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REVIEW

How to select the doses of vitamin D in the management of osteoporosis

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Abstract
The dose of vitamin D in the management of osteoporosis should be no less than 700–800 IU per day. An optimal dose of vitamin D should raise serum concentrations of 25 (OH)D to the desirable range of at least 75 nmol/l. Higher intermittent oral doses of vitamin D may overcome low adherence. Vitamin D supplementation in the management of osteoporosis holds a significant public health potential because of its low cost, excellent tolerability, and combined musculo-skeletal benefits. Fall and fracture prevention with vitamin D is especially appealing in the treatment of older individuals at risk for fall-related fractures. However, bone density, strength, and function benefits with vitamin D include active and inactive subgroups of community-dwelling older men and women. Based on a recent expert panel and supportive evidence presented in this review, serum concentrations of at least 75 nmol/l 25(OH)D will be referred to as desirable. Today, desirable serum 25(OH)D levels of at least 75 nmol/l may only be reached in about one third of US older individuals and even fewer European older individuals. Two main factors discussed in this review may help public health efforts to ensure desirable vitamin D levels for fall and fracture prevention, including (1) a sufficient dose of vitamin D and (2) improved adherence to supplementation.

Keywords Adherence · Calcium · Fractures · Osteoporosis · Vitamin D

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Desirable 25-hydroxyvitamin D levels for fall and fracture prevention

In a recent quasi-consensus of vitamin D experts (five out of six), a threshold of 75 nmol/l was proposed as the serum 25(OH)D concentration at which older men and women will be at a lower risk of fracture [1]. This is supported by a recent meta-analysis of primary prevention high-quality trials (n=9,829) where 700–800 IU of vitamin D per day (with or without calcium) could prevent about one fourth of all hip and non-vertebral fractures in both ambulatory and institutionalized older persons [2], while 400 IU did not reduce fracture risk. A total of 700–800 IU vitamin D per day reduced the relative risk (RR) of hip fracture by 26% [pooled RR=0.74; 95% CI (0.61, 0.88)] and any non-vertebral fracture by 23% (pooled RR=0.77; 95% CI [0.68, 0.87]) compared to calcium or placebo. Notably, across all trials there was a statistically significant positive association between higher 25(OH)D levels achieved in the treatment group and anti-fracture efficacy. Anti-fracture efficacy was observed with achieved mean serum 25(OH)D levels of at least 74 nmol/l, and this threshold was only reached in trials that provided 700–800 IU vitamin D (cholecalciferol) per day. Whether fracture efficacy would be even higher with higher doses of vitamin D moving a majority of individuals into the desirable range of 75 nmol/l 25(OH)D and above is likely, but has not been investigated. However, indirect support is provided by data from the large population-based US survey NHANES III (National Health and Nutrition Examination Survey), where both hip bone density [3] and lower extremity function improved continuously with higher serum 25(OH)D concentrations [4], and serum concentrations between 75 to 100 nmol/l appeared to be most advantageous for both outcomes in individuals age 60 and older.

The effect of vitamin D on the risk of falling in older persons has been addressed in a recent meta-analysis [5]. Based on five RCTs (n=1,237), vitamin D reduced the risk of falling by 22% [pooled corrected OR=0.78; 95% CI (0.64, 0.92)] compared to calcium or placebo [6–10]. Subgroup analyses suggested that 400 IU of vitamin D may not be clinically effective in preventing falls in the elderly [10], while two trials that used 800 IU of vitamin D per day plus calcium reduced the risk of falling [6, 7]. For the two short-term trials with 259 subjects using 800 IU of cholecalciferol (study duration 3 to 12 months), the corrected pooled OR was 0.65 [95% CI (0.40, 1.00)] [5].

