Original Article

TREATMENT WITH 50 000 IU VITAMIN D_2 EVERY OTHER WEEK AND EFFECT ON SERUM 25-HYDROXYVITAMIN D_2, 25-HYDROXYVITAMIN D_3, AND TOTAL 25-HYDROXYVITAMIN D IN A CLINICAL SETTING

Emily T. W. Demetriou, MD[1]; Thomas G. Travison, PhD[2,3]; Michael F. Holick, PhD, MD[2,3]

ABSTRACT

Objective: To examine the effect of 50 000 IU–vitamin D_2 supplementation in a clinical setting on serum total 25-hydroxyvitamin D (25[OH]D), 25-hydroxyvitamin D_2 (25[OH]D_2), and 25-hydroxyvitamin D_3 (25[OH]D_3).

Methods: This retrospective cohort study was performed in an urban tertiary referral hospital in Boston, Massachusetts. Patients who had been prescribed 50 000 IU vitamin D_2 repletion and maintenance programs were identified through a search of our electronic medical record. Baseline and follow-up total serum 25(OH)D, 25(OH)D_2, and 25(OH)D_3 levels were compared.

Results: We examined the medical records of 48 patients who had been prescribed 50 000 IU vitamin D_2 in our clinic. Mean ± standard deviation baseline total 25(OH)D was 31.0 ± 10.6 ng/mL and rose to 48.3 ± 13.4 ng/mL after treatment (P<.001). 25(OH)D_2 increased from 4.2 ± 4.3 ng/mL to 34.6 ± 12.3 ng/mL after treatment (P<.001), for an average of 158 days (range, 35-735 days). Serum 25(OH)D_3 decreased from 26.8 ± 10.8 ng/mL to 13.7 ± 7.9 ng/mL (P<.001).

Conclusions: 50 000 IU vitamin D_2 repletion and maintenance therapy substantially increases total 25(OH)D and 25(OH)D_2 despite a decrease in serum 25(OH)D_3. This treatment program is an appropriate and effective strategy to treat and prevent vitamin D deficiency. **(Endocr Pract. 2012;18:pp)**

Abbreviations:
25(OH)D = 25-hydroxyvitamin D; **25(OH)D_2** = 25-hydroxyvitamin D_2; **25(OH)D_3** = 25-hydroxyvitamin D_3

INTRODUCTION

With increasing awareness of widespread vitamin D deficiency, it is important to define appropriate repletion programs for vitamin D–deficient patients. There is a great deal of heterogeneity in treatment practices with respect to dosage, dosing interval, and formulation of vitamin D supplements (1,2). Although humans make vitamin D_3 endogenously, vitamin D supplements are composed of either vitamin D_2 or vitamin D_3. Vitamin D_2 supplements are made by ultraviolet irradiation of ergosterol from yeast, whereas vitamin D_3 supplements are made by the ultraviolet irradiation of 7-dehydrocholesterol from lanolin (3). Only vitamin D_2 is available as a prescription in the United States. There have been conflicting data published about the equipotency of vitamin D_2 and vitamin D_3, and concern that vitamin D_2 might increase catabolism of 25-hydroxyvitamin D_3 (25[OH]D_3) (4-6). This retrospective study attempts to help the practicing endocrinologist predict response to treatment with 50 000 IU vitamin D_2 capsules for correction and prevention of vitamin D deficiency and also to examine the effect of vitamin D_2 supplementation on serum 25(OH)D_3.

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From the [1]Section of Endocrinology and Diabetes, Maine Medical Center, Portland, Maine; [2]Section of Endocrinology, Diabetes, Nutrition, and Weight Management, Boston Medical Center, Boston, Massachusetts; [3]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
Address correspondence to Dr. Michael F. Holick, Boston University Medical Center Section of Endocrinology Diabetes, Nutrition, and Weight Management, Building M-1013, 85 E Newton Street, Boston, MA 02118. E-mail: MFHolick@bu.edu.
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PATIENTS AND METHODS

We examined the medical records of patients who had been started on a regimen of 50 000 IU vitamin D_2 in our clinic. We compared total serum 25-hydroxyvitamin D (25[OH]D), 25-hydroxyvitamin D_2 (25[OH]D_2), and 25(OH)D_3 at baseline and while on vitamin D_2.

