Original Communication

Vitamin D Effects on Bone and Muscle

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Abstract: Increasing data suggest that higher 25-hydroxyvitamin D [25(OH)D] serum concentrations are advantageous for health. At present, strong evidence for causality is available for fracture and fall prevention, while promising epidemiologic and mechanistic studies suggest a key role of vitamin D in the preservation of cardiovascular health, and the prevention of cancer and other common chronic disease. For lower extremity function, fall prevention, hip bone density, and for fracture prevention optimal benefits are observed with 25(OH)D levels of at least 75 nmol/L to 100 nmol/L [1]. This threshold may be reached in 50 % of adults with 800 to 1000 IU vitamin D per day. This manuscript will discuss the evidence of vitamin D in fall and fracture prevention and how these data transfer to the most recent recommendations by the IOF (International Osteoporosis Foundation) and the IOM (Institute of Medicine).

Key words: Vitamin D, fractures, falls, prevention, chronic diseases, bone density, threshold, optimal benfit

Vitamin D sources

Vitamin D can be made in the skin from exposure to sunlight [2]. Solar ultraviolet radiation, UVB in particular, is the main light source for the synthesis of vitamin D in humans. However, solar radiation is not a reliable source of vitamin D since there are also associated risks of skin aging and cancer. Notably, all of Europe gets insufficient UVB irradiation intensity during the months of November through the end of March, resulting in minimal skin production of vitamin D during the winter season independent of age. Thus, the lowest seasonal 25(OH)D status is reached in April/May. As the half-life of vitamin D is 3 to 6 weeks, the seasonal peak of 25(OH)D status in September decreases rapidly with a nadir beginning already in November. Additionally, skin production of vitamin D declines with age [3], leaving seniors with a four-fold lower capacity to produce vitamin D in their skin compared to younger adults [4]. Further, seniors tend to avoid direct sun exposure, which explains the large segment of seniors with vitamin D deficiency residing in the Mediterranean area of Europe [5]. In addition, the use of sunscreen and sun-protective clothing reduces skin production of vitamin D independent of age [6].

Alternatively, natural nutritional sources of vitamin D are rare. Vitamin D_2 is obtained from the ultraviolet irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. Vitamin D_3 is present in fatty fish such as salmon, mackerel, and herring. To cover a daily recommended intake of 800 IU vitamin D, we would need to consume two servings of wild salmon per day (farmed salmon has much less vitamin D) [4], a diet difficult to maintain for the large majority of the population.

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In the European SENECA study, 36 % of senior men and 47 % senior women had 25(OH)D serum concentrations below 30 nmol/L [5]. Most vulnerable to severe vitamin D deficiency are seniors with acute hip fracture who were found to have severe vitamin D deficiency (< 30 nmol/L) in 50 % of cases, both in the ambulatory and institutionalized setting [7], while adequate 25(OH)D levels of at least 75 nmol/L were achieved in less than 5 percent of hip fracture patients [7]. Notably, vitamin D deficiency is not limited to the senior population. A 2010 hearing at the European parliament established that 50 to 70 % of the general adult population, depending on a threshold of 50 nmol/L or 75 nmol/L, is vitamin D-deficient [8]. Thus, broad supplementation strategies, especially in the senior population, are needed, as recommended by the IOF [9] for fall and fracture prevention.

Efficacy of vitamin D supplementation on fall and fracture prevention

Vitamin D modulates fracture risk in two ways: by decreasing falls and increasing bone density. Two most recent meta-analyses of double-blind, randomized controlled trials came to the conclusion that vitamin D reduces the risk of falls by 19 % [10], the risk of hip fracture by 18 % [11] and the risk of any non-vertebral fracture by 20 % [11], however this benefit was dose-dependent. Fall prevention was only observed in trials of at least 700 IU vitamin D per day, and fracture prevention required a received dose (treatment dose multiplied by adherence) of more than 400 IU vitamin D per day. Anti-fall efficacy started with achieved 25-hydroxyvitamin D levels of at least 60 nmol/L (24 cm/mL) and anti-fracture efficacy started with achieved 25-hydroxyvitamin D levels of at least 75 nmol/L (30 cm/mL) and both endpoints improved further with higher achieved 25-hydroxyvitamin D levels (see Figure 1). At the higher dose, fracture prevention was documented in all subgroups of the senior population (see Table I).