Since then, two long-term trials confirmed fall reduction with vitamin D supplementation [11, 12]. In one double-blind RCT, a 3-year supplementation with cholecalciferol 700 IU plus 500 mg calcium reduced the odds of falling in community-dwelling Boston women by 46% (OR=0.54; 95% confidence interval, 0.30–0.97) and was most pronounced in less active women by 65% (OR=0.35; 95% CI, 0.15–0.81) [11]. Mean serum 25(OH)D increased to 99 nmol/l (diasorin-adjusted level) in the treatment group. In a multicenter study of assisted living facilities and nursing homes across Australia, vitamin D supplementation (ergocalciferol, initially 10,000 IU given once weekly and then 1,000 IU daily) reduced the incident rate ratio for falling by 26% (RR=0.73, 95% confidence interval, 0.57–0.95) [12].

Impact of adherence to treatment on fracture efficacy with vitamin D

Since the 2005 meta-analysis [2], two large double-blind RCTs have been published. One trial, the UK Record trial, tested 800 IU vitamin D with or without calcium among 5,292 people aged 70 years or older who were mobile before developing a low-trauma fracture [13]. Their baseline mean 25(OH)D serum levels were low with 38 nmol/l [13]. The incidence of new, low-trauma fractures did not differ significantly between participants allocated to 800 IU vitamin D per day and those who were not [HR= 1.02 (0.88–1.19)]. However, the treatment group achieved mean 25(OH)D levels of only 62 nmol/l, which is not in the desirable range for fracture efficacy according to the previous meta-analysis [2]. The small increase in serum 25 (OH)D may be explained by the low adherence rate, which was 60% at 12 months and 47% at 24 months among persons who returned the 4-monthly questionnaire.

In the second most recently published trial, the Women's Health Initiative (WHI) trial, 400 IU vitamin D plus 1,000 mg calcium per day compared to placebo did not reduce hip fracture risk in 36,282 calcium-replete postmenopausal women aged 50 to 79 years with a mean baseline vitamin D intake of 360 IU per day (HR=0.88; 95% CI, 0.72 to 1.08). This is consistent with the 2005 meta-analysis, where 400 IU vitamin D per day was not enough to reduce fracture risk. However, if women who ceased to adhere to the study medication were excluded in the WHI trial, hip fracture risk was reduced by 29% (HR=0.71, 95% CI, 0.52 to 0.97).

Adherence to treatment is an important determinant of fracture efficacy with vitamin D supplementation. Figure 1 illustrates hip fracture efficacy by total vitamin D intake in the treatment group considering compliance and additional vitamin D intake (WHI women consumed a mean of 360 IU vitamin D throughout the trial [14]). The graph suggests that efficacy increases with higher predicted actual mean intake of vitamin D in the treatment group. Studies that were successful in fracture reduction had an actual mean estimated intake of more than 600 IU per day, and associated achieved mean 25(OH)D levels were close to 75 nmol/l. Levels of 25(OH)D are expressed in DiaSorin equivalent levels in Fig. 1 as measurements of 25-OHD vary between assays [15], and the DiaSorin assay is widely used.

What dose is needed to achieve adequate 25-hydroxyvitamin D levels in the management of osteoporosis?

Studies suggest that 700 to 1,000 IU of vitamin D per day may bring 50% of younger and older adults up to 75–100 nmol/l [16–18]. Thus, to bring most older adults to the desirable range of 75–100 nmol/l, vitamin D doses higher than 700–1,000 IU would be needed. The current intake recommendation for older persons (600 IU per day) may bring most individuals to 50–60 nmol/l, but not to 75–100 nmol/l [3]. According to studies in younger adults, intakes of as high as 4,000 IU to 10,000 IU are safe [19, 20], and 4,000 IU may bring 88% of healthy young men and women to at least 75 nmol/l [20]. Heaney and colleagues, in a study of healthy men estimated that 1,000 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 2,200 IU vitamin D to reach and maintain 80 nmol/l [19, 21]. 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.

If 75 nmol/l were the minimum target level of a revised RDA (recommended daily allowance), the new RDA should meet the requirements of 97% of the population [22]. Based on a dose-response calculation proposed by Dr.

