

## **PERSPECTIVES**

### **The Role of Vitamin D in Fracture Prevention**

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Osteoporosis is an enormous public health problem. Worldwide, the number of hip fractures was estimated at 1.3 million in 1990, and this number is expected to reach 2.3 million by 2020 (1). Low-cost, population-based strategies to lower fracture rates are important. Vitamin D has long been known to promote calcium absorption and influence bone mass, but its role in reducing fracture risk is still being defined. This article reviews the mechanisms by which vitamin D is thought to affect fracture risk in older adults and considers a plausible definition of the optimal serum concentration of 25-hydroxyvitamin D (25OHD), and the intake of vitamin D needed to reach the optimal level.

#### **Physiology**

Vitamin D is produced in skin in response to exposure to ultraviolet light. With aging, there is a decline in the skin content of 7-dehydrocholesterol, the precursor to vitamin D, and a corresponding decline in vitamin D production (2). Vitamin D is also acquired in the diet, although relatively few foods naturally contain vitamin D. Healthy older subjects do not generally have impaired absorption of vitamin D<sub>3</sub>, compared with young adults (3). Vitamin D is converted to 25OHD in the liver and then to 1,25(OH)<sub>2</sub>D in the kidney. The serum 25OHD level is the best indicator of overall vitamin D status. Serum 25OHD varies inversely with serum PTH, which is a well known promoter of bone resorption. Estimates of the serum 25OHD level associated with the lowest serum parathyroid hormone (PTH) levels vary widely (i.e., from 30-99 nmol/L, or 12-39.6 ng/ml) in different data sets (4;5). It has been suggested that the optimal 25OHD level be defined as that associated with maximal suppression of serum PTH, but the variability in this estimate lowers enthusiasm for this definition.

#### **Bone Mineral Density**

Low serum 25OHD levels have been associated with low levels of bone mineral density (BMD) at the hip in white, Hispanic, and African American adults in the Health and Nutrition Evaluation Survey (HANES) III (6). HANES III serum samples were assayed for 25OHD with kits from DiaSorin (Stillwater, MN), using a reference range 22.5 – 94 nmol/L (9-38 ng/ml). In this cross-sectional study, the positive association persisted into and throughout the reference range for 25OHD; adjustment was made for sex, age, body mass index, smoking, calcium intake, and in women, estrogen use. Adjustment for physical activity level did not affect the pattern of results. Study findings suggest that 25OHD levels at the top of the reference range may be preferred to lower levels within the reference range.

Vitamin D supplementation has also been shown to lower the rate of bone loss in several randomized placebo-controlled trials (7;8). In one three-year placebo-controlled intervention study, older men and women taking calcium and vitamin D supplements had a significant reduction in biochemical markers of bone turnover and gains in BMD of the spine, femoral neck, and total body, compared with those taking placebo (9). Over the two-year period after discontinuing the supplements, however, markers of bone turnover returned to their starting levels, and BMD gains were gradually lost (10). This finding indicates that adequate intakes of vitamin D and calcium are needed on a continuous, long-term basis to hold down the remodeling rate and preserve bone mass.

#### **Muscle Function**

One of the hallmarks of severe vitamin D deficiency is muscle weakness, but the

weakness is reversible with vitamin D treatment. Vitamin D receptors present in muscle tissue are responsive to physiologic concentrations of 1,25-dihydroxy vitamin D (11;12). Stimulation of the receptors results in an increase in area of type II muscle fibers (13). With aging, there is a gradual decline in the area of muscle tissue occupied by type II fibers (14).

Several clinical studies have addressed the link between vitamin D and lower extremity performance. In men and women age 60 years and older who participated in HANES III, higher serum 25OHD levels were associated with faster walking speed and more rapid sit-to-stand test performances (15). In both tests, the strongest association was seen as serum 25OHD increased from very low levels to approximately 50 nmol/L (20 ng/ml), but ongoing increases in test speeds occurred as 25OHD levels increased from 50 nmol/L to 94 nmol/L (20 ng/ml to 38 ng/ml), the upper end of the reference range. These observations persisted after adjustment for a number of covariates, including age, ethnicity, calcium intake, and physical activity. Several short-term intervention studies have been reported. In one study, administration of a single oral dose of 300,000 IU of vitamin D had no significant effect on quadriceps strength or lower extremity function in frail elderly men and women over a six-month period (16). In contrast, another study found that supplementation with 800 IU of vitamin D per day increased body sway, an index of balance (and an inverse indicator of risk of falling), by 9% over a two-month period (17). In a third study, 800 IU of vitamin D per day lowered the risk of falling in frail elderly women by 49% (18). In the latter two studies, both the control and the vitamin D groups received supplemental calcium. Overall, these findings, which are completely consistent, suggest a clinically important role for vitamin D in the preservation of lower extremity muscle performance in the elderly.

### Falls

More than 90% of fractures in elderly people are caused by falls. Predisposing factors include use of sedatives, gait or balance disturbances, poor vision, disabilities of the lower extremities (19;20), and perhaps, low

25OHD levels. The effect of vitamin D on risk of falling in men and women aged 60 years and older was addressed in a recent metaanalysis (21). Five randomized vitamin D intervention studies and 1237 subjects were included in the analysis. The interventions tested were vitamin D<sub>3</sub> at doses of 400 and 800 IU (two studies), 1-alpha-hydroxy-calcidiol, and calcitriol. In these studies, vitamin D reduced the odds of falling by 22% (odds ratios [OR], 0.78; 95% confidence interval [CI], 0.64 – 0.92). The number needed to treat to prevent one fall was 15 (95% CI, 8 – 53). The least effective intervention evaluated in the metaanalysis was 400 IU of vitamin D per day (OR, 0.91; 95% CI, 0.59 – 1.40). This finding suggests that an intake of vitamin D<sub>3</sub> > 400 IU per day is needed to reduce risk of falling.