Vitamin D: its role in muscle health

In humans, several lines of evidence support a role of vitamin D in muscle health. First, proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [12]. Vitamin D deficiency myopathy includes proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [13]. Second, the vitamin D receptor (VDR) is expressed in human muscle tissue [14], and VDR activation may promote *de novo* protein synthesis in muscle [15]. Suggesting a role of vitamin D in muscle development, mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life [16, 17]. These abnormalities persist after correction of systemic calcium metabolism by a rescue diet [17].

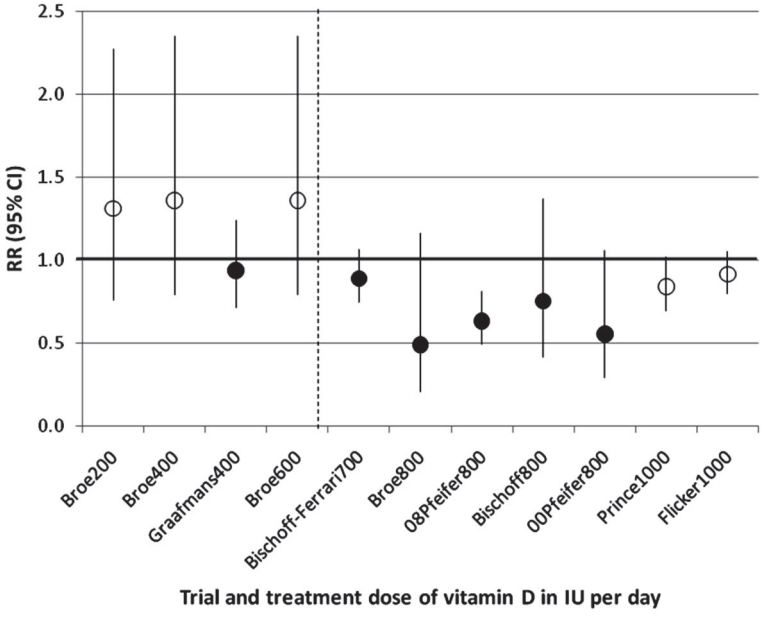

Figure 1: Fall prevention by dose of vitamin D. Circles show the relative risk of falling in 8 double-blind RCTs testing vitamin D supplementation with or without calcium supplementation against calcium or placebo. Markers filled indicate trials with oral vitamin D3 (cholecalciferol) and markers unfilled indicate trials with oral vitamin D2 (ergocalciferol) [10, 31]. By visual inspection, fall reduction only occurs in trials that tested a vitamin D dose of at least 700 IU per day. Including all trials (regardless of dose level), there was a significant reduction in the odds of falling: OR = 0.73 [0.62, 0.87]; p = .0004. When the model is expanded to capture the impact of both high dose and low dose treatment, high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling (OR = 0.66 [0.53, 0.82] p = .0002), while low dose vitamin D did not (OR = 1.14 [0.69, 1.87]; p = .61).

Table I: Non-vertebral fracture reduction with vitamin D based on evidence from double-blind RCTs.

Subgroups by received dose of vitamin D	Fracture	reduction
Pooled analysis from 3 trials with low-dose vitamin D (340–380 IU/day)	+2 %	Ø
Pooled analysis from 9 trials with higher dose vitamin D (482–770 IU/day):	–20 %	Sig.
Pooled subgroup analysis from trials with higher-dose vitamin D (482–770 IE / day):		
Vitamin D2	–10 %	Ø
Vitamin D3	–23 %	Sig.
age 65–74	–33 %	Sig.
age 75+	–17 %	Sig.
institutionalized 65+	–15 %	Sig.
community-dwelling 65+	–29 %	Sig.
Vitamin D plus Calcium	–21 %	Sig.
Vitamin D main effects	–21 %	Sig.

