L (27.6 ng/mL) and 71.1 nmol/L (28.4 ng/mL) in vitamin D and placebo groups, respectively], reaching 98.6 nmol/L (39.4 ng/mL) in the former [23]. However, in participants with low free 25(OH)D concentrations (<14.2 pmol/L) at baseline, vitamin D induced a modest, but significant, increase in spine areal BMD (0.75% vs 0.0%; $p=0.043$) and attenuated bone loss in total hip areal BMD (-0.42% vs. -0.98%; $p=0.044$) [23]. The limitations regarding the evidence of a post-hoc analysis over the initial RCT as well as its marginal statistical significance, should be considered before generalization of these findings. Moreover, although the clinical implications of measuring free rather than total 25(OH)D concentrations have not been fully elucidated, it is free 25(OH)D that exerts its direct effects on bone and is highly associated with total 25(OH)D [24].

A beneficial effect of vitamin D supplementation cannot be excluded in patients with nadir 25(OH)D concentrations [<30 nmol/L (<12 ng/mL)]. Indeed, this was shown in two recent studies, the Vitamin D Assessment (ViDA) Study from New Zealand and the Aberdeen study from the UK [22]. With regard to the former, 452 community-dwelling adults (mean age 69 years), with normal BMD at baseline, were randomized to either monthly doses of 100,000 IU vitamin D or placebo. Mean baseline 25(OH)D concentrations were 55 ± 23 and 56 ± 22 nmol/L (22 ± 9.2 and 22.4 ± 8.8 ng/mL), respectively. Although no effect was observed in spinal BMD, with a modest attenuation of bone loss at both hips ($\sim 0.5\%$), subgroup analysis showed an interaction between baseline 25(OH)D concentrations and treatment effect. In particular, in those with 25(OH)D <30 nmol/L (<12 ng/mL) ($n=46$), both spinal and hip BMD increased by $\sim 2\%$ over two years, compared with a 0.5% increase only in the total hip in those with baseline 25(OH)D >30 nmol/L [25]. According to the Aberdeen study, 305

postmenopausal women [mean age 64.5 years; mean 25(OH)D concentrations 34 ± 15 nmol/L (13.6 ± 6 ng/mL) and normal BMD] were randomized to placebo, vitamin D 400 IU/day or 1,000 IU/day. Only the highest dose mitigated the reduction in hip BMD after 12 months. However, when the analysis was performed according to a baseline 25(OH)D threshold of 30 nmol/L, both 400 IU and 1,000 IU doses attenuated bone loss at the lumbar spine and hip (with 1,000 IU only). These benefits were prominent, when a threshold of 25 nmol/L (10 ng/mL) was used (achieving 2% and 1% increases in spinal and hip BMD, respectively, with 1,000 IU/day) [22].

2.2.2 Effects on falls and fractures

A cascade of interventional studies, either RCTs or no RCTs has provided inconclusive results, on this context. A large meta-analysis, published in 2018 (81 RCTs, $n=53,537$), showed no overall benefit of vitamin D supplementation as monotherapy on total (RR 1.00, 95% CI 0.93–1.07) and hip fracture risk (RR 1.11, 95% CI 0.97–1.26) or falls (RR 0.97, 95% CI 0.93–1.02). No effect was also revealed with respect to BMD. Moreover, subgroup analysis, according to vitamin D dose (<800 vs ≥ 800 IU/day) did not alter these findings. In 41 (57%) of the included trials, baseline 25(OH)D concentrations were <50 nmol/L (<20 ng/mL) and in 76 studies (91%) patients had achieved 25(OH)D >50 nmol/L (20 ng/mL) [12], a threshold which is regarded as critical for optimal bone health [4, 6].

Nonetheless, some points should be underlined regarding this meta-analysis. Briefly, the percentage of studies with populations with severe vitamin D deficiency [25(OH)D <25 nmol/L (10 ng/mL)] at baseline was relatively low (6%), a population in which an anti-fracture benefit of vitamin D might be expected. A separate examination of outcome risks according to baseline and achieved 25(OH)D concentrations could

provide a more accurate estimate. Another shortcoming was the exclusion of studies using vitamin D in combination with calcium, which probably masked their beneficial effect on fracture risk, especially for older individuals. The latter point will be further analysed below, in section 4.