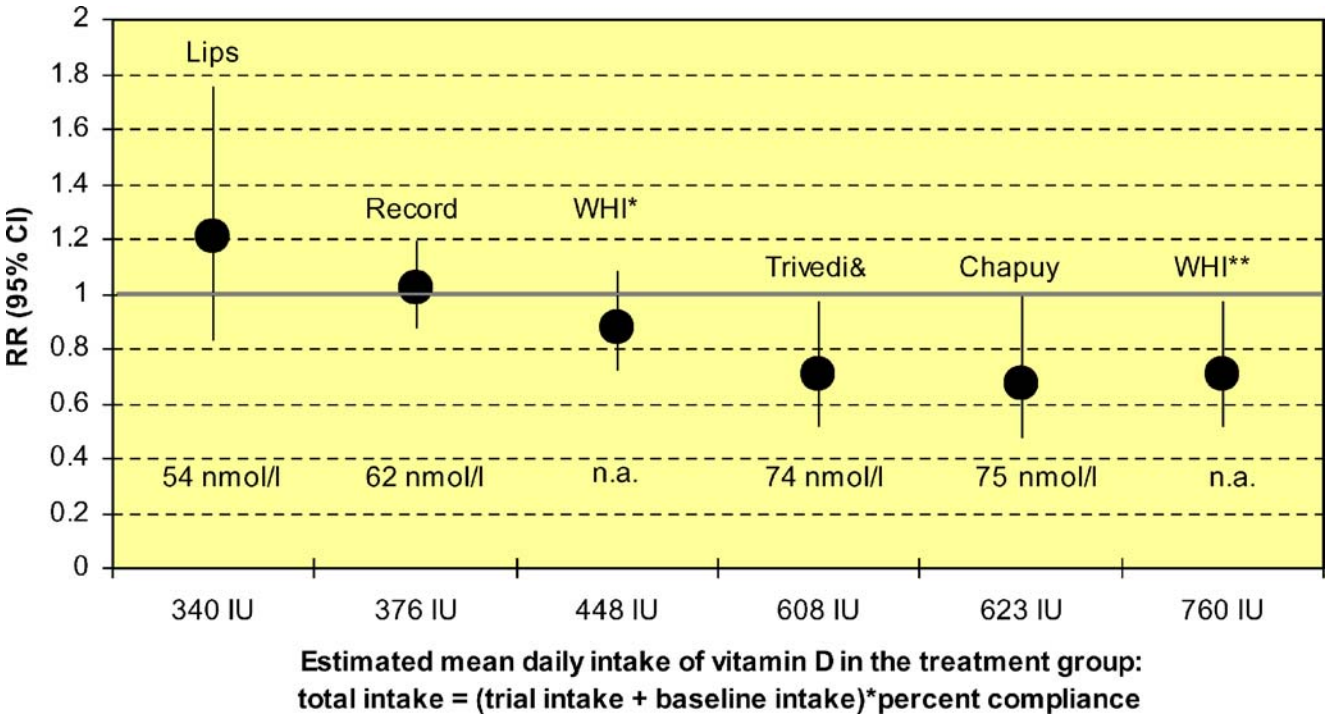

Fig. 1 Hip fracture efficacy by total estimated vitamin D intake (all trials used oral cholecalciferol) considering adherence to treatment. Compliance in the different trials was reported as follows: Lips (400 IU per day)=85% [36], Record (800 IU per day)=47% [13], WHI* intent-to-treat analysis (400 IU per day plus additional reported mean vitamin D intake of 360 IU)=59% [14], Trivedi (100,000 IU every 4 months equals 820 IU per day)=76% (&includes hip plus forearm fractures) [38], Chapuy (800 IU per day)=84% [57], WHI**-compliant women (400 IU per day plus additional reported mean vitamin D intake of 360 IU)=100% [14]. In most studies, being compliant was defined as taking 80% or more of the study medication. The x-axis gives the DiaSorin equivalent 25(OH)D levels in nmol/l achieved in the treatment arm of the trials. #For the Record trial a HPLC method has been used for 25(OH)D measurement with an unknown DiaSorin equivalent value. In the WHI trial, 25(OH)D levels have not been measured at follow-up in the study population (n.a. = not available)

