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Bischoff-Ferrari H

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Contribution of vitamin D to fracture prevention

H. Bischoff-Ferrari

Abstract: Several recent meta-analyses have addressed the benefit of vitamin D on fracture reduction with conflicting findings. This article will first summarize anti-fracture efficacy from double-blind randomized trials of oral vitamin D supplementation. Then, this article will address why meta-analyses with alternative approaches, extending to open design trials and trials that tested intra-muscular vitamin D, have reported differential findings.

Finally, as vitamin D modulates fracture risk in two ways, by decreasing falls and increasing bone density, the efficacy of vitamin D on fall prevention will be reviewed, and the optimal 25-hydroxyvitamin D level to achieve these benefits, will be suggested in this context. **J Miner Stoffwechs 2010; 17 (Suppl 1): 34–8**.

Falls and fractures

Over 90 % of fractures occur after a fall and fall rates increase with age and poor muscle strength or function [1]. Thus, a benefit of vitamin D on both fall and fracture prevention is of significant clinical importance. 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 [2]. Vitamin D deficiency myopathy includes proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [3]. Second, VDR is expressed in human muscle tissue [4], and VDR activation may promote de novo protein synthesis in muscle [5]. Finally, suggesting a role of vitamin D in muscle development, mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers [6, 7].

Evidence from double-blind randomized controlled trials of oral vitamin D supplementation in seniors age 65 and older (fall and fracture prevention)

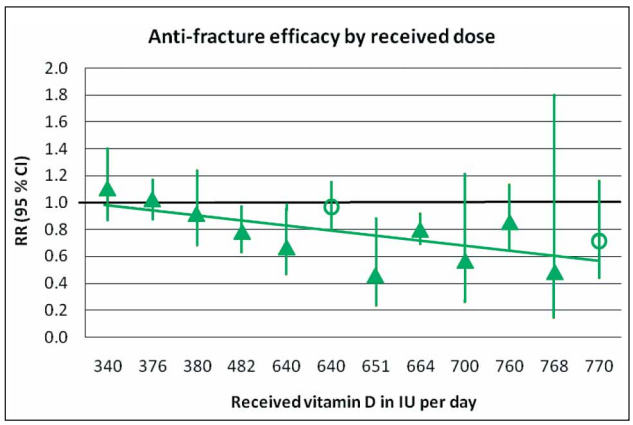
Two 2009 meta-analyses of double-blind randomized controlled trials came to the conclusion that vitamin D reduces the risk of falls by 19 % [8], the risk of hip fracture by 18 % and the risk of any non-vertebral fracture by 20 % [9], however this benefit was dose-dependent. Fall prevention was only observed in trials with a treatment dose of at least 700 IU vitamin D per day, and fracture prevention required a received dose (treatment dose*adherence) of more than 400 IU vitamin D per day. Any lower dose did not reduce fracture or fall risk, while the benefit of fall prevention and fracture prevention was present in all subgroups of the senior population at the higher dose of vitamin D. The primary use of received dose (dose*adherence) as opposed to treatment dose from double-blind RCTs allowed for the assessment of anti-fracture efficacy by a dose that accounts for the low adherence in several recent large trials [10, 11].

The 2009 meta-analysis on fall prevention included 8 double-blind RCTs with predefined fall assessment throughout the trial period (n = 2426) and found significant heterogeneity by dose (low-dose: < 700 IU per day versus higher dose: 700–1000 IU per day; p-value 0.02) and achieved 25-hydroxyvitamin D level (< 60 nmol/l versus ≥ 60 nmol/l; p-value = 0.005) [12]. Higher dose supplemental vitamin D reduced fall risk by 19 % (pooled relative risk [RR] = 0.81; 95%-CI: 0.71–0.92; n = 1921 from seven trials) versus a lower dose did not (pooled RR = 1.10, 95%-CI: 0.89–1.35 from 2 trials), also achieved serum 25-hydroxyvitamin D concentrations < 60 nmol/l did not reduce the risk of falling (pooled RR = 1.35, 95%-CI: 0.98–1.84). Notably, at the higher dose of 700–1000 IU vitamin D, this meta-analysis documented a 38 % reduction in the risk of falling with treatment duration of 2 to 5 months and a sustained significant effect of 17 % fall reduction with treatment duration of 12–36 months, and the benefit was independent of type of dwelling and age. Thus, benefits of 700–1000 IU vitamin D per day on fall prevention are rapid and sustained and include all subgroups of the senior population.