Therefore, although vitamin D deficiency is associated with increased fracture risk, vitamin D monotherapy does not seem to exert a beneficial effect on fracture risk. However, vitamin D may be beneficial, especially at higher doses, in patients with severe vitamin D deficiency.

Nonetheless, except for the fragile nature of subgroup analysis, the confounding role of other states should also be taken under consideration, such as frailty and advanced age per se, which may lead to increased fracture risk, irrespectively of low vitamin D status. The latter may simply be due to decreased sun exposure raising the question that correlation does not imply causality, since low vitamin D status may be just an index and not the cause of bad health [26].

3. How much of vitamin D is too much for bone protection?

Overall, the accumulating body of evidence from RCTs has increasingly shown a detrimental effect on musculoskeletal health with high vitamin D doses. In particular, annual oral dose of 500,000 IU administered in 2,256 community-dwelling women (median age 76 years) at high fracture risk (history of maternal hip fracture, past fracture or self-reported faller) increased the risk of falls and fractures by 16% and 25%, respectively, compared with placebo [adjusted HR 1.16 (95% CI 1.03–1.31) and 1.25 (96% 0.99–1.58), respectively]. These risks were prominent even at three months of follow-up. Median baseline 25(OH)D concentrations in vitamin D and placebo groups

at baseline were 53 nmol/L (21.2 ng/mL) and 45 nmol/L (18 ng/mL), respectively. Of note, <3% had severe vitamin D deficiency. One month after vitamin D bolus, 25(OH)D concentrations reached 120 nmol/L (48 ng/mL), falling at 90 nmol/L (36 ng/mL) at three months [15].

On the same concept, monthly vitamin D doses of 100,000 IU for 12 months were administered in 55 long-term residents ≥ 60 years, from of 25 selected Colorado skilled nursing or assisted living facilities (mean age 80 ± 10 years; 60% females). Vitamin D increased the risk of falls more than two-fold, compared with monthly supplementation of 12,000 IU ($n=52$; mean age 82 ± 10 years; 56% females) (RR 2.33, 95% CI 1.49–3.63). Although the overall incidence of fractures was low, no difference was observed between groups. Remarkably, only one-third of each group were vitamin D deficient at baseline. Mean 25(OH)D concentrations at 12 months in high- and low-dose groups were 32 and 25 ng/mL (80 and 62.5 nmol/L), respectively [27]. In another RCT ($n=200$; 67% females; mean age 78 ± 5 years; 58% vitamin D deficient), monthly vitamin D doses of 60,000 IU were associated with increased risk of falls compared with monthly doses of 24,000 IU (1.47 vs 0.94; $p=0.02$). Mean baseline 25(OH)D concentrations were 52.2 nmol/L (20.9 ng/mL) and 46.7 nmol/L (18.7 ng/mL), respectively, whereas they increased to 97.5 nmol/L (39 ng/mL) 77.5 nmol/L (31 ng/mL), respectively, at 12 months. Remarkably, the highest fall rate was observed in those with 25(OH)D > 112.5 nmol/L (>45 ng/mL) [28].

Collectively, these data indicate a detrimental effect of high intermittent vitamin D doses on fall and fracture risk, in elderly populations, with average baseline 25(OH)D concentrations. It must be highlighted that a minority of them was diagnosed with severe vitamin D deficiency.

With regard to daily vitamin D supplementation, there is also evidence for a U-shaped effect on falls and fractures in case of high doses. A case-control study (n=800 postmenopausal women) suggested an optimal daily vitamin D dose of 1,600-3,200 IU for protection from falls, in cases with baseline 25(OH)D concentrations <50 nmol/L (<20 ng/mL). This beneficial effect dissipated when doses exceeded 4,000 IU/day, leading to serum 25(OH)D concentrations of 103–121 nmol/L (41.2–48.4 ng/mL) and to a six-fold higher risk of falls, compared with doses of 1,600–3,200 IU/day (OR 5.6, 95% CI 2.1–14.8) [19]. A more recent double-blind RCT in 163 vitamin D-deficient postmenopausal women (mean age 66 years) assessed the anti-fall efficacy of different vitamin D doses (400–4,800 IU/day). After 12 months, patients at the lowest [<50 nmol/L (<20 ng/mL)], high-middle [95–115 nmol/L (38–46 ng/mL)] and highest 25(OH)D quintile [115–165 nmol/L (46–66 ng/mL)] manifested higher fall rates (72%, 60% and 45%) compared with the low-middle 25(OH)D quintile [80–95 nmol/L (32–38 ng/mL)]. Interestingly, fall rates with high daily vitamin D doses (4,000–4,800 IU) were significantly increased compared with medium doses (1,600, 2,400 or 3,200 IU) (OR 5.6, 95% CI 2.1–14.8). Fallers and non-fallers did not differ in baseline 25(OH)D concentrations (11–15 ng/mL) and calcium intake (~1200 mg/day) [29].

