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**Contribution of vitamin D to fracture prevention**

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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).

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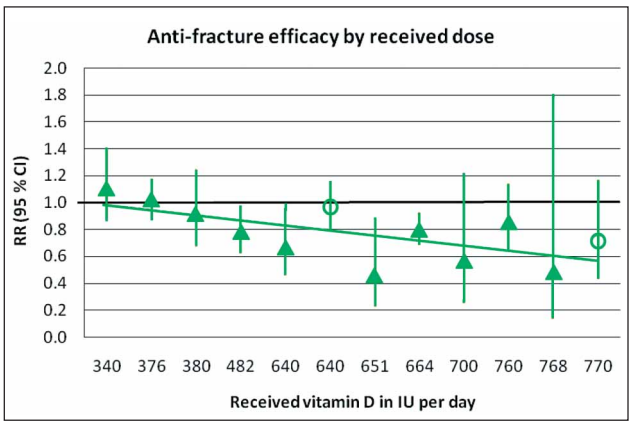
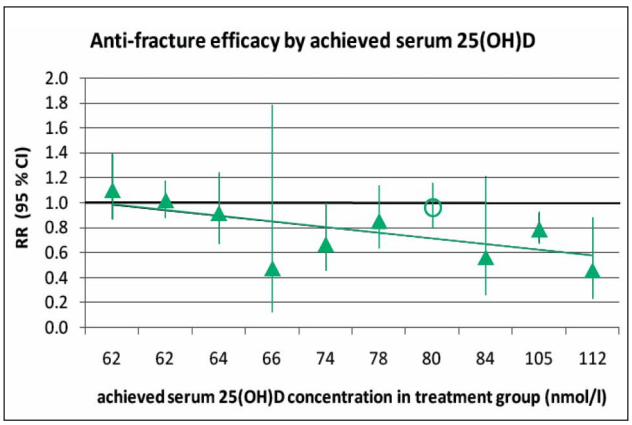



**1a:** Data points and represented trial from left to right: 340 IU = Lips [65], 376 IU = Record [11], 380 IU = Meyer [21], 482 = WHI (study medication plus personal intake) [10], 640 IU (D3) = Trivedi [66], 640 IU = Lyons [20], 651 IU = Dawson-Hughes [67], 664 IU = Chapuy 1992 [68], 700 IU = Pfeifer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

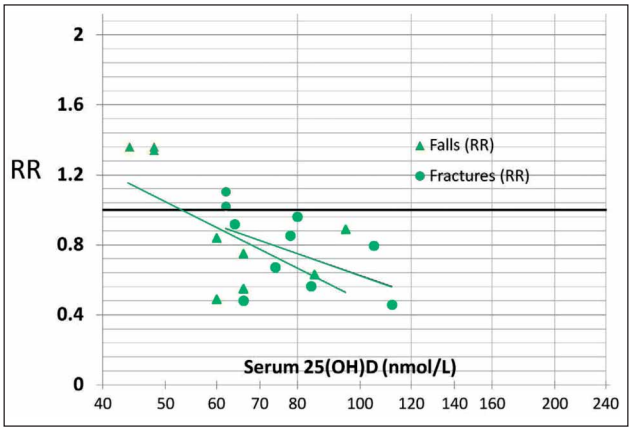



**Figure 2:** Threshold for optimal fall and fracture prevention based on double-blind randomized controlled trials.

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.

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.

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.

### References:


1. Tinetti ME. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988; 319: 1701–7.

2. Glerup H, Mikkelsen K, Poulsen L, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int 2000; 66: 419–24.

3. Schott GD, Wills MR. Muscle weakness in osteomalacia. Lancet 1976; 1: 626–9.

4. Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 2004; 19: 265–9.

5. Sorensen OH, Lund B, Saltin B, et al. Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. Clin Sci (Colch) 1979; 56: 157–61.

6. Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and Health: Perspectives from Mice and Man. J Bone Miner Res 2008; 28: 28.

7. Endo I, Inoue D, Mitsui T, et al. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 2003; 144: 5138–44.

8. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009; 339: b3692.

9. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009; 169: 551–61.

10. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006; 354: 669–83.

11. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005; 365: 1621–8.

12. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and alpha-hydroxylated vitamin D: a meta-analysis of randomized controlled trials. BMJ; in press 2009.

13. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. J Am Geriatr Soc 2007; 55: 234–9.

14. Cranny A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. http://wwwahrqgov/clinic/tp/vitadtphtm 2007.

15. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2007; 30: 30.

16. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 2010; 340: b5463. doi: 10.1136/bmj.b5463.

17. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ 2005; 330: 1003.

18. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents severe falls in elderly community-dwelling women: a pragmatic population-based 3-year intervention study. Aging Clin Exp Res 2005; 17: 125–32.

19. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. 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) 2007; 46: 1852–7.

20. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int 2007; 18: 811–8.

21. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res 2002; 17: 709–15.

22. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin d levels and bone mineral density: a population-based study of younger and older adults. Am J Med 2004; 116: 634–9.

23. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥ 60 y. Am J Clin Nutr 2004; 80: 752–8.

24. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007; 6: 6.

25. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomized placebo-controlled trial. Lancet 2005; 365: 1621–8.

26. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004; 89: 5387–91.

27. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 2006; 84: 694–7.

28. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ 2005; 330: 1003.

29. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int 2009.

30. Heaney RP, Barger-Lux MJ, Dowell MS, Chen TC, Holick MF. Calcium absorptive effects of vitamin D and its major metabolites. J Clin Endocrinol Metab 1997; 82: 4111–6.

31. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 2005; 294: 2336–41.

32. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. J Bone Miner Res 2009; 24: 935–42.

33. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003; 22: 142–6.

34. Heaney RP. The Vitamin D requirement in health and disease. J Steroid Biochem Mol Biol 2005; 15: 15.

35. Feskanich D, Ma J, Fuchs CS, et al. Plasma vitamin d metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2004; 13: 1502–8.

36. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. Cancer Epidemiol Biomarkers Prev 2006; 15: 2467–72.

37. Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension 2007; 19: 19.

38. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008; 168: 1174–80.

39. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 2008; 168: 1340–9.

40. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007; 167: 1730–7.

41. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 23: 23.

42. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004; 79: 820–5.

43. Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and health: perspectives from mice and man. J Bone Miner Res 2008; 23: 974–9.

44. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002; 112: 659–62.

45. Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. Osteoporos Int 1998; 8: 222–30.

46. Dawson-Hughes B. Impact of vitamin D and calcium on bone and mineral metabolism in older adults. In: Holick MF (ed) Kluwer Academic Publishers. Biologic Effects of Light 2001, Boston, MA 2002; 175–83.

47. Bischoff-Ferrari HB, Dawson-Hughes B, Platz A, et al. Effect of high-dosage vitamin D3 cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. Arch Intern Med 2010;in press.

48. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003; 77: 204–10.

49. Dawson-Hughes B, Harris SS, Dallal GE. Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. Am J Clin Nutr 1997; 65: 67–71.

50. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev 2005; 10: 94–111.

51. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. Am J Med 1992; 93: 69–77.

52. Theiler R, Stahelin HB, Kraenzlin M, et al. Influence of physical mobility and season on 25-hydroxyvitamin D-parathyroid hormone interaction and bone remodelling in the elderly. Eur J Endocrinol 2000; 143: 673–9.

53. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995; 61 (Suppl 3): 638S–645S.

54. Theiler R, Stahelin HB, Tyndall A, Binder K, Somorjai G, Bischoff HA. Calcidiol, calcitriol and parathyroid hormone serum concentrations in institutionalized and ambulatory elderly in Switzerland. Int J Vitam Nutr Res 1999; 69: 96–105.

55. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988; 67: 373–8.

56. Parikh SJ, Edelman M, Uwaifo GI, et al. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 2004; 89: 1196–9.

57. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone 2002; 30: 771–7.

58. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 2002; 76: 187–92.

59. Haddock L, Corcino J, Vazquez MD. 25(OH)D serum levels in the normal Puerto Rican population and in subjects with tropical sprue and paratyroid disease. Puerto Rico Health Sci J 1982; 1: 85–91.

60. Haddad JG, Chyu KJ. Competitive protein-binding radioassay for 25-hydroxycholecalciferol. J Clin Endocrinol Metab 1971; 33: 992–5.

61. Gertner JM, Domenech M. 25-Hydroxyvitamin D levels in patients treated with high-dosage ergo- and cholecalciferol. J Clin Pathol 1977; 30: 144–50.

62. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999; 69: 842–56.

63. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc 2005; 53: 1881–8.

64. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006; 354: 669–83.

65. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med 1996; 124: 400–6.

66. Trivedi DP, Doll R, Khaw KT. 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 2003; 326: 469.

67. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337: 670–6.

68. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992; 327: 1637–42.

69. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int 2009; 20: 315–22.

70. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002; 13: 257–64.

71. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000; 15: 1113–8.

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