Adapted from Bischoff-Ferrari et al. Prevention of non-vertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch. Intern. Med. 2009 Mar 23;169(6):551^–^61, Copyright© (2009), American Medical Association [11].

Third, several observational studies suggest a positive association between 25-hydroxyvitamin D and muscle strength or lower extremity function in older persons [18, 19]. This was confirmed in several double-blind randomized controlled trials (RCTs), where vitamin D supplementation increased muscle strength and balance [20, 21]. Three recent double-blind RCTs with 800 IU vitamin D3 resulted in a 4–11 % gain in lower extremity strength or function [20, 21], and in up to a 28 % improvement in body sway [21, 22] in older adults 65+ years of age, within 2 to 12 months of treatment. *In some of the same trials,* this resulted in a reduction in the risk of falling, as summarized in several recent meta-analyses [10, 23–30]. Notably, a study by Glerup and colleagues suggest that vitamin D deficiency may cause muscular impairment even before adverse effects on bone occur [12].

Dose-response relationship between vitamin D and muscle strength and falling

Notably, a dose-response relationship between vitamin D status and muscle health was suggested in the large NHANES III survey (The Third National Health and Nutrition Examination Survey), including 4100 ambulatory adults aged 60 years and older. Muscle function as measured by the 8-foot walk test and the repeated sit-to-stand test was poorest in subjects with the lowest 25-hydroxyvitamin D (below 20 nmol/L) levels. Similar results were found in a Dutch cohort of older individuals [18]. Notably, while from the smaller Dutch cohort a threshold of 50 nmol/L has been suggested for optimal function [18], a threshold beyond which function would not further improve was not identified in the larger NHANES III survey, even beyond the upper end of the reference range (>100 nmol/L) [19].

Similarly**,** a dose-dependent benefit of vitamin D in regard to fall prevention was suggested by two meta-analyses [10, 23]. The most recent meta-analysis of 8 high-quality, double-blind RCTs (n = 2426) found significant heterogeneity by dose (low-dose: < 700 IU/day versus higher dose: 700 to 1000 IU/day; p-value 0.02) and achieved 25-hydroxyvitamin D level (< 60 nmol/L versus ≥ 60 nmol/L; p-value = 0.005) [10], but was criticized by the 2010 Institute of Medicine (IOM) Report. In a rebuttal [31], the authors confirmed their selection of trials and re-analyzed their data to account for the stochastic dependencies (correlations) between the corresponding risk ratios in the multiple dosing trial by Broe et al. as suggested by the IOM. In the re-analysis, when treatment was the only predictor (regardless of dose level), there was a significant reduction in the odds of falling based on the primary analysis of the same 8 trials: OR = 0.73 [0.62, 0.87]; p = .0004. When the model was expanded to capture the impact of both high dose and low dose treatment (see Figure 2),

high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling by 34 % (OR = 0.66 [0.53, 0 .82] p=.0002), while low dose vitamin D did not (OR = 1.14 [0.69, 1.87]; p = .61) [31].