With respect to fractures, observational data in community-dwelling men (n=1,662; mean age 76.9±5.5 years) showed that participants at the lowest [≤ 36 nmol/L (≤ 14.4 ng/mL) and highest [> 72 nmol/L (> 28.8 ng/mL)] 25(OH)D quintile were at higher fracture risk compared with those with 25(OH)D concentrations of 60–72 nmol/L (24–28.8 ng/mL) [HR 3.5 (95% CI 1.7–7.0) and 2.7 (95% CI 1.4–5.4), respectively]. Interestingly, these associations were independent of BMD, physical activity and fall risk [30]. Furthermore, analysis of data from 11 RCTs on oral vitamin D supplementation alone or with calcium, as compared with placebo or calcium alone

(n=31,022; mean age 76 years; 91% women) showed an overall non-significant reduction in the risk of hip fractures (HR 0.90, 95% CI 0.80–1.01) and a slight reduction in the risk of non-vertebral fractures (HR 0.93, 95% CI 0.87–0.99). However, subgroup analysis, according to vitamin D intake, did show a benefit in the hip (HR 0.70, 95% CI 0.58–0.86) and non-vertebral fracture risk (HR 0.86, 95% CI 0.76–0.96) only with daily vitamin D doses of 800–2,000 IU (but not with doses of <800 IU), compared with placebo [31].

With regard to BMD, there is also evidence for a U-shaped effect. A recent 3-year, single-centre, double-blind RCT aimed to assess the dose-dependent effect of vitamin D supplementation on volumetric BMD and strength, assessed by high-resolution peripheral quantitative computed tomography, in community-dwelling adults (aged 55–70 years) [32]. Three groups were included according to daily vitamin D dose: 400 IU (n=109), 4,000 IU (n=100) and 10,000 IU (n=102). Mean 25(OH)D concentrations achieved at three years were: 77.4 nmol/L (30.9 ng/mL), 132.2 nmol/L (52.8 ng/mL) and 144.4 nmol/L (57.7 ng/mL), respectively. Optimal calcium supplementation was provided in all groups. Compared with the 400 IU group, both 4000 IU and 10,000 IU doses exerted a detrimental effect on radial BMD (-2.4% and -3.5%, respectively). The 10,000 IU dose also led to a significant bone loss in tibial BMD (-1.7%) [32]. It must be underlined that all participants were vitamin D-sufficient with normal areal BMD (assessed with DXA) in both spine and hip, which, however, was not affected [32]. Compared with low-dose, high-dose vitamin D was associated with higher rates of mild hypercalcemia (0%, 3% and 9%, respectively; p=0.002) and hypercalciuria (17%, 22%, 31%, respectively; p=0.01) [33]. *Post-hoc* analysis did not show any benefit or harm of high-dose vitamin D on postural sway compared with the dose of 400 IU [14].

Therefore, high vitamin D doses seem to be harmful with regard to falls, fracture risk and BMD. The exact pathogenesis is not clear. Increased osteoclastogenesis, as supported by increased serum concentrations of bone resorption markers, such as C-terminal telopeptide of type 1 collagen, may contribute to increased fracture risk related to high doses [32, 34]. Another explanation could be the increased physical activity that is observed in these individuals after quick repletion of their vitamin D status and their ensuing increased chance of falls, although this is not supported by all authors [28]. Genetic susceptibility may also interfere with the association between vitamin D supplementation (alone or with calcium) and fracture risk [35].

