

Vitamin D and Fracture Prevention

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KEYWORDS

- Vitamin D • Falls • Bone density • Fractures
- Supplementation • 25-Hydroxyvitamin D

Vitamin D modulates fracture risk in 2 ways: by decreasing falls and increasing bone density. Two most recent meta-analyses of double-blind randomized controlled trials (RCTs) came to the conclusion that vitamin D reduces the risk of falls by 19%, the risk of hip fracture by 18%, and the risk of any nonvertebral fracture by 20%. 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. Antifall efficacy started with achieved 25-hydroxyvitamin D levels of at least 60 nmol/L (24 ng/mL) and antifracture efficacy started with achieved 25-hydroxyvitamin D levels of at least 75 nmol/L (30 ng/mL). Both end points improved further with higher achieved 25-hydroxyvitamin D levels. Based on these evidence-based data derived from the general older population, vitamin D supplementation should be at least 700 to 1000 IU per day and taken with good adherence to cover the needs for fall and fracture prevention. Desirable 25-hydroxyvitamin D for optimal fracture prevention may be at least 75 nmol/L for both end points. Further work is needed to better define the doses that will achieve optimal blood levels in most of the population.

GOING BEYOND BONE

Antiresorptive treatment alone may not reduce fractures among individuals 80 years and older in the presence of nonskeletal risk factors for fractures despite an improvement in bone metabolism.¹ This is explained by a close relationship between fracture risk and muscle weakness² and falling^{3,4} at an older age, and falls being the primary risk factor for hip fractures.⁵ Moreover, falling may affect bone density through

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increased immobility from self-restriction of activities.⁶ After their first fall, about 30% of persons develop a fear of falling resulting in self-restriction of activities and decreased quality of life.⁶ Based on new evidence, vitamin D reduces nonvertebral fractures, including those at the hip, irrespective of prevalent nonskeletal risk factors and offers an inexpensive and comprehensive primary fracture prevention strategy at higher age.⁷ Nonvertebral fracture prevention by vitamin D may be largely modulated by its effect on muscle strength and fall prevention.⁸ Thus, if antiresorptive treatment is initiated at an older age, it should be partnered with vitamin D in a dose of at least 700–1000 IU per day for fall prevention.⁸

VITAMIN D: ITS ROLE IN MUSCLE HEALTH

In humans, 4 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.⁹ Vitamin D deficiency myopathy includes proximal muscle weakness, diffuse muscle pain, and gait impairments such as a waddling way of walking.¹⁰ Second, vitamin D receptor (VDR) is expressed in human muscle tissue,¹¹ and VDR activation may promote *de novo* protein synthesis in muscle.¹² Mice lacking VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life, which suggests a role of vitamin D in muscle development.^{13,14} These abnormalities persist after correction of systemic calcium metabolism by a rescue diet.¹⁴ Third, several observational studies suggest a positive association between 25-hydroxyvitamin D and muscle strength or lower extremity function in older persons.^{15,16} Fourth, in several double-blind RCTs, vitamin D supplementation increased muscle strength and balance,^{17,18} and reduced the risk of falling in community-dwelling individuals,^{18–20} as well as in institutionalized individuals.^{17,21} A study by Glerup and colleagues⁹ suggested that vitamin D deficiency may cause muscular impairment even before adverse effects on bone occur.

A dose-response relationship between vitamin D status and muscle health was examined in NHANES III (The Third National Health and Nutrition Examination Survey), which included 4100 ambulatory adults aged 60 years and older. Muscle function measured as the 8-ft walk test and the repeated sit-to-stand test was poorest in subjects with the lowest level of 25-hydroxyvitamin D (<20 nmol/L). Similar results were found in a Dutch cohort of older individuals.¹⁵ A threshold of 50 nmol/L has been suggested for optimal function from the smaller Dutch cohort.¹⁵ 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).¹⁶ In NHANES III, a similar benefit of higher 25-hydroxyvitamin D status was documented by gender, level of physical activity, and level of calcium intake.

These associations between higher 25-hydroxyvitamin D status and better function observed in epidemiologic studies in the United States and Europe were confirmed by 3 recent double-blind RCTs with 800 IU vitamin D₃ resulting in a 4% to 11% gain in lower extremity strength or function,^{17,18} and up to 28% improvement in body sway^{18,20} in older adults aged 65+ years, within 2 to 12 months of treatment.

A dose-dependent benefit of vitamin D with regard to fall prevention was suggested by a 2004 meta-analysis²² and a recent multidose double-blind RCT among 124 nursing home residents receiving 200, 400, 600, or 800 IU vitamin D compared with placebo for a 5-month period.²¹ 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% confidence interval [CI] 0.11–0.75).²¹ Including this trial, a most recent meta-analysis of 8 high-quality double-blind RCTs (n = 2426) found significant heterogeneity by

dose (low dose <700 IU/d versus higher dose 700–1000 IU/d; $P = .02$) and achieved 25-hydroxyvitamin D level (<60 nmol/L versus ≥ 60 nmol/L; $P = .005$).⁸ Higher-dose supplemental vitamin D between 700 and 1000 IU per day reduced fall risk by 19% (pooled relative risk (RR) 0.81; 95% CI 0.71–0.92; $n = 1921$ from 7 trials) versus a lower dose that did not (pooled RR = 1.10, 95% CI 0.89–1.35 from 2 trials). Achieved serum 25-hydroxyvitamin D concentrations less than 60 nmol/L did not reduce the risk of falling (pooled RR = 1.35, 95% CI, 0.98–1.84). At the higher dose, this meta-analysis documented a 38% significant 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 to 36 months. Thus, the benefits of vitamin D on fall prevention are rapid and sustained provided a high enough dose is given. Subgroup analyses for the prevention of falls at a dose of 700 to 1000 IU per day suggested a benefit in all subgroups of the older population, and possibly better fall reduction with D₃ compared with D₂.