### Fractures

A low level of vitamin D is expected to increase fracture risk because of its connection to low bone mass, reduced lower extremity performance, and increased risk of falling, as discussed above. However, the effect of vitamin D on fracture rate is not well established. Four trials have tested the combination of calcium and vitamin D vs. placebo on fracture rate. Chapuy *et al.* (22) found that 800 IU of vitamin D<sub>3</sub> and 1200 mg per day of calcium significantly reduced hip fracture and all non-vertebral fracture rates in frail elderly women residing in nursing homes. A similar intervention in free-living older French women identified a beneficial effect of supplementation on non-vertebral fractures (23). In a smaller study, supplementation of men and women aged 65 years and older with 700 IU of vitamin D<sub>3</sub> and 500 mg of calcium as the citrate malate significantly lowered non-vertebral fracture risk over a 3-year period (9). In contrast, in a recently reported study (24), combined calcium (1000 mg) and vitamin D<sub>3</sub> (800 IU) did not lower fracture rates. A potential explanation for this different result is that the mean 25OHD level achieved with supplements (in the small subset of subjects measured) was lower than that observed in the other studies. Low compliance was probably a factor (only 54% of subjects were taking study pills at 24 months). The compliance level of subjects who had 25OHD measurements was not specified.

Additionally the study population, men and women with recent fractures, differed, but the relevance of this is unclear.

Four studies have tested vitamin D alone, compared with placebo. In 2600 men and women in the Netherlands, supplementation with 400 IU of vitamin D<sub>3</sub> per day had no effect on hip fracture rate (25) and no significant effect on non-vertebral fractures in frail elderly nursing home residents (26). In contrast, quarterly oral doses of 100,000 IU of vitamin D<sub>3</sub> (equivalent to a dose of 833 IU/day) reduced risk of all clinical fracture in older men and women dwelling at home in England over a five-year period (27). Finally the recent RECORD Trial found no impact of vitamin D<sub>3</sub> alone on fracture rates, perhaps for the reasons cited above (24). Collectively, these studies indicate that vitamin D lowers fracture risk and that a dose > 400 IU per day is needed for this benefit. At this point, the contribution of calcium supplementation to the benefit is difficult to quantify. In the RECORD Trial, supplementation with calcium alone (1000 mg per day) did not lower fracture risk, although, again, poor pill compliance makes this hard to interpret (24).

### Optimal 25OHD

Currently, there is no consensus on the optimal serum level of 25OHD or on how it should be defined. At a round table discussion, six researchers in the field were asked to provide their estimates of the minimal serum level of 25OHD that would yield optimal for bone health (28). The estimates varied from 50-80 nmol/L (20-32 ng/ml), but for five of the six participants, the minimal desirable 25OHD levels clustered between 70 and 80 nmol/L (28-32 ng/ml). In view of the data reviewed above, 25OHD levels of 70 to 80 nmol/L seem to be beneficial, compared with lower levels.

### Optimal intake

Several circumstances influence basal serum 25OHD levels and changes in 25OHD concentration in response to oral vitamin D. Lower 25OHD levels occur in subjects who are older, those with higher body mass indices, those measured in winter, and those who have either little sun

exposure or use sun screen. The increase in serum 25OHD in response to oral vitamin D does not seem to be related to age (3) or calcium intake (29), but is inversely related to the starting level of 25OHD (30) and body mass index (unpublished observation). Serum 25OHD response is also influenced by the vitamin D supplement used (ergocalciferol vs cholecalciferol). Trang *et al.* (31) observed that the increase in serum 25OHD was greater with cholecalciferol than ergocalciferol after dosing with 4000 IU pwe day for two weeks. This discrepancy was again observed after a single oral dose of 50,000 IU of the two compounds (32). Although serum 25OHD levels were similar over the first three days after dosing with the two calciferols, by 14 days after dosing, the area under the curve with ergocalciferol was less than one third that with cholecalciferol. Under these test conditions, vitamin D<sub>2</sub> has lower potency and a shorter duration of action than does vitamin D<sub>3</sub>.

With respect to the dose of vitamin D<sub>3</sub> needed to reach a 25OHD level of 70-80 nmol/L (28-32 ng/ml), the researchers cited above concluded that an intake of 800-1600 IU per day would bring the mean 25OHD level of a group of healthy adults to 75 nmol/L (28). This level is equivalent to an estimated average requirement; accordingly, one-half of the adults treated with 800-1600 IU per day would not reach a serum level of 75 nmol/L.

### Conclusions

Vitamin D is important to bone health because it increases calcium absorption, improves lower extremity performance, and reduces the risk of falling and fracture. A growing body of research points to a 25OHD level  $\geq$  75 nmol/L (30 ng/ml) for optimal bone effect. Vitamin D<sub>3</sub> is more effective than vitamin D<sub>2</sub> in increasing the serum 25OHD level, and an intake of 800 IU or more of vitamin D<sub>3</sub> per day is needed to bring the 25OHD level of most adults to the desired threshold of 75 nmol/L. Broad-based vitamin D supplementation should be explored as a safe and low-cost strategy to lower fracture risk in elderly men and women.

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