However, it must be highlighted that, according to the Endocrine Society guidelines, high vitamin D doses (6,000–10,000 IU/day for eight weeks, followed by maintenance doses of 3,000–6,000 IU/day) [1] are needed in certain conditions, such as obesity, malabsorption syndromes or medications affecting vitamin D metabolism to achieve a sufficient vitamin D status [$25(\text{OH})\text{D} > 75 \text{ nmol/L}$ ($> 30 \text{ ng/mL}$)].

4. Is combination with calcium more beneficial compared with vitamin D monotherapy?

Current evidence shows that calcium intake, either by dietary sources or supplements, may foster a modest increase (0.7–1.8%) in both lumbar spine and hip BMD at two years, as shown by a meta-analysis of 28 RCTs. Although only two RCTs provided comparative data on BMD and fracture risk, the authors did not find any difference between calcium monotherapy and its combination with vitamin D on this context [36]. Moreover, this effect seems to be modified by serum $25(\text{OH})\text{D}$ concentrations, since it is mostly seen in patients with vitamin D deficiency, especially in women [18].

With regard to fracture risk, a meta-analysis of 29 RCTs (n=63,897), published in 2007, showed that calcium, either alone or in combination with vitamin D, may reduce the risk of fractures of all types by 12% (RR 0.88, 95% CI 0.83–0.95). It also decreased bone loss at the hip by 0.54% (95% CI 0.35–0.73%), with a negligible effect on spinal BMD. Subgroup analysis showed that this anti-fracture benefit was meaningful at doses ≥ 1200 mg/day, combined with vitamin D ≥ 800 IU/day, in patients ≥ 70 years old, mostly in institutionalized ones, with severe vitamin D deficiency and $\geq 80\%$ compliance [37]. These results were reinforced by a pooled analysis of 11 RCTs (n=31,022; 91% women; mean age 76 years) which showed a reduction in fracture risk only with vitamin D 800–2,000 IU/day (alone or with calcium) compared with placebo (with or without calcium) [hazard ratio (HR) for hip fractures: 0.70 (95% CI 0.58–0.86); HR for non-vertebral fractures: 0.86 (95% CI 0.76–0.96)]. However, there was no interaction with age, baseline 25(OH)D concentrations, type of dwelling or additional calcium intake [31].

Another meta-analysis of both RCTs (n=28) and cohort studies (n=44), published in 2015, evaluated the effect of calcium, either by dietary sources or with supplements (alone or combined with vitamin D) on fracture risk in individuals aged >50 years. Calcium supplementation reduced the risk of total fracture by 11% (RR 0.89, 95% CI 0.81–0.96), an effect attributed to the reduction in vertebral (RR 0.86, 95% CI 0.74–1.00), but not to hip or forearm fracture risk [38]. Notably, this anti-fracture efficacy was not altered in subgroup analyses evaluating vitamin D co-supplementation or baseline dietary calcium intake. However, most RCTs were characterized by a high or moderate risk of bias. Restricted analysis to RCTs with low risk of bias (n=4) did not replicate the results. Of note, no anti-fracture benefit was observed with dietary calcium [38].

In contrast, a large meta-analysis of 33 RCTs in community-dwelling adults (n=51,145; aged >50 years) did not show any effect of calcium or vitamin D or their combination on hip fracture risk, in comparison with placebo or no treatment. A null effect was also shown with regard to vertebral, non-vertebral and total fractures. These findings did not change in subgroup analysis according to dose, gender, fracture history, dietary calcium intake or baseline 25(OH)D concentrations [13]. However, prior to extrapolation of these results in clinical practice, one should take into consideration that the duration of the majority of the included studies was only 1-2 years (potentially not long enough to show any anti-fracture efficacy) and baseline fracture risk was low. In addition, participants had normal BMD or osteopenia and were marginally vitamin D-deficient, with daily vitamin D doses of 400–800 IU and low adherence rates (<60%). Nonetheless, a beneficial effect of calcium and vitamin D in those under severe vitamin D deficiency could not be excluded [39].

However, a more recent meta-analysis (December 2019), which did show a beneficial effect of combined vitamin D (400–800 IU/day) and calcium (1000–1200 mg/day) supplementation in reducing the risk of total (RR 0.94, 95% CI 0.89–0.99) and hip fractures (RR 0.84, 95% CI 0.72–0.97) compared with placebo or no treatment. Again, this effect was not evident with vitamin D monotherapy [20]. Of note, this meta-analysis differed from the previous ones by excluding RCTs of small sample size (i.e. <500 participants), of <10 fracture events and with too low vitamin D doses (<800 IU), in order to minimize the risk of bias.

