

Vitamin D₂ Is as Effective as Vitamin D₃ in Maintaining Circulating Concentrations of 25-Hydroxyvitamin D

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Context: Two reports suggested that vitamin D₂ is less effective than vitamin D₃ in maintaining vitamin D status.

Objective: Our objective was to determine whether vitamin D₂ was less effective than vitamin D₃ in maintaining serum 25-hydroxyvitamin D levels or increased the catabolism of 25-hydroxyvitamin D₃.

Subjects and Design: This was a randomized, placebo-controlled, double-blinded study of healthy adults ages 18–84 yr who received placebo, 1000 IU vitamin D₃, 1000 IU vitamin D₂, or 500 IU vitamin D₂ plus 500 IU vitamin D₃ daily for 11 wk at the end of the winter.

Results: Sixty percent of the healthy adults were vitamin D deficient at the start of the study. The circulating levels of 25-hydroxyvitamin D (mean ± sd) increased to the same extent in the groups that received 1000 IU daily as vitamin D₂ (baseline 16.9 ± 10.5 ng/ml; 11 wk 26.8 ± 9.6 ng/ml), vitamin D₃ (baseline 19.6 ± 11.1 ng/ml; 11 wk 28.9 ± 11.0 ng/ml), or a combination of 500 IU vitamin D₂ and 500 IU vitamin D₃ (baseline 20.2 ± 10.4 ng/ml; 11 wk 28.4 ± 7.7 ng/ml). The 25-hydroxyvitamin D₃ levels did not change in the group that received 1000 IU vitamin D₂ daily. The 1000 IU dose of vitamin D₂ or vitamin D₃ did not raise 25-hydroxyvitamin D levels in vitamin D-deficient subjects above 30 ng/ml.

Conclusion: A 1000 IU dose of vitamin D₂ daily was as effective as 1000 IU vitamin D₃ in maintaining serum 25-hydroxyvitamin D levels and did not negatively influence serum 25-hydroxyvitamin D₃ levels. Therefore, vitamin D₂ is equally as effective as vitamin D₃ in maintaining 25-hydroxyvitamin D status. (*J Clin Endocrinol Metab* 93: 677–681, 2008)

Vitamin D₂, which comes from the UV irradiation of ergosterol obtained from yeast, has been the mainstay for the prevention and treatment of vitamin D deficiency in children and adults for more than 80 yr (1, 2). As little as 100 IU vitamin D₂ was found to be effective in the prevention of rickets (2–4). When humans are exposed to sunlight, 7-dehydrocholesterol in the skin absorbs UVB (290–315 nm) radiation resulting in the production of vitamin D₃ (1, 3). Vitamin D₃ is found naturally in cod liver oil and oily fish such as salmon (1, 3). Vitamin D₃ is also made by irradiating 7-dehydrocholesterol obtained from lanolin from sheep's wool with UVB radiation (1). Both vitamin D₂ and

vitamin D₃ when ingested undergo metabolism in the liver to form 25-hydroxyvitamin D [25(OH)D; D represents either D₂ or D₃] and in the kidneys to 1,25-dihydroxyvitamin D (1, 3, 5, 6). Both vitamin D₂ and vitamin D₃ are available in supplements, but only vitamin D₂ is available as a pharmaceutical preparation because its use predated the Food and Drug Administration and, thus, was grandfathered as a pharmaceutical drug. Vitamin D₃ was commercially developed in the 1950s and has not been approved as a pharmaceutical agent in the United States but is used in food supplementation and vitamin supplements.

Since the 1930s, vitamin D₂ has been considered to be equally

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Abbreviation: 25(OH)D, 25-Hydroxyvitamin D.

as effective as vitamin D₃ for bone health (3, 7). Recently, it was suggested that vitamin D₂ was less effective than vitamin D₃ in maintaining serum 25(OH)D levels when given either as 4000 IU/d for 2 wk (8) or as a single dose of 50,000 IU (9). Furthermore, it was observed that when a single dose of 50,000 IU vitamin D₂ was given to healthy adults that the serum 25(OH)D levels decreased more rapidly than the placebo group, suggesting that vitamin D₂ not only was less effective in maintaining serum 25(OH)D levels but also enhanced the degradation of 25(OH)D₃ (9).