Notably, in the original publication of this meta-analysis[10], the authors performed a sensitivity analysis including 15 trials of any study design and fall assessment quality (n = 17,786) and documented a non-significant 7 % fall reduction with vitamin D (RR = 0.93; 95 % CI 0.87 – 1.01). Even at the comprehensive analysis level, significant variation among the 15 trials (Q-test: p = 0.009), could be explained by dose (700 IU + /day; n = 17,281; pooled RR was 0.92 (95 % CI, 0.85 – 1.00)), and further among trials that tested a higher dose by trial quality (Q-test: p = 0.005). Further, based on the primary analysis [10], the benefit of fall prevention was present in all subgroups of the senior population at the higher dose of vitamin D. At the higher dose of 700 to 1000 IU vitamin D, there was a 38 % reduction in the risk of falling with a treatment duration of 2 to 5 months and a sustained significant effect of 17 % fall reduction with treatment duration of 12 to 36 months, and the benefit was independent of type of dwelling and age. There was a suggestion that vitamin D_3 was superior to vitamin D_2 for fall prevention. Although the number of studies for active vitamin D and fall prevention was small, the authors pooled these trials separately and found a significant benefit on fall prevention (–22 %), which adds to the evidence that improved vitamin D status will reduce the risk of falling in older individuals.

Summary of the IOM report recommendations of vitamin D and fall prevention

The IOM did a thorough review on the effect of vitamin D on fall prevention [32]. Their synopsis is that the evidence of vitamin D on fall prevention is inconsistent, which is in contrast to all published and peer-reviewed meta-analyses [10, 23 – 30]. Notably, the IOM overall analysis of 12 RCTs (n = 14,101) showed a significant benefit of vitamin D on fall prevention (OR = 0.89; 95 % CI 0.80 – 0.99), as did the majority of their subset analyses, clearly supporting the use of vitamin D in the prevention of falling. The set of analyses which showed no benefit were based on only 4 studies, which cannot be considered reliable indicators of true treatment efficacy, as these trials either used low dose vitamin D [33], had less than 50 % adherence [34], had a low-quality fall assessment [35] or used one large bolus dose of vitamin D among seniors in unstable health [36].

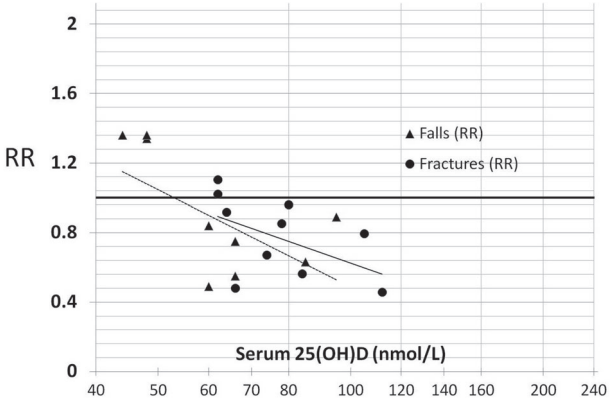

Figure 2: Threshold for optimal fall and fracture prevention based on double-blind randomized controlled trials. Data points show the relative risk of falls and the relative risk of sustaining any non-vertebral fracture from double-blind RCTs, by achieved 25-hydroxyvitamin D levels in the treatment groups. Data was extracted from two 2009 meta-analyses [10, 11] and summarized in a recent benefit-risk analysis of vitamin D [1]. Based on these data, 75 or better 100 nmol/L (30 or better 40 cm/mL) are suggested as an optimal threshold of 25-hydroxyvitamin D for fall and fracture prevention.

Recent recommendations on vitamin D and fall prevention:

Several recent peer-reviewed meta-analyses of randomized, controlled trials have addressed the effect of vitamin D on fall risk reduction [23, 25 – 27, 29 – 31] , all of them suggesting a benefit. Thus, given the available evidence today, vitamin D supplementation for fall prevention should not be delayed as a recommendation among the senior population. This suggestion is in line with *the Agency for Healthcare Research and Quality (AHRQ) for the* U.S. Preventive Services Task Force [29] , the 2010 American Geriatric Society/ British Geriatric Society Clinical Practice Guideline [37], *the 2010 assessment by the IOF[9], and the 2011 recommendations on vitamin D by the Endocrine Society[38],* all 4 of which identified vitamin D as an effective intervention to prevent falling in older adults.