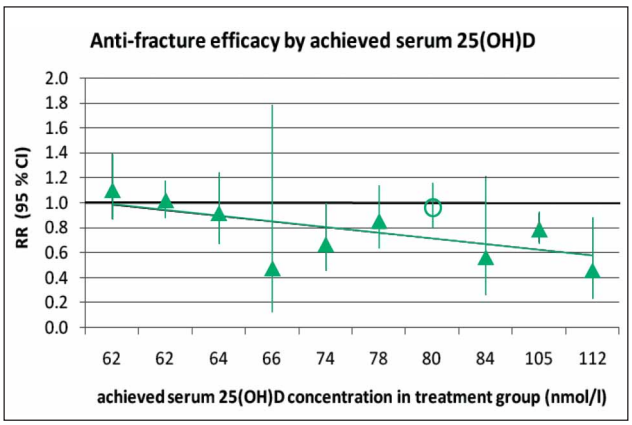
Further support of a dose-response relationship of vitamin D and fall reduction comes from a multi-dose double-blind RCT among 124 nursing home residents receiving 200, 400, 600 or 800 IU vitamin D compared to placebo over a 5 month period [13]. Participants in the 800 IU group had a 72 % lower rate of falls than those taking placebo or a lower dose of vitamin D (rate ratio = 0.28; 95%-CI = 0.11–0.75) [13].

The 2009 meta-analysis on fracture prevention included 12 double-blind RCTs for non-vertebral fractures (n = 42.279) and 8 RCTs for hip fractures (n = 40.886), and, similar to the meta-analysis on fall prevention, it found significant heterogeneity for received dose of vitamin D and achieved level of 25-hydroxyvitamin D in the treatment group for hip and any non-vertebral fractures (Fig. 1a, b) [9]. No fracture reduction was observed for a received dose of 400 IU or less per day or achieved 25-hydroxyvitamin D levels of less than 75 nmol/l. Conversely, a higher received dose of 482–770 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 (Table 1).

Korrespondenzadresse: Heike Bischoff-Ferrari, MD, DrPh., Director, Centre on Aging and Mobility, University of Zurich; Swiss National Foundations Professor, Dept. of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, CH-8091 Zurich, Rämistraße 100; E-Mail: HeikeABischoff@aol.at



1a: Data points and represented trial from left to right: 340 IU = Lips [65], 376 IU = Record [11], 380 IU = Meyer [21], 482 = WHI (study medication plus personal intake) [10], 640 IU (D3) = Trivedi [66], 640 IU = Lyons [20], 651 IU = Dawson-Hughes [67], 664 IU = Chapuy 1992 [68], 700 IU = Pfeifer 2009 [69], 760 IU = Chapuy 2002 [70], 768 IU = Pfeifer 2000 [71], 770 IU = Flicker [63].



1b: Data points and represented trial from left to right: 62 nmol/l = Lips [65], 62 nmol/l = Record [11], 64 nmol/l = Meyer [21], 66 nmol/l = Pfeifer 2000 [71], 74 nmol/l = Trivedi [66], 78 nmol/l = Chapuy 2002 [70], 80 nmol/l = Lyons [20], 84 nmol/l = Pfeifer 2009 [69], 105 nmol/l = Chapuy 1992 [68], 112 nmol/l = Dawson-Hughes [67].

Figure 1a, b: Prevention of non-vertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Triangles indicate trials with D3, circles trials with D2. Line = Trendline. All 12 high quality trials were included for the received dose meta-regression (n = 42,279 individuals). For achieved 25(OH)D levels 2 trials did not provide serum 25(OH)D levels measured in the study population during the trial period [63, 64]. For any non-vertebral fractures, anti-fracture efficacy increased significantly with higher received dose (meta-regression: Beta = –0.0007; p = 0.003) and higher achieved 25-hydroxyvitamin D levels (meta-regression: Beta = –0.005; p = 0.04) (adapted from [9]).

Results from meta-analyses that included double-blind and open-design trials in their primary analysis

In August 2007, a review and meta-analysis commissioned by the US Department of Health and Human Services (HHS) addressed the effect of vitamin D supplementation on all fractures in postmenopausal women and men ages 50 and older [14]. The pooled results for all fractures included 10 double-blinded and 3 open design trials (n = 58.712) and did not support a significant reduction of fractures with vitamin D (pooled odds ratio = 0.90; 95%-CI: 0.81–1.02). The report suggested that the benefit of vitamin D may depend on additional calcium and may be primarily seen in institutionalized individuals, which is consistent with the meta-analysis of Boonen et al. [15].