These two observations have led to the conclusion that vitamin D₂ is approximately 30–50% as effective as vitamin D₃ in maintaining serum 25(OH)D in humans (8, 9). Our purpose was to evaluate in healthy adults what the effect of ingesting 1000 IU vitamin D₂, 1000 IU vitamin D₃, or a combination of 500 IU vitamin D₂ and 500 IU vitamin D₃ daily for 11 wk at the end of the winter had on circulating levels of total 25(OH)D as well as 25(OH)D₂ and 25(OH)D₃.

Subjects and Methods

Subjects

Healthy, white, African-American, Hispanic, Asian, and Native American adults between the ages of 18 and 84 yr were enrolled in February 2007 after signing a consent form approved by our Institutional Review Board at Boston University Medical Center. We excluded those with chronic liver and kidney disease and those taking medications, in-

cluding anticonvulsants, glucocorticoids, and barbiturates, that might affect vitamin D metabolism as well as subjects who were taking a vitamin D supplement. Subjects were permitted to take their multivitamin, a majority of which contained 400 IU vitamin D₃ (Table 1).

Design

Sixty-eight subjects were randomly assigned in a double-blinded fashion to receive daily in a capsule for 11 wk 1) placebo, 2) 1000 IU (25 μg) vitamin D₂ (ergocalciferol), 3) 1000 IU (25 μg) vitamin D₃ (cholecalciferol), or 4) 500 IU vitamin D₂ plus 500 IU vitamin D₃. All of the capsules made by Tishcon Corp. (Salisbury, MD) contained lactose (98.75%), magnesium stearate (1.0%), and silicon dioxide (1.25%). All of the products were analyzed in our laboratory by HPLC and found to contain either no vitamin D (placebo) or concentrations within 10% of their specified content. All subjects had blood samples collected at baseline and every week for a total of 11 wk. Each subject was given a dietary questionnaire at baseline to assess multivitamin and milk consumption. Pill compliance (Table 1) was determined by a pill count at each visit.

Analytical methods

Serum 25(OH)D₂ and 25(OH)D₃ were determined by liquid chromatography tandem mass spectroscopy at Quest Diagnostics Nichols Institute, San Juan Capistrano, CA (10). The detection limit for the assay was 4 ng/ml, and the interassay coefficient of variation was about 10%. Values for serum 25(OH)D₂ reported as less than 4 ng/ml were obtained by subtracting 25(OH)D₃ from the total 25(OH)D.

Statistical methods

The results are presented as means ± SD. Data were analyzed using mixed-effects regression to perform a repeated-measures analysis of 25(OH)D levels across time and groups. Pairwise comparisons were