Vitamin D: its role in bone health and fracture reduction

Data from several study-level meta-analyses and one pooled participant-level analysis are conflicting on the evidence of vitamin D supplementation and fracture reduction. One study-level meta-analysis of double-blind randomized trials suggested an 18 % reduction of hip and 20 % reduction of any non-vertebral fractures

at an adherence-adjusted dose of more than 400 IU vitamin D per day with or without calcium supplementation (Figure 2; Table I). Conversely, two other study-level meta-analyses and one pooled analysis of participant-level data from open-design and blinded trials, suggested that vitamin D may have a neutral effect on fracture reduction [39], or may reduce any fractures [40] and fractures at the hip by about 8 % [41], but only if combined with calcium supplementation irrespective of vitamin D dose [39, 41, 42]. The difference in findings may in part be explained by the alternative inclusion criteria of trials, and a dose-dependent benefit of vitamin D may have been missed because a mix of open and double-blind trials of oral and intra-muscular vitamin D were chosen [39, 41, 42], or the treatment dose evaluation did not incorporate adherence [39, 41, 42]. A dose-response relationship between vitamin D and fracture reduction is supported by one meta-analysis of 12 randomized-controlled trials for the risk of hip and any non-vertebral fracture [11] (Figure 1) and by a large population-based survey (NHANES III) showing a significant positive trend between higher serum 25-hydroxyvitamin D concentrations and better hip bone density [43] and lower extremity strength [18, 19].

The 2009 trial-level meta-analysis of 12 double-blind RCTs for non-vertebral fractures (n = 42,279) and 8 RCTs for hip fractures (n = 40,886) that incorporated adherence and supplement dose outside the study protocol documented that the anti-fracture efficacy of vitamin D is dose-dependent and increases significantly with a higher achieved level of 25-hydroxyvitamin D in the treatment group starting at 75 nmol/L [11]. No fracture reduction was observed for a received dose of 400 IU or less per day, while a higher received dose of 482 to 770 IU supplemental vitamin D per day reduced non-vertebral fractures by 20 % (pooled RR = 0.80; 95 % CI, 0.72 – 0.89; n = 33,265 from 9 trials) and hip fractures by 18 % (pooled RR = 0.82; 95 % CI, 0.69 – 0.97; n = 31,872 from 5 trials). Notably, subgroup analyses for the prevention of non-vertebral fractures with the higher received dose suggested a benefit in all subgroups of the older population, and possibly better fracture reduction with D3 compared to D2, while additional calcium did not further improve anti-fracture efficacy (see Table I).

Recent recommendations on vitamin D and fracture prevention:

The recommended daily allowance (RDA) of vitamin D as defined by the Institute of Medicine in 2010 is 600 IU per day for all children age 1 to 18 and all adults up to age 70, and 800 IU per day for those aged 70 years and over. The IOM sets a target 25-hydroxyvitamin D at 50 nmol/L coupled with the observation that the RDA of vitamin D per day is adequate to maintain this level [44]. While the IOM recommendation of an increase in vitamin D intake is supported by the available data from double-blind RCTs of fracture risk, a threshold of 50 nmol/L for its 25(OH)D blood level is not. In two 2009 meta-analyses of double-blind RCTs, a threshold of 50 nmol/L was insufficient for fracture or fall reduction based on achieved 25(OH)D levels in the treatment groups [10, 11] (see Figure 1). Also, in the large population-based NHANES analysis, bone density increased with higher 25(OH)D levels far beyond 50 nmol/L in younger and older adults, suggesting that the IOM threshold recommendation is too low for optimal bone health in adults[43]. In contrast to the IOM report, the IOF recommended in their 2010 position paper on vitamin D a threshold of 75 nmol/L for optimal fall and fracture reduction and recommended 800 to 1000 IU vitamin D per day for seniors age 60 years and older [9].