Patients

Participants were patients seen in the Section of Endocrinology, Diabetes, Nutrition, and Weight Management at Boston Medical Center in Boston, Massachusetts. Eligible patients had baseline and follow-up 25(OH)D, 25(OH)D_2, and 25(OH)D_3 measurements. Baseline measurements took place between January 2008 and January 2010. Some patients were taking over-the-counter vitamin D_3 supplements at baseline, which totaled 2000 IU daily or less, although most took either no supplemental vitamin D or only the vitamin D contained within multivitamins or calcium + D tablets. Patients taking more than 2000 IU daily of over-the-counter vitamin D_3 at baseline were excluded. Patients were not asked to stop over-the-counter supplements at the time they began 50 000 IU vitamin D therapy. Those with known intestinal malabsorption (celiac disease or gastric bypass) and those with sarcoidosis were excluded. Adherence to the vitamin D therapeutic regimen was expressed verbally during patient follow-up visits.

Analytic Methods

Liquid chromatography tandem mass spectrometry was used to measure serum 25(OH)D_2 and 25(OH)D_3 at Quest Diagnostics as described previously (7). The detection limit for 25(OH)D_2 and 25(OH)D_3 was 4 ng/mL. The intra-assay coefficients of variation for 25(OH)D_2 and 25(OH)D_3 were 6% to 9% and 7% to 11%, respectively, whereas the interassay coefficients of variation were 9% to 12% and 8% to 13%, respectively.

Statistical Methods

Statistical analysis was performed using R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria). Exploratory analyses were conducted using box-and-whisker and scatter plots. Pretreatment and posttreatment serum 25(OH)D values were compared using 2-tailed paired *t* tests. Sensitivity analyses were performed using paired Wilcoxon signed rank tests.

RESULTS

We examined the medical records of 48 patients who had been prescribed 50 000 IU vitamin D_2 in our clinic. Of the 48 patients, 39 (81%) had been prescribed 50 000 IU once weekly for 8 weeks and then every other week thereafter and 9 (19%) had been prescribed 50 000 IU vitamin D_2 every other week as a maintenance dosage. Mean baseline and follow-up total 25(OH)D, 25(OH)D_2, and 25(OH)D_3 values ± standard deviation are presented in Table 1, and the overall distribution of values and changes with time are plotted in Figure 1. The average time between baseline and follow-up measurement was 158 days (range, 35-735 days). Between baseline and follow-up, mean total 25(OH)D increased by 17.3 ± 11.9 ng/mL (P<.001), with a concurrent increase in 25(OH)D_2 of 30.4 ± 11.4 ng/mL (P<.001) and decrease in 25(OH)D_3 of 13.1 ± 8.9 ng/mL (P<.001). At baseline, 33 patients (69%) had undetectable serum 25(OH)D_2. Results did not change when replicated using nonparametric Wilcoxon tests. The difference between baseline and follow-up values did not vary systematically according to the time between measurements (results not shown). There were no cases of vitamin D intoxication. We did not observe a seasonal influence on serum 25(OH)D levels. The increase in total 25(OH)D and 25(OH)D_2 and decrease in 25(OH)D_3 did not depend on the baseline total 25(OH)D.

DISCUSSION

Several groups have compared the ability of vitamin D_2 and vitamin D_3 to increase serum 25(OH)D. Some have found that vitamin D_3 is more effective than vitamin D_2 in raising total 25(OH)D. This had led some to suggest that vitamin D_3 is a preferable supplement (4,5). In 1998, Trang et al (6) found that a daily dosage of 4000 IU of vitamin

Table 1
Mean Total 25-Hydroxyvitamin D, 25-Hydroxyvitamin D_2, and 25-Hydroxyvitamin D_3 at Baseline and Follow-Up[a]

Analyte	Baseline	Follow-Up	*P* value[b]
25-Hydroxyvitamin D	31.0 ± 10.6	48.3 ± 13.4	<.001
25-Hydroxyvitamin D_2	4.2 ± 4.3	34.6 ± 12.3	<.001
25-Hydroxyvitamin D_3	26.8 ± 10.8	13.7 ± 7.9	<.001

[a] Data are presented as mean (±standard deviation).
[b] Paired *t* test of equality of baseline and follow-up.