TABLE 1. Subject demographics

Characteristics	Placebo group (n = 14)	D ₂ +D ₃ group (n = 18)	D ₃ group (n = 20)	D ₂ group (n = 16)
Age (yr)				
Mean ± SD	40.5 ± 11.7	35.5 ± 14.6	40.0 ± 18.0	38.4 ± 12.0
Range	22–59	18–70	20–81	18–59
Females, n (%)	11 (78.6)	13 (72.2)	13 (65)	10 (62.5)
Males, n (%)	3 (21.4)	5 (27.8)	7 (35)	6 (37.5)
Body mass index	29.3	31.7	30.0	31.0
Multivitamin, n (%)	6 (42.9)	4 (22.2)	5 (25)	6 (37.5)
Multivitamin-D ₃ , n (%)	4 (28.6)	3 (16.7)	5 (25)	6 (37.5)
Vitamin D supplement intake	0	0	0	0
Dropout, n (%)	4 (20)	2 (10)	0 (0)	4 (20)
Menopausal status, n (%)	3 (21.4)	2 (11.1)	5 (25)	3 (18.8)
Oral contraceptive pill use, n (%)	0 (0)	2 (11.1)	1 (5)	0 (0)
Compliance (%)	96.6	95.0	95.3	93.6
Mean initial 25(OH)D ± SD (ng/ml)	18.6 ± 8.9	20.2 ± 10.4	19.6 ± 11.1	16.9 ± 10.5
Mean final 25(OH)D ± SD (ng/ml)	18.8 ± 7.9	28.4 ± 7.7	28.9 ± 11.0	26.8 ± 9.6
Mean differences ± SD	0.2 ± 5.3	8.2 ± 7.8 ^{a,d}	9.3 ± 7.1 ^{b,d}	9.9 ± 3.2 ^{c,d}
95% CI	–2.6–3.0	4.6–11.8	6.2–12.7	5.2–14.6
Demographics, n (%)				
Asian	2 (14.3)	1 (5.6)	4 (20)	1 (6.3)
American Indian	0 (0)	0 (0)	0 (0)	1 (6.3)
Black	6 (42.9)	9 (50)	8 (40)	9 (56.3)
Hispanic	0 (0)	2 (11.1)	2 (10)	1 (6.3)
White	6 (42.9)	6 (33.3)	6 (30)	4 (25)

CI, Confidence interval.

^a *P* = 0.041 for D₃+D₂ vs. placebo.

^b *P* = 0.027 for D₃ vs. placebo.

^c *P* = 0.023 for D₂ vs. placebo.

^d No statistically significant difference between D₃+D₂, D₃, and D₂ (*P* = 0.957).

performed between all treatment groups as well as each treatment group *vs.* placebo. Interactions between treatment group and time compared the linear change in 25(OH)D over time between the groups. A repeated-measures mixed-effect model also compared the 25(OH)D₂ and 25(OH)D₃ across visits for each of the treatment groups. Statistical analysis was performed using SAS (SAS Institute, Inc., Cary, NC).

Results

Sixty percent of our healthy adult subjects were vitamin D deficient [25(OH)D < 20 ng/ml], and 87% were insufficient [25(OH)D < 30 ng/ml], even though about 29% took a multivitamin daily that contained 400 IU vitamin D and about 47% drank about 1.2 glasses of milk per day. Adults who received the placebo capsule daily for 3 months demonstrated no significant change in their total 25(OH)D levels during the winter and early spring (Fig. 1). Adults who ingested 1000 IU vitamin D₂/d gradually increased their total 25(OH)D levels from 16.9 ± 10.5 ng/ml to 25.8 ± 6.6 ng/ml during the first 6 wk and then remained stable (Fig. 1). Adults who ingested 1000 IU vitamin D₃ had a baseline 25(OH)D of 19.6 ± 11.1 ng/ml that was statistically no different from the baselines of either the placebo group or the groups that took 1000 IU vitamin D₂/d or 500 IU vitamin D₂ plus 500 IU vitamin D₃/d (*P* = 0.79). The vitamin D₃ group increased their serum 25(OH)D levels similar to that of the group that ingested vitamin D₂. The 25(OH)D levels in the vitamin D₃ group began to plateau by wk 6 and was 28.9 ± 11.0 ng/ml at the end of the study, which was not statistically different from the vitamin D₂ group (26.8 ± 9.6 ng/ml) (Fig. 1).