One 2010 patient-based meta-analysis of a subgroup of 7 large trials of vitamin D included 68.500 individuals age 47 and older [16]. The authors defined alternative criteria that permitted the inclusion of two open design trials [17, 18], one trial with intra-muscular vitamin D [19], and 4 of the 12 double-blind RCTs of oral vitamin D included in the 2009 meta-analysis described above (one RCT using intermittent vitamin D2 without calcium [20], one RCT with 400 IU vitamin D3 without calcium [21], one trial with 800 IU vitamin D3 per day with and without calcium and less than 50 % adherence [11], and one trial with 400 IU vitamin D with calcium [10]). The authors did not account for adherence to treatment. Based on these criteria, their findings showed a reduced overall risk of fracture (hazard ratio = 0.92; 95%-CI: 0.86–0.99) and a non-significant reduction of hip fractures (hazard ratio = 0.84; 95%-CI: 0.70–1.01) for trials that used vitamin D plus calcium. Vitamin D alone, irrespective of dose, did not reduce fracture risk. The authors concluded that vitamin D, even in a dose of 400 IU vitamin D per day reduces the risk of fracture if combined with calcium. Notably, this regimen was tested in 36.282 postmenopausal women in the Women's Health Initiative Trial over a treatment period of 7 years and did not reduce the risk of fracture.

Table 1: 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 effect	–21 %	Sig.

Prevention of non-vertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials (adapted from [9]).

In all 3 reports reviewed under this section, heterogeneity by dose may have been missed due to the inclusion of open design trials plus a dose evaluation that did not incorporate adherence. Biologically, the exclusion of heterogeneity by dose seems implausible even if a formal test of heterogeneity is not statistically significant. A dose-response relationship between vitamin D and fracture reduction is supported by epidemiologic data showing a significant positive trend between serum 25(OH)D concentrations and hip bone density [22], lower extremity strength [23, 24], and trial data for fall prevention [8].

Factors that may obscure a benefit of vitamin D are low adherence to treatment [25], low dose of vitamin D, or the use of

less potent D2 [26, 27]. Furthermore, open design trials [28] may bias results towards the null because vitamin D is available over the counter.

Notably, the 2009 meta-analyses on fall [8] and fracture [9] prevention from double-blind RCTs performed sensitivity analyses that included 4 open-design trials for fracture prevention and 3 open-design trials for fall prevention. Both analyses found significant variation in results between open design and double-blind trials at any dose of vitamin D, the lower and the higher dose suggesting that trial quality introduces heterogeneity.

Finally, the consistency of the results for both received dose and achieved 25(OH)D levels in the treatment group across all 12 masked trials lends support to the presence of a dose-response relationship between supplemental vitamin D and fracture reduction (Fig. 1a, b).

Optimal 25-Hydroxyvitamin D levels for bone and muscle health

A threshold for optimal 25(OH)D and fracture and fall prevention has been addressed in a recent benefit-risk analysis [29] and is illustrated in figure 2. Based on these data, 75 or better 100 nmol/l (30 or better 40 ng/ml) are suggested as an optimal threshold of 25-hydroxyvitamin D for fall and fracture prevention.

Adding calcium to vitamin D

The pooled RR reduction was 21 % with or without additional calcium for the higher dose of vitamin D in the 2009 meta-analysis of double-blind RCTs [9]. 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 [30, 31]. This is supported by two recent epidemiologic studies suggesting that both PTH suppression [31] and hip bone density [32] may only depend on a higher calcium intake if serum 25-hydroxyvitamin D levels are very low.

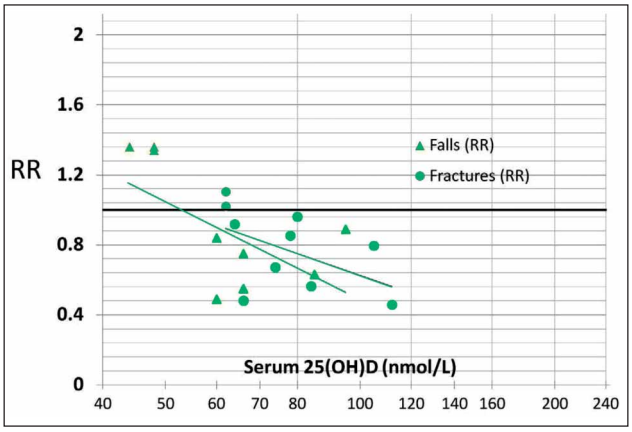


Figure 2: Threshold for optimal fall and fracture prevention based on double-blind randomized controlled trials.

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 [8, 9] and summarized in a recent benefit-risk analysis of vitamin D [29]. Based on these data, 75 or better 100 nmol/l (30 or better 40 ng/ml) are suggested as an optimal threshold of 25-hydroxyvitamin D for fall and fracture prevention.