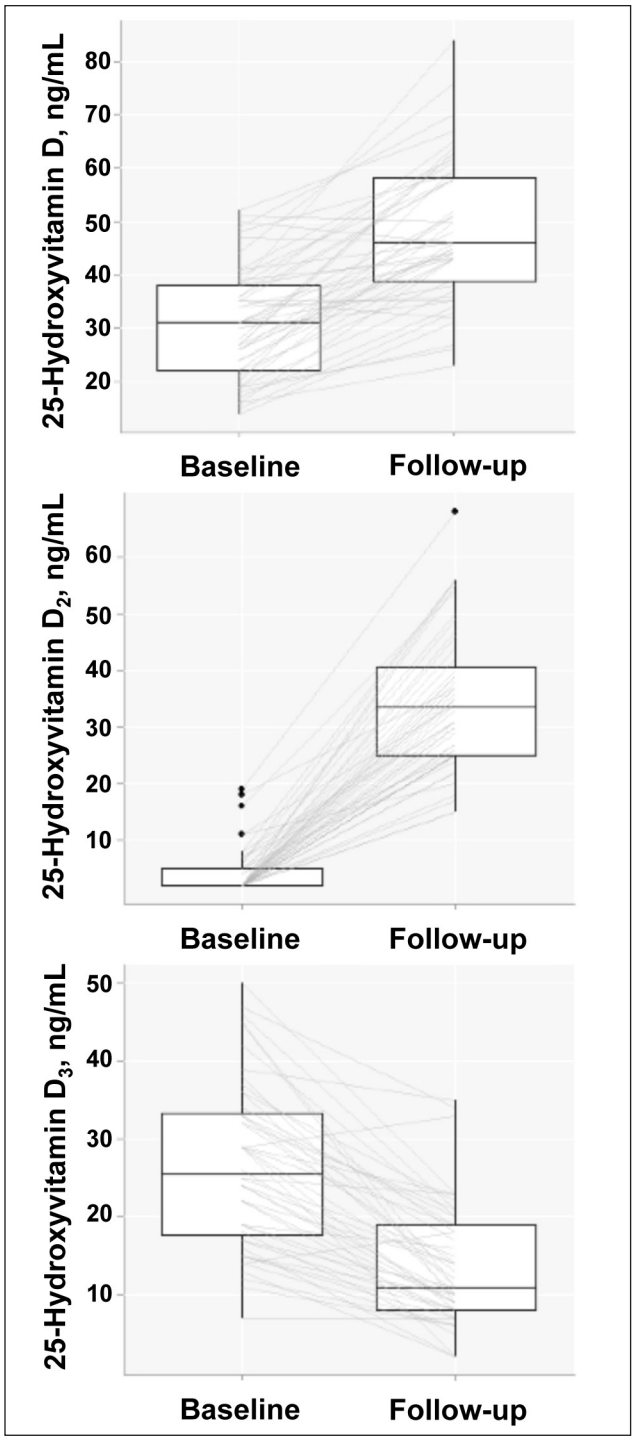

Fig. 1. Baseline and follow-up total 25-hydroxyvitamin D (*top panel*), 25-hydroxyvitamin D_2 (*middle panel*), and 25-hydroxyvitamin D_3 (*lower panel*). The preponderance of patients who exhibited increases in total 25-hydroxyvitamin D and in 25-hydroxyvitamin D_2 with time is indicated by the generally upward-trending line segments overlaid on the upper 2 panels, whereas decreases in 25-hydroxyvitamin D_3 are indicated by the downward trend of those segments overlaid on the lower panel. The horizontal line in the center of each box represents the median. The top and bottom boundaries of each box represent the 75th and 25th percentiles, respectively. Individual data points lying more than 1.5 times the interquartile range above the 75th percentile are displayed as dots.