To determine whether vitamin D₂ ingestion had any effect on circulating levels of 25(OH)D₃, we determined 25(OH)D₂ and 25(OH)D₃ in the samples. The 25(OH)D₂ levels increased from undetectable (<4 ng/ml) to 14 ± 5.3 ng/ml by wk 6 and remained at approximately 14 ng/ml for the ensuing 5 wk in the group that received 1000 IU vitamin D₂ (Fig. 2A). The

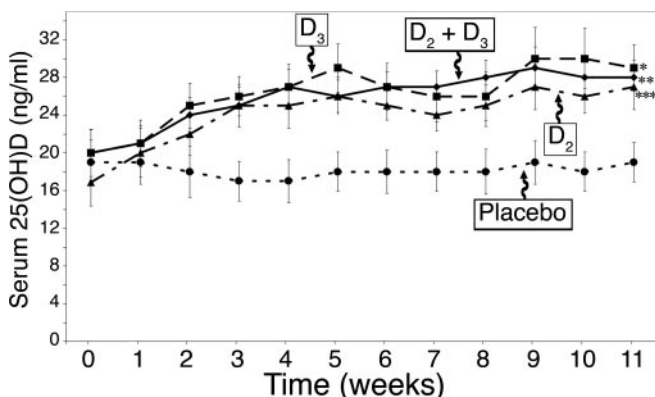


FIG. 1. Mean (± SEM) serum 25(OH)D levels after oral administration of vitamin D₂ and/or vitamin D₃. Healthy adults recruited at the end of the winter received placebo (●; n = 14), 1000 IU vitamin D₃ (D₃, ■; n = 20), 1000 IU vitamin D₂ (D₂, ▲; n = 16), or 500 IU vitamin D₂ and 500 IU vitamin D₃ [D₂ and D₃, ◆; n = 18] daily for 11 wk. The total 25(OH)D levels are demonstrated over time. *, *P* = 0.027 comparing 25(OH)D over time between vitamin D₃ and placebo; **, *P* = 0.041 comparing 25(OH)D over time between 500 IU vitamin D₃ plus 500 IU vitamin D₂ and placebo; ***, *P* = 0.023 comparing 25(OH)D over time between vitamin D₂ and placebo.