Therefore, it appears that vitamin D supplementation may modestly increase BMD and reduce the risk of falls and fractures only when co-administered with calcium (≥ 1000 –1200 mg/day). This effect is mainly observed at doses of 800–2000 IU/day, in older

patients (>70 years) and those with severe vitamin D deficiency. This evidence seems to be more robust in institutionalized compared with community-dwelling populations [2], as well as in cases with high compliance (>80%) and after five years of treatment [40]. Although few direct comparative data exist, calcium combination with vitamin D does not seem to be superior to calcium monotherapy. However, recent international guidelines, such as those by the Endocrine Society (suggesting that calcium plus vitamin D combination is more beneficial in hip fracture risk than either treatment alone, without difference in vertebral and non-vertebral fracture risk) [11] and the IOF [41], still recommend calcium plus vitamin D combination and not either treatment alone

5. Conclusions

In conclusion, despite the well-documented detrimental effect of vitamin D deficiency on fractures, vitamin D supplementation alone does not seem to reduce this risk, especially in individuals <70 years old, with normal BMD and without vitamin D deficiency. A cascade of meta-analyses has yielded inconsistent results, owing to differences in inclusion criteria and heterogeneity among studies, with regard to vitamin D dose, co-supplementation of calcium, design, the dwelling of participants and baseline 25(OH)D concentrations. These results are briefly presented in Table 1. In any case, there is evidence for a modest anti-fracture and anti-fall benefit, only when intermediate (800–2,000 IU/day) vitamin D doses are co-administered with calcium, especially in elderly populations, with severe vitamin D deficiency at baseline. On the other hand, high vitamin D doses, provided either at monthly (60,000–100,000 IU) or daily intervals (>4,000 IU), especially in cases with 25(OH)D concentrations above the deficiency threshold and without osteoporosis, seem to be harmful with regard to falls,

fracture risk and BMD. Therefore, an individualized approach is suggested, which will take the specific patient characteristics into account, such as age, BMI, baseline 25(OH)D concentrations, BMD and medical history (i.e. malabsorption syndromes, medications interfering with vitamin D metabolism) to designate the appropriate vitamin D dose needed for achieving optimal musculoskeletal health.

Contributors

Panagiotis Anagnostis designed the research, analyzed the extractable data and wrote the first draft of the paper.

Julia K. Bosdou searched the literature and analyzed the data.

Eustathios Kenanidis searched the literature and analyzed the data.

Michael Potoupnis reviewed the manuscript and provided critical scientific input.

Eleftherios Tsiridis reviewed the manuscript and provided critical scientific input.

Dimitrios G. Goulis resolved discrepancies regarding the quality of the studies included, provided critical scientific input and had the primary responsibility for the paper's final content.

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Table 1. Characteristics of meta-analyses regarding vitamin D and/or calcium supplementation and their musculoskeletal outcomes

Study characteristics			Intervention				Comparator	Outcomes				
ID	First author, Year of publication	Number of studies included / total number of participants	25(OH)D concentrations	Vitamin D monotherapy	Calcium monotherapy	Vitamin D plus calcium		Total fractures	Hip fractures	Vertebral fractures	BMD	Falls
1.	Tang, 2007*	29 RCTs / 63,897			500-1,200 mg/day		placebo	RR 0.90 (0.80-1.00)			Difference in means: a) LS: 1.19% (0.76–1.61%) b) TH: 0.54% (0.35–0.73)	
						-vitamin D 200-800 IU/day -calcium 500-1,200 mg/day	placebo	RR 0.87 (0.77-0.97)				
2.	Bischoff-Ferrari, 2009**	8 RCTs / 2426	≥60 nmol/L (≥24 ng/mL)				25(OH)D <60 nmol/L (<24 ng/mL)					RR 0.77 (0.65-0.90)
				700-1,000 IU/day			200-600 IU/day					RR 0.81 (0.71-0.92)
3.	Reid, 2014***	23 RCTs / 4,082		300-1,600 IU/day or 10,000-50,000 IU/week			placebo				-WMD in LS: 0% (-0.2 to 0.3%) -WMD in TH: 0.8% (0.2-1.4%) -WMD in FN: 0.2% (-0.1 to 0.4%)	
4.	Bolland, 2015****	26 RCTs / 69,107			500-1,200 mg/day		placebo	RR 0.89 (0.81-0.96)	RR 0.95 (0.76-1.18)	RR 0.86 (0.74-1.00)		