As calcium absorption is improved with higher serum 25-hydroxyvitamin D levels [31, 33], future studies may need to evaluate whether current calcium intake recommendations with higher doses of vitamin D beyond 2000 IU per day are safe or require downward adjustment [33]. If dietary calcium is a threshold nutrient, as suggested by Dr. Heaney [34], then that threshold for optimal calcium absorption may be at a lower calcium intake when vitamin D supplementation is adequate.

Other potential benefits of vitamin D supplementation

Many lines of evidence also suggest that low vitamin D status increases the risk of colon [35] and possibly other cancers [36], increases the risk of hypertension [37], myocardial infarction [38], cardiovascular [39] and overall mortality [40], infections [41] and diabetes [42]. The development of mice lacking the receptor for vitamin D (VDR) provided insight of the global physiologic role of vitamin D. These mice express phenotypes that are consistent with epidemiologic studies of 25-hydroxyvitamin D deficiency in humans [43].

What are optimal intakes of vitamin D for bone and muscle health?

Studies suggest that 700–1000 IU of vitamin D per day may bring 50 % of younger and older adults up to 75–100 nmol/l [44–46]. Thus, to bring most older adults to the desirable range of 75–100 nmol/l, vitamin D doses higher than 700–1000 IU would be needed. According to a recent benefit-risk analysis on vitamin D, mean levels of 75–110 nmol/l were reached in most RCTs with 1800 IU to 4000 IU vitamin D per day without risk [29]. In a recent trial among acute hip fracture patients, 70 % reached the 75 nmol/l threshold with 800 IU vitamin D3 per day, and 93 % with 2000 IU vitamin D3 per day, at 12 month follow-up and with over 90 % adherence [47].

Consistently, Heaney et al., in a study of healthy men, estimated that 1000 IU cholecalciferol per day are needed during winter months in Nebraska to maintain a late summer starting level of 70 nmol/l, while baseline levels between 20–40 nmol/l may require a daily dose of 2200 IU vitamin D to reach and maintain 80 nmol/l [34, 38]. These results indicate that individuals with a lower starting level may need a higher dose of vitamin D to achieve desirable levels, while relatively lower doses may be sufficient in individuals who start at higher baseline levels.

Due to seasonal fluctuations of 25(OH)D levels [49], some individuals may be in the desirable range during summer months. However, these levels will not sustain during the winter months even in sunny latitudes [50, 51]. Thus winter supplementation with vitamin D is needed even after a sunny summer. Furthermore, several studies suggest that many older

persons will not achieve optimal serum 25(OH)D levels during summer months suggesting that vitamin D supplementation should be independent of season in older persons [51–53]. Even among younger persons, the use of sunscreen or sun-protective clothing may prevent a significant increase in 25-hydroxyvitamin D levels [53].

Most vulnerable to low vitamin D levels are older individuals [51, 54], individuals living in northern latitudes with prolonged winters [49, 55], obese individuals [56], and individuals of all ages with dark skin pigmentation living in northern latitudes [22, 57, 58]. Naturally high 25-hydroxyvitamin D levels observed in healthy outdoor workers are 135 nmol/l [59] in farmers and 163 nmol/l [60] in lifeguards. As a first sign of toxicity, only serum 25(OH)D levels of above 220 nmol/l have been associated with hypercalcemia [61, 62].

In summary

Based on evidence from double-blind randomized-controlled trials, vitamin D supplementation reduces both falls and non-vertebral fractures, including those at the hip. However, this benefit is dose-dependent. According to two 2009 meta-analysis of double-blind RCTs, no fall reduction was observed for a dose of less than 700 IU per day, while a higher dose of 700–1000 IU supplemental vitamin D per day reduced falls by 19 % [12]. Similarly, no fracture reduction was observed for a received dose of 400 IU or less per day, while a higher received dose of 482–770 IU supplemental vitamin D per day reduced non-vertebral fractures by 20 % and hip fractures by 18 %. Notably, the anti-fracture benefit was present in all subgroups of the older population and was most pronounced among those community-dwelling (-29 %) and those age 65–74 years of age (–33 %).

Consistently, fall prevention and non-vertebral fracture prevention increased significantly with higher achieved 25-hydroxyvitamin D levels in the 2009 meta-analyses. Fall prevention started at 25-hydroxyvitamin D levels of 60 nmol/l [12], while at least 75 nmol/l were required for non-vertebral fracture prevention [9]. Optimal fall and fracture prevention was observed with 25-hydroxyvitamin D levels of close to 100 nmol/l [29]. Given the absence of data beyond this beneficial range, the recent meta-analyses do not preclude the possibility that higher doses or higher achieved 25-hydroxyvitamin D concentrations would have been even more efficient in reducing falls and non-vertebral fracture.

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