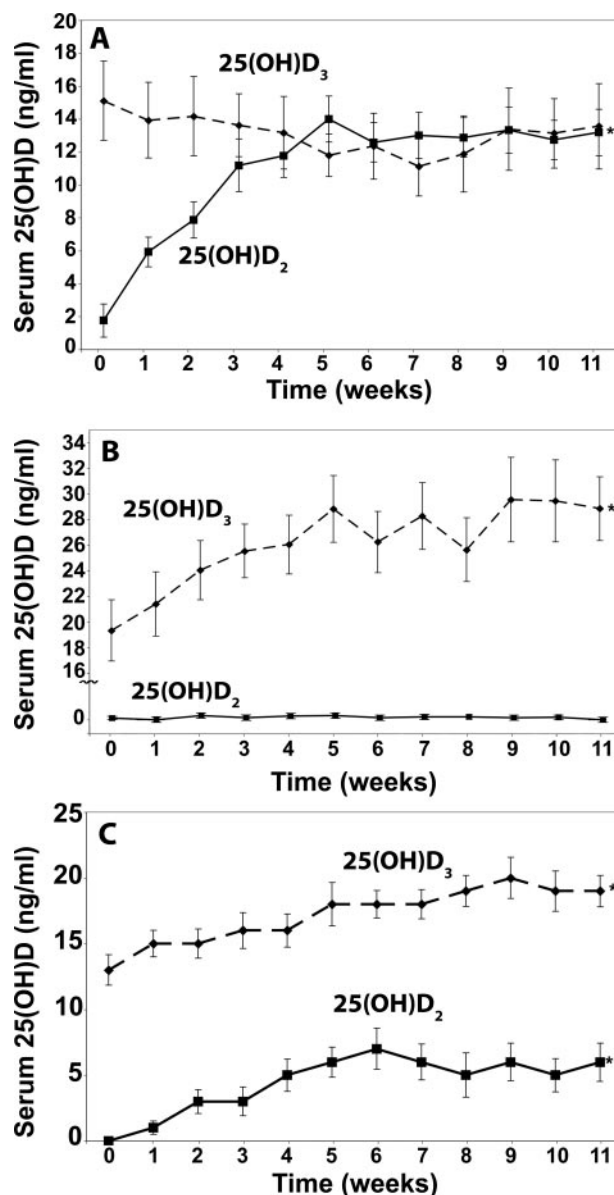


FIG. 2. Effect of vitamin D₂ or vitamin D₃ on serum 25(OH)D₂ and 25(OH)D₃ levels. Serum levels of 25(OH)D₂ (■) and serum 25(OH)D₃ (◆) were measured in healthy subjects receiving 1000 IU vitamin D₂ (A), 1000 IU vitamin D₃ (B), or 500 IU vitamin D₂ plus 500 IU vitamin D₃ (C) daily for 11 wk. Results are presented as means ± SEM over time. *, *P* < 0.0001 comparing 25(OH)D₂ between baseline and 11 wk (A); *, *P* < 0.0001 comparing 25(OH)D₃ between baseline and 11 wk (B); *, *P* = 0.0014 comparing between 25(OH)D₃ and placebo group (C); **, *P* = 0.0031 comparing 25(OH)D₂ and placebo group (C). Note serum 25(OH)D₂ levels less than 4 ng/ml were obtained by subtracting the total 25(OH)D₃ from the total 25(OH)D levels.

baseline 25(OH)D₃ level in the same subjects was 15.1 ± 9.8 ng/ml and did not significantly change during the entire study and was 13.6 ± 10.2 ng/ml at the end of the study (*P* = 0.14) (Fig. 2A). Similarly, the group that received vitamin D₃ showed no significant change in the serum 25(OH)D₂ throughout the study (*P* = 0.33) (Fig. 2B).

To determine further whether vitamin D₂ interfered with vitamin D₃ metabolism, we gave one group of subjects 500 IU vitamin D₂ mixed with 500 IU vitamin D₃. The rise in the total 25(OH)D was identical to that observed for the groups who received either 1000 IU vitamin D₂ or 1000 IU vitamin D₃

daily, and the total 25(OH)D levels at the end of the study were no different in all three groups ($P = 0.957$) (Fig. 1). An analysis of the 25(OH)D₂ and 25(OH)D₃ also demonstrated a comparable increase in both levels in the group that received the combination of 500 IU vitamin D₂ (5.7 ± 4.5 ng/ml) and 500 IU vitamin D₃ (6.1 ± 4.3 ng/ml) (Fig. 2C).

Discussion

Many multivitamin preparations and some foods are fortified with vitamin D₂. Two recent observations have raised questions as to whether vitamin D₂ should be used either as a pharmaceutical agent or as a supplement because it appeared that vitamin D₂ not only was less effective than vitamin D₃ in maintaining 25(OH)D levels (8, 9) but that it also had a negative effect on 25(OH)D status (9). There has also been concern that vitamin D₂ may not be bioequivalent to vitamin D₃ in maintaining bone health (11).

The Food and Nutrition Board has recommended that adults up to the age of 50 yr require 200 IU vitamin D/d, whereas adults 51–70 yr and 71 yr and older require 400 and 600 IU/d, respectively (12). However, many experts now agree that in the absence of adequate sun exposure, at least 1000 IU vitamin D/d is required to maintain 25(OH)D in the sufficient range (1, 13).

Because the placebo group did not demonstrate any change in their circulating levels of 25(OH)D, there was little influence of environmental sun exposure or dietary or supplemental vitamin D intake on their vitamin D status. Subjects who received 1000 IU vitamin D₂ or 1000 IU vitamin D₃ daily gradually increased blood levels of 25(OH)D to the same levels throughout the study. The increase from baseline in the total 25(OH)D levels at the end of the study was 9.3 ng/ml for the vitamin D₃ group, 9.9 ng/ml for the vitamin D₂ group, and 8.2 ng/ml for the vitamin D₂ plus vitamin D₃ group, which is consistent with the observation that serum 25(OH)D levels increased by 1 ng/ml for every 100 IU vitamin D₃ (14). However, the 25(OH)D levels did not rise above 30 ng/ml, which is now considered to be the vitamin D-sufficient range, suggesting that more than 1000 IU vitamin D₂ or vitamin D₃ is necessary to maintain serum 25(OH)D levels above 30 ng/ml when the sun provides no vitamin D₃.