D_3 was more effective than the same dosage of vitamin D_2 in increasing serum total 25(OH)D after 14 days. As several others have also observed, they found an inverse correlation between starting serum total 25(OH)D and an increase in total 25(OH)D, suggesting that those who are most deficient metabolized vitamin D more efficiently. Armas et al (5) showed that after a single dose of 50 000 IU of either vitamin D_2 or vitamin D_3, patients initially experienced a similar rise in 25(OH)D. However after 20 days, those treated with vitamin D_2 exhibited a decline in total 25(OH)D to below baseline values, while those treated with vitamin D_3 were stable (5). They also found that in patients treated with a single dose of vitamin D_2, the serum 25(OH)D_3 decreased significantly at 30 days. This prompted speculation that supplementation with vitamin D_2 might increase the catabolism of preexisting 25(OH)D_3 and would not sustain serum total 25(OH)D (5). Most recently, Heaney et al (8) treated 33 patients for 12 weeks with either 50 000 IU vitamin D_2 weekly (administered as a single gelcap) or 50 000 IU vitamin D_3 (administered as 5 10 000-IU gelcaps. They found vitamin D_3 was 56% to 87% more potent than vitamin D_2 depending on the parameters used. A main weakness of this study was that patients were not treated with the same number of capsules, and the vitamin D_3 capsules contained more vitamin D_3 than indicated on the label, whereas vitamin D_2 capsules contained less.

In contrast, Holick and colleagues (9) have shown that an 11-week course of treatment with 1000 IU daily of vitamin D_2, 1000 IU daily of vitamin D_3, or a combination of the 2 caused an equivalent increase in serum total 25(OH)D. Furthermore, the group that received vitamin D_2 did not experience a significant change in serum 25(OH)D_3. Gordon et al (10) have also shown that in infants and toddlers treated for 6 weeks, 2000 IU of vitamin D_2 and 2000 IU of vitamin D_3 daily were equally effective in increasing the serum total 25(OH)D. Also in 2010, Thacher et al (11) showed that over 14 days, a single vitamin D_2 dose of 50 000 IU caused an increase in total serum 25(OH)D equivalent to that of a single vitamin D_3 dose of 50 000 IU in Nigerian children without nutritional rickets. In previous work, we have shown that when vitamin D therapy is initiated, serum 25(OH)D levels begin to plateau at 28 days (12). Pietras et al (13) reported that 50 000 IU vitamin D_2 once weekly then every other week thereafter maintains vitamin D sufficiency for up to 6 years.

Several case reports in the past decade have described severe vitamin D intoxication due to mislabeled over-the-counter nutritional supplements (14-16). An advantage to our repletion program is that 50 000 IU vitamin D_2 capsules are pharmaceutical-grade and produced in compliance with US Food and Drug Administration regulations. Thus, 50 000 IU–vitamin D_2 capsules may be safer, currently, than high-dose, over-the-counter supplements.

Our data confirm that this treatment program effectively raises and maintains the total serum 25(OH)D level in the desirable range. The hepatic 25-hydroxylase enzymes are not known to preferentially hydroxylate vitamin D_3 over vitamin D_2. Given the large amount of vitamin D_2 present in our supplement and the subsequent high ratio of vitamin D_2 to vitamin D_3 in the patient's serum after supplementation, it would be expected that more vitamin D_2 would be hydroxylated by the 25-hydroxlyase enzymes to 25(OH)D_2 than vitamin D_3 to 25(OH)D_3. Therefore, it was not unexpected that 25(OH)D_3 levels decreased with vitamin D_2 supplementation. This would account for the observed decrease in 25(OH)D_3 without suggesting that vitamin D_2 increases the catabolism of vitamin D_3.