					(≥1,000 mg/day in 20 studies)							
5.	Tai, 2015	51 RCTs / 12,257			500-2,500 mg/day	-vitamin D 400- 1400 IU/day (300.000 IM in two studies) -calcium 500- 1,200 mg/day	placebo				At one year: -WMD in LS: 1.2% (0.8-1.7%) -WMD in FN: 1.2% (0.7-1.8%) -WMD in TH: 1.4% (0.6-2.3%) At two years: -WMD in LS: 1.1% (0.7-1.6%) -WMD in FN: 1% (0.5-1.4%) -WMD in TH: 1.3% (0.8-1.8%)	
6.	Zhao, 2017*****	33 RCTs / 51,145		any vitamin D dose			placebo	RR 1.01 (0.87-1.17)	RR 1.21 (0.99- 1.47)	RR 0.97 (0.54-1.77)		
					600-1,500 mg/day		placebo	RR 0.88 (0.75-1.03)	RR 1.53 (0.97- 2.42)	RR 0.83 (0.66-1.05)		
						-any vitamin D dose -calcium 600- 1,500 mg/day	placebo	RR 0.90 (0.78-1.04)	RR 1.09 (0.85- 1.39)	RR 0.63 (0.29-1.40)		
7.	Bolland, 2018*****	81 RCTs / 53,537		any vitamin D dose			placebo	RR 1.01 (0.94-1.1)			-WMD in LS: 0.25% (0.00- 0.49%) -WMD in TH: 0.34% (0.13- 0.55%)	RR 0.97 (0.93-1.02)

				>800 IU/day			≤800 IU/day	RR 0.61 (0.36-1.06)				-WMD in FN: 1.12% (0.58-1.65)
												RR 0.94 (0.64-1.49)
8.	Yao, 2019*****	11 observational studies / 39,141	each ↑ 25 nmol/L in 25(OH)D					RR 0.93 (0.89-0.96)	RR 0.80 (0.75-0.86)			
8.		11 RCTs / 34,243		daily or intermittent dose 400-30,000 IU			placebo	RR 1.06 (0.98-1.14)	RR 1.14 (0.98-1.32)			
9.		6 RCTs / 49,282				-vitamin D 400- 800 IU/day -calcium 1,000- 1,200 mg Ca/day	placebo	RR, 0.94 (0.89-0.99)	RR 0.84 (0.72-0.97)			

Notes:

*mean age ≥50 years; fracture risk reduction greater with high compliance, with calcium doses of ≥1,200 mg and with vitamin D doses of ≥800 IU

** mean age ≥65 years

***mean age 22-80 years; benefit only in studies with baseline 25(OH)D concentrations <40 nmol/L (16 ng/mL); no difference according to vitamin D dose (<800 IU vs ≥800 IU), study duration (≤12 vs >12 months) or calcium supplementation, between subgroups

****mean age >50 years; no difference between the subgroups of calcium monotherapy or calcium plus vitamin D combination

*****community dwelling adults >50 years; mean baseline 25(OH)D concentrations <50 nmol/L (<20 ng/mL) in 11/33 studies; no difference in subgroup analysis according to calcium dose, sex, previous fractures, dietary calcium intake and baseline 25(OH)D concentrations

*****mean age >18 years (41% of participants <65 years old); subgroup analysis, according to vitamin D dose (<800 vs ≥800 IU/day) did not alter the results; 6% of studies were conducted in populations with severe vitamin D deficiency [<25 nmol/L (<10 ng/mL)]

*****mean 52-84 years (>65 years in 24/28 studies); exclusion of RCTs of small sample size (i.e. <500 participants), of <10 fracture events and with too low vitamin D doses (<800 IU)

-Bold indicates statistical significance

Abbreviations: 25(OH)D: 25-hydroxy-vitamin D; BMD: bone mineral density; FN: femoral neck; IM: intramuscular; LS: lumbar spine; OR: odds ratio; RR: relative risk; TH: total hip; ↓: decrease; ↑: increase