Armas *et al.* (9) reported that a single dose of 50,000 IU vitamin D₂ was less effective than 50,000 IU vitamin D₃ in maintaining serum 25(OH)D levels over the ensuing 30 d in the summer. Furthermore, when compared with the group that received placebo, the group that received 50,000 IU vitamin D₂ had a significant reduction in serum 25(OH)D at the end of the study. We did not observe any negative influence of vitamin D₂ on either total 25(OH)D or 25(OH)D₃ levels (Figs. 1 and 2). The maintenance of the serum 25(OH)D₃ levels observed in this report (Fig. 1) was most likely due to the release of vitamin D₃ stored in the body fat because skin synthesis of vitamin D₃ does not occur during the winter in Boston (1). It is possible that a single pharmacological dose of vitamin D₂ enhanced the destruction of both vitamin D₂ and vitamin D₃ and their 25-hydroxy derivatives. However, when 50,000 IU vitamin D₂ was given weekly for 8 wk (15) or twice a week for 5 wk (16), there was on

average a 100% increase in serum 25(OH)D levels (15) and a significant increase in bone mineral density in both the hip and spine (16). Thus, vitamin D₂ when given in pharmacological doses is effective in maintaining serum 25(OH)D levels and is beneficial for skeletal health (16). Why Trang *et al.* (8) observed that the daily dosing of 4000 IU vitamin D₃ for 2 wk was 1.7 times more effective in raising blood levels of 25(OH)D (increased 9.0 ± 2 ng/ml) than 4000 IU vitamin D₂/d (increased 4.2 ± 2 ng/ml) is unclear at this time. The rise in serum 25(OH)D₃ was only about 20% of what would have been expected for a 4000 IU dose, *i.e.* 40 ng/ml. This may be due to their ethanol formulation. This could also be due to the short time course because we observed that 25(OH)D levels did not begin to plateau until 6 wk. When vitamin D₂ was combined with vitamin D₃, there was no significant difference in the rise in 25(OH)D (Fig. 1). Furthermore, the group that received 1000 IU vitamin D₂ had no significant change in the level of 25(OH)D₃, suggesting that vitamin D₂ at least at 1000 IU/d had no influence on the catabolism of vitamin D₃ or 25(OH)D₃. Thus, 1000 IU vitamin D₂/d is as effective as vitamin D₃ in maintaining 25(OH)D status. These observations are consistent with those of Markestad *et al.* (17) and Rapuri *et al.* (18) who observed that vitamin D₂ and vitamin D₃ contributed equally to serum 25(OH)D levels in mothers and their neonates and elderly women, respectively. Furthermore, the concentrations of 1,25-dihydroxyvitamin D₂ and 1,25-dihydroxyvitamin D₃ were reported to be proportional to the distribution of 25(OH)D₂ and 25(OH)D₃ (19, 20), implying that the 25(OH)D-1-hydroxylase (CYP27B-1) recognized 25(OH)D₂ equally as well as 25(OH)D₃. Therefore, collectively, these data and our results suggest that vitamin D₂ is as effective as vitamin D₃ in sustaining both 25(OH)D and 1,25(OH)₂D levels (19, 20) and improving bone health (16). More studies are needed to determine whether the carrier (*i.e.* ethanol *vs.* oil *vs.* lactose) that vitamin D₂ and vitamin D₃ are dissolved in influence either their bioavailability or catabolism. Our observations also suggest that 1000 IU vitamin D₂ or vitamin D₃ is required to sustain blood levels of 25(OH)D above a mean of 20 ng/ml but was insufficient in raising the levels above a mean of 30 ng/ml.

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