Heaney of about 1.0 nmol/(l μg day) at the lower end of the distribution and 0.6 nmol/(l μg day) at the upper end [21], a daily oral dose of 2,000 IU (50 mcg/day), the safe upper intake limit as defined by the National Academy of Science [23], may shift the NHANES III distribution so that only about 10–15% of individuals are below 75 nmol/l. This may result in a 35 nmol/l shift in already replete individuals from between 75–140 nmol/l (NHANES III distribution) to 110–175 nmol/l, which are levels observed in healthy outdoor workers (i.e., farmers: 135 nmol/l [24] and lifeguards: 163 nmol/l [25]). Thus, 2,000 IU may be a safe RDA even at the higher end of the normal 25(OH)D serum level distribution, and for the lower end it may be conservative. As a first sign of toxicity, only serum 25 (OH)D levels of above 220 nmol/l have been associated with hypercalcemia [26, 27]. Thus, the upper end of the acceptable range should probably not exceed 200 nmol/l (80 ng/ml).

Due to seasonal fluctuations of 25(OH)D levels [28], some individuals may be in the desirable range during the summer months. However, these levels will not be sustained during the winter months, even in sunny latitudes [29, 30]. 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 the summer months, suggesting that vitamin D supplementation should be independent of the season in older persons [30–32].

Treatment strategies to overcome low compliance to vitamin D

Adherence may be increased by intermittent higher doses of vitamin D applied by intra-muscular injection or orally. Unfortunately, no classically randomized clinical trial with intramuscular 300,000 IU ergocalciferol was successful in fracture reduction. The serum concentrations achieved with annual injections of 300,000 IU ergocalciferol are similar to those produced by daily oral 400 IU cholecalciferol and do not ensure that individuals reach desirable 25(OH)D levels of 75 nmol/l. Based on two fracture trials with this regimen in older individuals, 25(OH)D levels rose by about 20 to 30 nmol/l to between 45 and 65 nmol/l [33–35], and fracture reduction was seen in one of the two trials [33]. But since the authors of

the smaller positive trial did not use a classic randomization technique, the observed fracture reduction in 899 older individuals with annual 150,000 to 300,000 IU ergocalciferol has been questioned [33], especially as a recent larger trial with 9,440 community-dwelling older individuals aged 75 to 100 years that used classic randomization did not document fracture or fall reduction with annual intra-muscular 300,000 IU ergocalciferol. Thus, intra-muscular vitamin D may increase 25(OH)D, similarly to what has been observed with oral daily 400 IU cholecalciferol [36, 37], but is, like oral daily 400 IU cholecalciferol, insufficient to achieve desirable 25(OH)D levels of at least 75 nmol/l for anti-fall and anti-fracture efficacy [2, 5, 35–37].

Another high-dose strategy tested in a large double-blind RCT of 2,686 older individuals aged 65–85 years living in the general community compared an oral dose of 100,000 IU cholecalciferol every 4 months to a placebo [38]. In this trial, hip plus forearm fractures were reduced significantly by 23% [RR=0.67; 95% CI (0.46, 0.99)] over 5 years, while mean serum 25(OH)D levels increased to the desirable range in the treatment group (74 nmol/l). The authors, as documented in a preceding study among 189 healthy free-living men and women aged 63–76 years, found this regimen to be safe [39].

Although not tested for fracture prevention and based on limited data, another approach to improve adherence to vitamin D may be artificial UV-B radiation. Older individuals avoid sunshine exposure, and the production of vitamin D3 in the skin is four times lower plus contains 50% less 7-dehydrocholesterol, which is the substrate of photoconversion to previtamin D, if compared to young individuals [40, 41]. Still, Chel and colleagues found that UV-B radiation at half the minimal erythemal dose of the lower back (1,000 cm^2) for a few minutes three times a week over 12 weeks increased serum 25(OH)D concentrations in institutionalized older individuals similar to a daily oral dose of 400 IU cholecalciferol [42]. Both groups achieved mean serum 25(OH)D concentrations of about 60 nmol/l at the 12-week follow-up. Safety and efficacy data over longer periods of time are needed for this approach [43].

