



# How much vitamin D should I take?

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**Clinical vignette: A 68-year-old woman consults you after a recent bone mineral density screening revealed osteopenia, total hip T score of -1.8. Further evaluation shows her only other abnormal lab value is a serum 25-hydroxyvitamin D [25(OH)D] level of 13 ng/ml (normal 30–80). You find no evidence of malabsorption. What vitamin D supplement regimen should you recommend to reduce her risk of fractures?**

## Current therapy

There is a growing interest in vitamin D supplementation in older adults. Randomized placebo-controlled trials have demonstrated that vitamin D supplementation prevents falls (1) and fractures (2, 3), at least in the 35%–60% of the population with insufficient serum 25-hydroxyvitamin D [25(OH)D] levels (4, 5). In addition, epidemiologic evidence links low vitamin D levels with a variety of illnesses, including diabetes, cardiovascular disease, COPD, respiratory infections, autoimmune diseases, and cancers (6), although it remains to be proven that supplements prevent adverse outcomes in these diseases.

## Knowledge gap

Vitamin D supplements are commercially available over the counter as ergocalciferol (D<sub>2</sub>) and cholecalciferol (D<sub>3</sub>; the form of vitamin D<sub>3</sub> made in humans when ultraviolet light strikes the skin). Randomized trials demonstrating fall and fracture reduction have used both D<sub>2</sub> and D<sub>3</sub>, with no clear pattern of results to suggest differential efficacy.

In 2010, the Institute of Medicine (IOM) increased the recommended daily allowance (RDA) of vitamin D to 600 IU daily for adults under 70 years, and 800 IU for adults 70 years and over, with an upper level intake of 4,000 IU daily. This recommendation was viewed as conservative by many in the field and fueled a debate about the appropriate target serum 25(OH)D level. Target levels are determined in part by the inflection point at which serum iPTH tends to rise in normal adults and in part from the results of

randomized trials; a target 25(OH)D level of 20–30 ng/ml has been suggested as minimal for fall and fracture prevention. However, studies in healthy volunteers show that 700–1,000 IU of vitamin D per day will bring only about half of adults up to a 25(OH)D level of 30 ng/ml (7). Thus, adhering to the IOM RDA would result in a substantial proportion of older Americans remaining under recommended thresholds for fall and fracture prevention. When it is not possible to raise 25(OH)D levels with oral vitamin D<sub>2</sub> or D<sub>3</sub>, some experts recommend exposing the arms and legs for 5–30 minutes (depending upon time of day, season, latitude, and skin pigmentation) between 10:00 am and 3:00 pm twice weekly (8). Alternatively, exposure to a minimal erythemal dose of sunlight or in a tanning booth while wearing a bathing suit is equivalent to taking approximately 20,000 IU vitamin D<sub>2</sub> (8). Darker skin pigmentation and higher latitudes may decrease the effectiveness of this strategy.

## Research advances

Similar serum 25(OH)D levels can be achieved with intermittent dosing; for example, 1,600 IU daily and 50,000 IU monthly schedules result in a similar proportion of patients reaching target levels at one year (6). High-dose trials have produced inconsistent results. One study providing 100,000 IU D<sub>3</sub> quarterly was effective in reducing fractures in community-dwelling women (9), but another found that an annual intramuscular dose of 300,000 IU D<sub>2</sub> was ineffective in preventing nonvertebral fractures in community-dwelling men and women (10), and an annual oral dose of oral 500,000 IU D<sub>3</sub> paradoxically increased falls and fractures in elderly postmenopausal women (11).

Such unanticipated results are in part explained by the work of Lieben et al. in

this issue of the *JCI* (12). They show that mice maintain serum calcium levels in a normal range at the expense of mineralizing skeletal tissue. The active form of vitamin D, 1,25(OH)<sub>2</sub>D (i.e., D<sub>3</sub>), stimulates calcium absorption by the gut as well as skeletal resorption, thus maintaining serum calcium levels within a narrow range. The authors further show that 1,25(OH)<sub>2</sub>D stimulates the production of inorganic pyrophosphate and small integrin binding ligand N-linked glycoprotein, both inhibitors of mineralization of osteoid tissue in bone. Are there clinical implications of these findings? Perhaps. In the study by Smith et al. (10), in which annual 300,000 IU D<sub>2</sub> was ineffective in preventing fractures, 1,25(OH)<sub>2</sub>D levels were found to be increased, which may have led to increased skeletal resorption and impaired bone formation. Thus, the present work offers one explanation why high intermittent doses of vitamin D<sub>2</sub> or D<sub>3</sub> do not reduce, and may actually increase, fracture rates.

## Recommendations

Given the relative safety of vitamin D within a wide serum range, the IOM recommendations appear overly cautious, and a higher dose of at least 1,000–1,200 IU daily appears prudent. For the patient described above, we would prescribe 50,000 IU D<sub>2</sub> orally weekly for six weeks, followed by 2,000 IU D<sub>3</sub> daily. Based on the recent work by Lieben et al. and others, we do not recommend high-dose intermittent vitamin D until a better understanding of its effect on bone, falls, and fractures is achieved.

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