Limitations of the study include its retrospective design and lack of patient compliance data. Also, we have not definitively proven that 25(OH)D_3 is not destroyed by vitamin D_2 treatment. Although over-the-counter vitamin D supplementation was heterogeneous at baseline, all patients were taking less than 2000 IU daily, and we believe this mix to be a realistic representation of what an average endocrinologist in the community might see. Although previous data conflict with those obtained here, it is important to note that none of the previous research related to the treatment schedule prescribed in our clinic of 50 000 IU of vitamin D_2 once weekly for 8 weeks then every other week thereafter as maintenance therapy. Our results indicate, contrary to recent concerns, that vitamin D_2 supplementation is an effective long-term treatment for vitamin D deficiency or insufficiency. There is no evidence, to our knowledge, that low 25(OH)D_3 levels are deleterious when total overall 25(OH)D is within the desirable range. 50 000 IU–vitamin D_2 capsules are inexpensive, easy to administer, and widely available. Insurance companies may cover prescription-strength vitamin D, and every-other-week dosing may also improve long-term regimen adherence. The predictable response and safety of this repletion strategy raise the important question of whether it is necessary to screen and monitor patients with serial serum 25(OH)D testing, or whether empiric therapy for at-risk patients is indicated.

CONCLUSION

Vitamin D_2 repletion and maintenance therapy with 50 000 IU substantially increased total 25(OH)D and 25(OH)D_2 despite a decrease in serum 25(OH)D_3. This treatment program is an appropriate and effective strategy to treat and prevent vitamin D deficiency.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Binkley N**. Rapid correction of low vitamin D status in nursing home residents. *Osteoporos Int*. 2008;19: 1621-1628.
2. **Trivedi DP, Doll R, Khaw KT**. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. *BMJ*. 2003;326:469.
3. **Holick MF**. Vitamin D deficiency. *N Engl J Med*. 2007;357: 266-281.
4. **Romagnoli E, Mascia ML, Cipriani C, et al**. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J Clin Endocrinol Metab*. 2008;93:3015-3020.
5. **Armas LA, Hollis BW, Heaney RP**. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab*. 2004;89:5387-5391.
6. **Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R**. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr*. 1998;68:854-858.
7. **Holick MF, Siris ES, Binkley N, et al**. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab*. 2005;90:3215-3224.
8. **Heaney RP, Recker RR, Grote J, Horst RL, Armas LA**. Vitamin D(3) is more potent than vitamin D(2) in humans. *J Clin Endocrinol Metab*. 2011;96:E447-E452.
9. **Holick MF, Biancuzzo RM, Chen TC, et al**. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab*. 2008;93:677-681.
10. **Gordon CM, Williams AL, Feldman HA, et al**. Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab*. 2008;93:2716-2721.
11. **Thacher TD, Fischer PR, Obadofin MO, Levine MA, Singh RJ, Pettifor JM**. Comparison of metabolism of vitamins D2 and D3 in children with nutritional rickets. *J Bone Miner Res*. 2010;25:1988-1995.
12. **Biancuzzo RM, Young A, Bibuld D, et al**. Fortification of orange juice with vitamin D(2) or vitamin D(3) is as effective as an oral supplement in maintaining vitamin D status in adults. *Am J Clin Nutr*. 2010;91:1621-1626.
13. **Pietras SM, Obayan BK, Cai MH, Holick MF**. Vitamin D2 treatment for vitamin D deficiency and insufficiency for up to 6 years. *Arch Int Med*. 2009;169:1806-1808.
14. **Lowe H, Cusano NE, Binkley N, Blaner WS, Bilezikian JP**. Vitamin D toxicity due to a commonly available "over the counter" remedy from the Dominican Republic. *J Clin Endocrinol Metab*. 2011;96:291-295.
15. **Koutkia P, Chen TC, Holick MF**. Vitamin D intoxication associated with an over-the-counter supplement. *N Engl J Med*. 2001;345:66-67.
16. **Klontz KC, Acheson DW**. Dietary supplement-induced vitamin d intoxication. *N Engl J Med*. 2007;357:308-309.