Does vitamin D₃ dosing schedule influence treatment efficacy in nursing home residents with vitamin D deficiency?

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SUMMARY
Vitamin D deficiency is a common problem among elderly nursing home residents. In this Practice Point commentary, I discuss the findings and limitations of a randomized, controlled trial by Chel et al. that evaluated the effect of equivalent oral doses of vitamin D₃ given as 800 IU daily, 4,200 IU weekly or 18,000 IU monthly. Regardless of the dosing schedule, oral administration of vitamin D₃ was associated with increased levels of serum 25-hydroxyvitamin D and reduced levels of parathyroid hormone in the study cohort. Daily administration of vitamin D₃ was found to be more effective than either weekly or monthly administration. The addition of calcium supplementation for a 2-week period did not appreciably augment the effects of vitamin D₃ supplementation. Here, I highlight the issues to consider when interpreting studies of vitamin D₃ supplementation, its effect on vitamin D status, and the consequences for calcium and bone metabolism.

KEYWORDS calcium, deficiency, nursing home, supplementation, vitamin D₃

COMMENTARY
Vitamin D deficiency is one of the most common medical conditions diagnosed in both children and adults worldwide. Furthermore, this condition is especially prevalent in nursing home residents, up to 100% of whom are reported to be vitamin D deficient.

Vitamin D deficiency can lead to the development of secondary hyperparathyroidism. Elevated parathyroid hormone levels result in increased bone resorption, which reduces the matrix and mineral content of the skeleton. This deficit causes a decrease in BMD that in turn can lead to osteopenia and osteoporosis. In addition, increased parathyroid hormone levels lead to loss of phosphorus by excretion in the urine. As a consequence, an inadequate calcium phosphorus product in the circulation results in osteomalacia, a mineralization defect of the skeleton. Unlike osteoporosis, which is a silent disease, osteomalacia is often associated with nonspecific aches and pains in muscles and bones and so can be misdiagnosed as fibromyalgia or chronic fatigue syndrome. Osteopenia, osteoporosis and osteomalacia all increase the risk of fracture. Correction of vitamin D deficiency can increase the BMD of affected individuals. In addition, vitamin D₃ supplementation also improves muscle strength, which reduces the risk of falls and so further decreases the overall fracture risk.

The study by Chel et al. is the first to evaluate the effects of vitamin D₃ dosing schedule on the vitamin D status of nursing home residents. The authors enrolled 338 elderly individuals (mean age 84 years; 77.5% female) who were randomly allocated to receive 600 IU vitamin D₃ once-daily, 4,200 IU once-weekly, 18,000 IU once-monthly, or placebo. After 4 months, calcium carbonate or placebo was added to the treatment regimen for a 2-week period. The mean serum 25-hydroxyvitamin D level at baseline was 25 nmol/l. After 4 months' treatment with vitamin D₃, however, the mean serum 25-hydroxyvitamin D level had increased to 62.5 nmol/l. Treatment with vitamin D₃ was also associated with a reduction in the mean serum parathyroid hormone level from 7.2 pmol/l at baseline to 5.5 pmol/l after 4 months. Overall, daily administration of vitamin D₃ was found to be the most effective dosing schedule; however, the addition of calcium carbonate did not augment the positive effects of vitamin D₃ supplementation.

What message can we take from the findings of Chel et al.? The good news is that, regardless of the dosing schedule, vitamin D₃ raised the serum 25-hydroxyvitamin D level, which is the measure of an individual’s vitamin D status. Essentially 100% of the study participants were found to be...
vitamin D deficient. Administration of 600 IU of vitamin D₃ daily (or the weekly or monthly equivalent) reduced the parathyroid hormone levels when the serum 25-hydroxyvitamin D level was increased to >60 nmol/l, which confirms previous findings.¹

On the basis of their observations, Chel et al. suggested that daily administration of vitamin D₃ was better at maintaining the serum 25-hydroxyvitamin D level than was weekly administration, which in turn was better than the monthly dosing schedule (69.9 nmol/l versus 67.2 nmol/l versus 53.1 nmol/l, respectively). Nonetheless, treatment compliance could not be accurately determined. We do not know, therefore, whether daily administration of vitamin D₃ was associated with greater compliance than was weekly or monthly dosing. Patients who received the weekly dose were required to take seven pills at one time, which might have decreased compliance. By contrast, patients administered the monthly dose received a powdered form of vitamin D₃. How this powder was dispensed or whether there was any chance for partial ingestion is unclear. We also do not have any information as to the amount of vitamin D₃ that was present in the study medication. In general, manufacturers often put at least 10%, and as much as 50%, above what is stated on the label in order to maintain shelf life.

Debate continues as to the serum 25-hydroxyvitamin D level that should be achieved for maximum bone health. Chel et al. suggest that a level of 50 nmol/l is satisfactory. By contrast, however, Heaney et al.⁶ reported that intestinal calcium transport is maximal only when the serum 25-hydroxyvitamin D level is >80 nmol/l. In the study by Chel et al., most of the patients who received vitamin D₃ did not achieve a serum 25-hydroxyvitamin D level of 80 nmol/l. Furthermore, it seems that the serum 25-hydroxyvitamin D levels were continuing to rise in all three vitamin D₃ treatment groups, which suggests that the participants did not reach a plateau level for 25-hydroxyvitamin D during the study period. When healthy adults ingested 1,000 IU of vitamin D₃ for 11 weeks at the end of the winter, the serum 25-hydroxyvitamin D levels rose from ~46 nmol/l to ~72 nmol/l.⁷ For every 100 IU vitamin D₃ ingested, the 25-hydroxyvitamin D level can be expected to increase by 2.5 nmol/l. In order to achieve a healthy 25-hydroxyvitamin D level of >75 nmol/l, therefore, adults need to ingest at least 1,000 IU vitamin D₃ daily or its equivalent (i.e. 7,000 IU weekly or 30,000 IU monthly).¹⁴.⁶.⁷

In conclusion, the study of Chel et al. confirms that vitamin D deficiency is a major problem for the residents of nursing homes. Administration of 600 IU of vitamin D₃ daily (or its equivalent) was only able to elevate the serum 25-hydroxyvitamin D level to a point that is considered by many clinicians to be within the vitamin-D-insufficient range (i.e. 51–74 nmol/l). Hopefully, this study will alert physicians and other health-care professionals to this insidious deficiency, which puts nursing home residents at an increased risk of falls and fracture. In addition, vitamin D deficiency can increase the risk of heart disease, type 2 diabetes mellitus, cancer, and infectious diseases in this vulnerable population.¹

References
5 Chel V et al. (2008) Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents. Osteoporos Int 19: 663–671
7 Holick MF et al. (2008) Vitamin D₃ is as effective as vitamin D₂ in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 93: 677–681

Competing interests
The author declared associations with the following companies: Amgen, Eli Lilly, Merck, Novartis, Procter and Gamble, and Quest Diagnostics. See the article online for full details of the relationships.

PRACTICE POINT
The study of Chel et al. confirms that nursing home residents are often vitamin D deficient and that the provision of at least an additional 600 IU of vitamin D₃ daily (or the weekly or monthly equivalent) will help to correct this deficit.

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