In clinical practice with the target of vitamin D adequacy in mind, a combination of the annual intra-muscular injection with 300,000 IU vitamin D plus a daily multivitamin containing 400 IU vitamin D and/or an oral calcium plus vitamin D combination may be a possibility. The annual intra-muscular injection of 300,000 IU vitamin D is not enough to reach vitamin D desirable 25(OH)D levels, but may serve as a basis to build on. Table 1 summarizes treatment options with vitamin D and their potential to reach 25(OH)D adequacy for fall and fracture reduction.

Table 1 Different vitamin D regimens, achieved 25(OH)D serum concentrations, and fall and fracture efficacy

Application	Expected mean 25(OH)D serum concentrations	Anti-fall efficacy	Anti-fracture efficacy
Oral daily 400 IU cholecalciferol [36, 37]	60 to 65 nmol/l	No	No
Oral daily 700–800 IU cholecalciferol [2]	74 to 110 nmol/l	Yes	Yes
Oral 100,000 IU cholecalciferol every 4 months [38]	74 nmol/l	?	Yes
Annual 300,000 IU ergocalciferol [33, 35]	45 to 65 nmol/l	No	No*

The data presented in the table assume adherence to treatment of at least 80%.

*As discussed in the text, two trials have been performed with conflicting results

Chronic kidney disease

In a large population-based survey in the US, 11% of individuals older than 65 years without hypertension or diabetes had stage 3 or worse chronic kidney disease (GFR <60 ml/min) [44]. According to the K/DOQI (National Kidney Foundation, Kidney Disease Outcome Initiative) clinical practice guidelines for bone metabolism and disease in chronic kidney disease, supplementation with vitamin D should be initiated if the serum level of 25(OH)D concentrations is below 75 nmol/l in individuals with a glomerular filtration rate of less than 60 ml/min (http://www.kidney.org/professionals/kdoqi/guidelines_bone). For chronic kidney disease stage 3 (GFR 30–59 ml/min) or 4 (15–29 ml/min), K/DOQI recomments 50,000 IU ergocalciferol once a week for 4 weeks and then 50,000 IU once per month in individuals with serum 25(OH)D levels of 12–37 nmol/l. In those with serum concentrations between 40–75 nmol/l, the recommendation is 50,000 IU once per month. Active vitamin D metabolites are not recommended for the treatment of vitamin D inadequacy in mild to moderate chronic kidney disease. However, there is no evidence that in patients with GFR below 20 ml/min or on dialysis, vitamin D supplementation alone will increase 1,25-dihydroxyvitamin D levels or lower PTH.

Importance of additional calcium supplementation

As a large part of older individuals are at risk for vitamin D and calcium deficiency [4, 45], there is a good rationale to supplement calcium in combination with vitamin D for non-vertebral fracture prevention. This is supported by the most recent meta-analysis by Boonen and colleagues, including the latest fracture trial data (WHI [14], Record

[13], Porthouse [46]) up to March 2006 as presented at the ASBMR meeting in Philadelphia, September 2006 [47]. The results of the meta-analysis indicate that based on four RCTs (9,083 individuals), the pooled RR of hip fracture for vitamin D supplementation alone was 1.10 [95% confidence intervals (CI), 0.89 to 1.36]. On the other hand, for six RCTs (45,509 individuals) of vitamin D supplementation with calcium supplementation, the pooled RR for hip fracture was 0.82 (95% CI, 0.71 to 0.94). Using a similar database, a Cochrane Review published in 2005 supported the benefits of combined vitamin D plus calcium [48]. The authors found that trials using vitamin D plus calcium compared to placebo or no treatment resulted in a statistically significant reduction in the incidence of both hip (seven RCTs, 10,376 individuals, pooled RR=0.81; 95% CI 0.68 to 0.96) and new non-vertebral fracture (seven RCTs, 10,376 individuals, pooled RR=0.87; 95% CI 0.78 to 0.97). The different trials used calcium supplementations between 500 to 1,200 mg per day in combination with vitamin D.