VITAMIN D: ITS ROLE IN BONE HEALTH

A threshold for optimal 25-hydroxyvitamin D and hip bone mineral density (BMD) has been addressed among 13,432 individuals in NHANES III including younger (20–49 years) and older (50+ years) individuals with different ethnic and racial backgrounds.²³ In the regression plots, higher serum 25-hydroxyvitamin D levels were associated with higher BMD throughout the reference range of 22.5 to 94 nmol/L in all subgroups. In younger whites and younger Mexican Americans, higher 25-hydroxyvitamin D level was associated with higher BMD even beyond 100 nmol/L.

A 2009 meta-analysis of 12 double-blind RCTs for nonvertebral fractures ($n = 42,279$) and 8 RCTs for hip fractures ($n = 40,886$) consistently found that antifracture 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.⁷ No fracture reduction was observed for a received dose of 400 IU or less per day, whereas a higher received dose (dose multiplied by adherence) of 482 to 770 IU supplemental vitamin D per day reduced nonvertebral 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). Subgroup analyses for the prevention of nonvertebral fractures with the higher received dose suggested a benefit in all subgroups of the older population, and possibly better fracture reduction with D₃ compared with D₂. Additional calcium did not further improve antifracture efficacy (Table 1).

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 aged 50 years and older.⁵ The pooled results for all fractures included 10 double-blind 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 seen primarily in institutionalized individuals, which is consistent with the meta-analysis of Boonen and colleagues²⁴ in the same year. However, in both reports heterogeneity by dose may have been missed because of 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.

Subgroups by Received Dose of Vitamin D	Fracture Reduction	
Pooled analysis from 3 trials with low-dose vitamin D (340–380 IU/d)	+2%	Non-significant
Pooled analysis from 9 trials with higher dose vitamin D (482–770 IU/d)	–20%	Significant
Pooled subgroup analysis from trials with higher dose vitamin D (482–770 IE/Tag)		
Vitamin D ₂	–10%	Non-significant
Vitamin D ₃	–23%	Significant
Age 65–74 years	–33%	Significant
Age >75 years	–17%	Significant
Institutionalized >65 years	–15%	Significant
Community-dwelling >65 years	–29%	Significant
Vitamin D plus calcium	–21%	Significant
Vitamin D main effect	–21%	Significant

Adapted from 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(6):551–61; with permission. Copyright © (2009), American Medical Association.

In 2007, Tang and colleagues²⁵ suggested in their meta-analysis that together with calcium supplementation a daily intake of 800 IU vitamin D reduces total fracture by 3% compared with calcium supplementation together with a lower dose of vitamin D. However, with their focus on calcium, the investigators excluded 4 high-quality trials of vitamin D alone compared with placebo.^{4,22,23,26}

ADDING CALCIUM TO VITAMIN D

The pooled RR reduction was 21% with or without additional calcium for the higher dose of vitamin D based on the 2009 meta-analysis (see **Table 1**). Previous meta-analyses may have missed this finding because their analyses included all doses of vitamin D. Physiologically, the calcium-sparing effect of vitamin D may explain why there was no additional benefit of calcium supplementation at a higher dose of vitamin D in the 2009 meta-analysis.^{27,28}

The calcium-sparing effect of vitamin D is supported by 2 recent epidemiologic studies suggesting that parathyroid suppression²⁹ and hip bone density³⁰ may only depend on a higher calcium intake if serum 25-hydroxyvitamin D levels are low.

Thus, as calcium absorption is improved with higher serum 25-hydroxyvitamin D levels,^{29,31} future studies may need to evaluate whether current calcium intake recommendations may require downward adjustment, especially with higher doses of vitamin D.³¹ If dietary calcium is a threshold nutrient, as suggested by Heaney,³² then that threshold for optimal calcium absorption may be at a lower calcium intake when vitamin D supplementation is adequate.

SUMMARY

Based on evidence from double-blind RCTs, vitamin D supplementation reduces falls and nonvertebral fractures, including those at the hip. However, this benefit is dose-

dependent. According to 2 meta-analysis in 2009 of double-blind RCTs, no fall reduction was observed for a dose of less than 700 IU per day. A higher dose of 700 to 1000 IU supplemental vitamin D per day reduced falls by 19%.⁸ Similarly, no fracture reduction was observed for a received dose of 400 IU or less per day. A higher received dose of 482 to 770 IU supplemental vitamin D per day reduced nonvertebral fractures by 20% and hip fractures by 18%. The antifracture effect was present in all subgroups of the older population and was most pronounced among community-dwellers (–29%) and those ages 65 to 74 years (–33%).

Consistently, fall prevention and nonvertebral fracture prevention increased significantly with higher achieved 25-hydroxyvitamin D levels in the 2009 meta-analyses. Fall prevention occurred with 25-hydroxyvitamin D levels of 60 to 95 nmol/L⁸; levels of 75 to 112 nmol/L were required for nonvertebral fracture prevention.⁷ Given the absence of data beyond this beneficial range, these 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 nonvertebral fractures.

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