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## Q / Which regimen treats vitamin D deficiency most effectively?

### EVIDENCE-BASED ANSWER

**A / SEVERAL VITAMIN D REPLACEMENT REGIMENS ARE EFFECTIVE.** Cumulative dosing may be more important than frequency of dosing (strength of recommendation [SOR]: **C**, inconsistent results from randomized controlled trials

[RCTs] of disease-oriented outcomes).

Vitamin D<sub>3</sub> (cholecalciferol) may increase serum 25-hydroxy vitamin D (25[OH]D) concentrations more effectively than vitamin D<sub>2</sub> (ergocalciferol) (SOR: **C**, a single RCT of disease-oriented outcomes).

### Evidence summary

The total cumulative dose of vitamin D may be more significant than frequency of dosing. An RCT evaluated 38 postmenopausal women (median age 61.5 years) randomized into 3 groups (placebo or daily oral vitamin D<sub>2</sub> in either 5000 or 10,000 IU doses).<sup>1</sup> Only 1 patient had a baseline serum 25(OH)D level greater than 34 ng/mL. After 3 months, 8% of the placebo group, 50% of the 5000 IU daily group, and 75% of the 10,000 IU daily group had levels greater than 34 ng/mL. The cumulative D<sub>2</sub> doses were 0, 450,000, and 900,000 IU, respectively. The number needed to treat (NNT), compared with placebo, was 3 (95% confidence interval [CI], 1-15) for the 5000 IU daily group and 2 (95% CI, 1-3) for the 10,000 IU daily group.

In another RCT that evaluated 48 women (average age 81±8 years) with hip fracture, the same cumulative dose of vitamin D<sub>3</sub> (1500 IU orally per day, 10,500 IU per week, or 45,000 IU per month) approximately doubled serum 25(OH)D levels over the 2-month study period. After a cumulative dose of 90,000 IU, serum 25(OH)D levels rose from 15.7 ng/mL at baseline to 33.2, 29.2, and 37.1 ng/mL, respectively, for the daily, weekly, and monthly dose groups. These levels didn't differ significantly from each other.<sup>2</sup>

### But frequent dosing also shows effects

On the other hand, an RCT of 338 nursing home patients concluded that dosing frequency makes a difference. Patients (78% female; mean age 84±6.2 years) were randomized to 4 treatment arms: placebo (n=172), daily oral doses of vitamin D<sub>3</sub> of 600 IU (n=55), weekly oral doses of 4200 IU (n=54), or monthly oral doses of 18,000 IU (n=57).

After 4 months, the 600 IU daily dose increased mean serum 25(OH)D levels the most, by 18.9 ng/mL; the 4200 IU weekly dose increased levels by 16.3 ng/mL, and the 18,000 IU monthly dose increased levels the least, by 11 ng/mL (*P*<.01 between groups). Serum 25(OH)D levels in the placebo group didn't change. The average patient age of 84 years and high dropout rate (18.3% died or withdrew) limit this study.<sup>3</sup>

### Oral D<sub>3</sub> may be the best bet

The best route and form of vitamin D may be oral D<sub>3</sub>. A prospective intervention study randomized 32 female nursing home patients (66-97 years of age) to 4 treatment arms: oral D<sub>3</sub>, intramuscular (IM) D<sub>3</sub>, oral D<sub>2</sub>, or IM D<sub>2</sub> (8 women per arm).<sup>4</sup> Oral D<sub>3</sub> in a dose of 300,000 IU increased 25(OH)D levels more effectively than the same dose of IM D<sub>3</sub>, oral D<sub>2</sub>, or IM D<sub>2</sub>.

All subjects had serum 25(OH)D levels below 32 ng/mL at baseline. One month after a single 300,000 IU dose, serum 25(OH)D levels increased by  $47.8 \pm 7.3$  ng/mL in the oral D<sub>3</sub> group. Comparable differences (baseline to 1 month after treatment) in serum 25(OH)D levels for the other 3 arms were  $15.9 \pm 11.3$  ng/mL for IM D<sub>3</sub>;  $17.3 \pm 4.7$  ng/mL for oral D<sub>2</sub>; and  $5 \pm 4.4$  ng/mL for IM D<sub>2</sub>;  $P < .001$  comparing 30-day serum 25(OH)D levels in the oral D<sub>3</sub> group with the other 3 groups.<sup>4</sup>

## Recommendations

The Institute of Medicine (IOM's) 2011 report on dietary requirements for calcium and vitamin D doesn't address the ideal treatment of deficiency, but it states that adequate levels of serum 25(OH)D are 20 ng/mL—not 30 ng/mL. The IOM advises that the upper limit of safe vitamin D intake is 4000 IU per day for people 9 years and older, and is lower for infants and young children.<sup>5</sup>

An online textbook recommends treating vitamin D deficiency (serum 25[OH]D levels below 20 ng/mL) with 50,000 IUs of vitamin D<sub>2</sub> or D<sub>3</sub> orally once a week for 6 to 8 weeks, followed by a maintenance dose (such as 800 to 1000 IUs of vitamin D<sub>3</sub> daily). The same textbook recommends treating nutritional insufficiency (serum 25[OH]D levels between 20 and 30 ng/mL) with 800 to 1000 units of vitamin D<sub>3</sub> daily. The authors recommend vitamin D<sub>3</sub> over vitamin D<sub>2</sub> for supplementation.<sup>6</sup> **JFP**

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