Dosing interval of vitamin D

In 2010, a large double-blind RCT by Sanders *et al.*, including 2256 community-dwelling women age 70 years and older, tested the benefit of 500,000 IU vitamin D3 given orally once a year, on fall and fracture prevention [45]. In those women, mean age 76, considered to be at risk of fracture, 500,000 IU vitamin D once a year did not reduce, but instead increased, the risk of falls by 15 % and the risk of fractures by 26 % compared to placebo, with the greatest increase in falls occurring during the first 3 months after dosing. These findings are consistent with another trial that tested 300,000 IU vitamin D2 as an intra-muscular injection once per year [46].

Whether the large dose of vitamin D tested in the Sanders trial was too much of a good thing or not enough to provide a sufficient supply of vitamin D over 12 months is speculative[47]. The temporal pattern of events may suggest that the high dose of vitamin D may have induced a "protective" reaction, resulting in an acute decrease in 1,25-dihydroxyvitamin D [48]. Alternatively, the undocumented potential effect of vitamin D on muscle strength [49] and overall health (i. e. fewer infections and hospital admissions) [50] in the Sanders trial, may have improved mobility and decreased "down time," ironically leading to an increased opportunity to fall and fracture.

As a result of the Sanders trial and given that the half-life of vitamin D is 3 to 6 weeks, a daily, weekly, or monthly dosing interval may be most advantageous and safe.

Adding calcium to vitamin D for bone health

In the 2009 meta-analysis of double-blind RCTs [11], the observed calcium-independent benefit of vitamin D on non-vertebral fracture prevention at a vitamin D dose greater than 400 IU per day may be explained by a calcium-sparing effect of vitamin D [51, 52], which is supported by two recent epidemiologic studies suggesting that both parathyroid hormone (PTH) suppression [52] and hip-bone density [53] may only depend on a higher calcium intake if serum 25-hydroxyvitamin D levels are very low.

Thus, as calcium absorption is improved with higher serum 25-hydroxyvitamin D levels [52, 54], future studies may need to evaluate whether current calcium intake recommendations with higher doses of vitamin D are safe or require downward adjustment [54]. If dietary calcium is a threshold nutrient, as suggested by Dr. Heaney [55], then that threshold for optimal calcium absorption may be at a lower calcium intake when vitamin D supplementation is adequate.

Recent recommendations on adding calcium to vitamin D for fracture prevention

The 2010 position paper on vitamin D by the IOF does not comment on calcium. The 2010 IOM report states that more data regarding the interaction of vitamin D and calcium on bone health are needed and no recommendation was provided on their combination. Notably, several data suggest that vitamin D increases calcium absorption [56] and that a higher intake of calcium beyond 800 mg per day may not contribute to PTH suppression [57] and hip-bone density [53] if 25(OH)D levels are above 40 to 50 nmol/L. In the trials that tested vitamin D plus calcium for fracture reduction, confounding by calcium intake cannot be completely eliminated, but two observations are important: (1) in one 2009 meta-analysis of double-blind RCTs, fracture reduction was the same for the main effect of vitamin D and trials that combined vitamin D with calcium if the adherence-adjusted vitamin D dose was more than 480 IU per day [11]; (2) calcium supplementation by itself did not reduce risk of fractures in one meta-analysis of double-blind RCTs [58]. As noted in the IOM review, in the analysis of NHANES data with more than 9000 subjects, calcium intake was associated with hip-bone density only among women with low 25(OH)D levels; in all other groups there was no relation between calcium intake and bone density. In contrast, 25(OH)D levels were consistently and positively associated with hip-bone density [53]. Thus, with adequate 25(OH)D levels or sufficient vitamin D intake, higher calcium intakes may not be correlated with bone health. Therefore, calcium recommendations could be downward adjusted with vitamin D supplementation – possibly also for safety reasons. This has not been considered by the IOM report.

In summary

Based on evidence from randomized-controlled trials, vitamin D supplementation reduces both falls and non-vertebral fractures, including those at the hip. Data from randomized controlled trials and epidemiologic data on lower extremity function and hip-bone density suggest that this benefit is dose-dependent with a desirable 25(OH)D threshold of at least 75 nmol/L.

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