There are limited data about the optimal combination of vitamin D and calcium. Some evidence, however, suggests that calcium absorption increases with higher 25-(OH)D levels and may plateau at 80 nmol/l as described by Heaney and colleagues [49]. Similarly, Steingrimsdottir and colleagues showed that serum PTH levels in older individuals were lowest with a serum 25-hydroxyvitamin D level of more than 18 ng/ml, independent of calcium intake [50]. Furthermore, in a large population-based survey, hip bone density increased with higher 25-hydroxyvitamin D levels in both younger (age 20–49 years) and older (age 50+) adults, independent of their calcium intake [3]. These observational data suggest that the benefits of vitamin D on bone may need a certain calcium intake threshold, but benefits given a certain calcium threshold are primarily driven by vitamin D. Findings from one large RCT by Trivedi and colleagues suggest that non-vertebral fracture prevention in ambulatory older individuals may be achieved with a daily intake of about 820 IU vitamin D (100,000 IU every 4 months) alone, provided a mean calcium intake of at least 740 mg per day [38]. However, as mean baseline calcium intakes in the general population aged ≥50 years are about 763 mg/day in men and 558 mg/day in women, there is a large part of the population with intakes below 740 mg per day [45].

Summary

The available evidence suggests that the dose of vitamin D in the management of osteoporosis targeting fall and fracture prevention should be no less than 700–800 IU per day. Based on the illustration of hip fracture efficacy by vitamin D treatment and adherence to treatment (Fig. 1), total estimated daily intakes below 600 IU vitamin D per day are insufficient for fall or fracture prevention. Also, desirable serum 25(OH)D concentrations of 75 nmol/l are not achieved.

Adherence may be improved with higher intermittent doses of vitamin D, such as oral 100,000 IU cholecalciferol every 4 months, which reduced fractures significantly in community-dwelling older individuals and shifted their mean 25(OH)D concentrations to the desirable range. Alternatively, the annual intra-muscular injection of 300,000 IU ergocalciferol or cholecalciferol may provide the equivalent of an oral daily dose of 400 IU cholecalciferol, which is not sufficient for fall or fracture prevention, but may help individuals with limited adherence to increase their total daily vitamin D supply beyond 600 IU per day.

Based on data from a recent worldwide survey among postmenopausal women diagnosed with osteoporosis, about 64% were below the desirable level of 75 nmol/l, indicating that public health efforts need further support [51]. Furthermore, a national US survey shows that only 31% of adult Caucasians between 20 and 49 years of age and less than 9% of older Caucasians, and an even smaller fraction of the Mexican-American and African-American adults have serum 25(OH)D levels of 90 nmol/l or more [3], and only about one third reach 75 nmol/l [52]. Most vulnerable to low vitamin D levels are older individuals [30, 53], individuals living in northern latitudes with prolonged winters [28, 54], obese individuals [55], and African Americans of all ages [3, 52, 56].

Thus, a large majority of the population could benefit from vitamin D supplementation. Hence, it would seem prudent to ensure that all individuals aged 65 years and older take at least 700–800 IU vitamin D per day [2], and a combination with calcium as suggested by a recent meta-analysis may be important at vitamin D intakes between 400–800 IU [47]. Future research should address the safety and efficacy of higher daily doses of vitamin D in older individuals. Especially 2,000 IU cholecalciferol per day appears to have an appealing potential to bring the large majority of older individuals into the desirable range of 25 (OH)D where optimal fall and fracture prevention is expected. As calcium absorption is improved with higher serum 25(OH)D levels [49, 50], these studies may also evaluate whether current calcium intake recommendations with higher doses of vitamin D beyond 2,000 IU are safe or require downward adjustment [49]. If dietary calcium is a threshold nutrient, as suggested by Dr. Heaney [21], then that threshold for optimal calcium absorption may be at a lower calcium intake when vitamin D nutrition is higher.

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