Vitamin D_2 Is as Effective as Vitamin D_3 in Maintaining Circulating Concentrations of 25-Hydroxyvitamin D

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Context: Two reports suggested that vitamin D_2 is less effective than vitamin D_3 in maintaining vitamin D status.

Objective: Our objective was to determine whether vitamin D_2 was less effective than vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels or increased the catabolism of 25-hydroxyvitamin D_3.

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 D_3, 1000 IU vitamin D_2, or 500 IU vitamin D_2 plus 500 IU vitamin D_3 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 $\pm$ SD) increased to the same extent in the groups that received 1000 IU daily as vitamin D_2 (baseline 16.9 $\pm$ 10.5 ng/ml; 11 wk 26.8 $\pm$ 9.6 ng/ml), vitamin D_3 (baseline 19.6 $\pm$ 11.1 ng/ml; 11 wk 28.9 $\pm$ 11.0 ng/ml), or a combination of 500 IU vitamin D_2 and 500 IU vitamin D_3 (baseline 20.2 $\pm$ 10.4 ng/ml; 11 wk 28.4 $\pm$ 7.7 ng/ml). The 25-hydroxyvitamin D_3 levels did not change in the group that received 1000 IU vitamin D_2 daily. The 1000 IU dose of vitamin D_2 or vitamin D_3 did not raise 25-hydroxyvitamin D levels in vitamin D-deficient subjects above 30 ng/ml.

Conclusion: A 1000 IU dose of vitamin D_2 daily was as effective as 1000 IU vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels and did not negatively influence serum 25-hydroxyvitamin D_3 levels. Therefore, vitamin D_2 is equally as effective as vitamin D_3 in maintaining 25-hydroxyvitamin D status. (***J Clin Endocrinol Metab*** **93: 677–681, 2008)**

Vitamin D_2, 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 D_2 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 D_3 (1, 3). Vitamin D_3 is found naturally in cod liver oil and oily fish such as salmon (1, 3). Vitamin D_3 is also made by irradiating 7-dehydrocholesterol obtained from lanolin from sheep's wool with UVB radiation (1). Both vitamin D_2 and vitamin D_3 when ingested undergo metabolism in the liver to form 25-hydroxyvitamin D [25(OH)D; D represents either D_2 or D_3] and in the kidneys to 1,25-dihydroxyvitamin D (1, 3, 5, 6). Both vitamin D_2 and vitamin D_3 are available in supplements, but only vitamin D_2 is available as a pharmaceutical preparation because its use predated the Food and Drug Administration and, thus, was grandfathered as a pharmaceutical drug. Vitamin D_3 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 D_2 has been considered to be equally

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as effective as vitamin D_3 for bone health (3, 7). Recently, it was suggested that vitamin D_2 was less effective than vitamin D_3 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 D_2 was given to healthy adults that the serum 25(OH)D levels decreased more rapidly than the placebo group, suggesting that vitamin D_2 not only was less effective in maintaining serum 25(OH)D levels but also enhanced the degradation of 25(OH)D_3 (9).

These two observations have led to the conclusion that vitamin D_2 is approximately 30–50% as effective as vitamin D_3 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 D_2, 1000 IU vitamin D_3, or a combination of 500 IU vitamin D_2 and 500 IU vitamin D_3 daily for 11 wk at the end of the winter had on circulating levels of total 25(OH)D as well as 25(OH)D_2 and 25(OH)D_3.

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, including 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 D_3 (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 D_2 (ergocalciferol), 3) 1000 IU (25 μg) vitamin D_3 (cholecalciferol), or 4) 500 IU vitamin D_2 plus 500 IU vitamin D_3. 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)D_2 and 25(OH)D_3 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)D_2 reported as less than 4 ng/ml were obtained by subtracting 25(OH)D_3 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 D_3+D_2 *vs.* placebo.

[b] $P = 0.027$ for D_3 *vs.* placebo.

[c] $P = 0.023$ for D_2 *vs.* placebo.

[d] No statistically significant difference between D_3+D_2, D_3, and D_2 ($P = 0.957$).

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 $25(OH)D_2$ and $25(OH)D_3$ 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 D_2/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 D_3 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 D_2/d or 500 IU vitamin D_2 plus 500 IU vitamin D_3/d ($P = 0.79$). The vitamin D_3 group increased their serum 25(OH)D levels similar to that of the group that ingested vitamin D_2. The 25(OH)D levels in the vitamin D_3 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 D_2 group (26.8 ± 9.6 ng/ml) (Fig. 1).

To determine whether vitamin D_2 ingestion had any effect on circulating levels of $25(OH)D_3$, we determined $25(OH)D_2$ and $25(OH)D_3$ in the samples. The $25(OH)D_2$ 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 D_2 (Fig. 2A). The baseline $25(OH)D_3$ 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 D_3 showed no significant change in the serum $25(OH)D_2$ throughout the study ($P = 0.33$) (Fig. 2B).

To determine further whether vitamin D_2 interfered with vitamin D_3 metabolism, we gave one group of subjects 500 IU vitamin D_2 mixed with 500 IU vitamin D_3. The rise in the total 25(OH)D was identical to that observed for the groups who received either 1000 IU vitamin D_2 or 1000 IU vitamin D_3

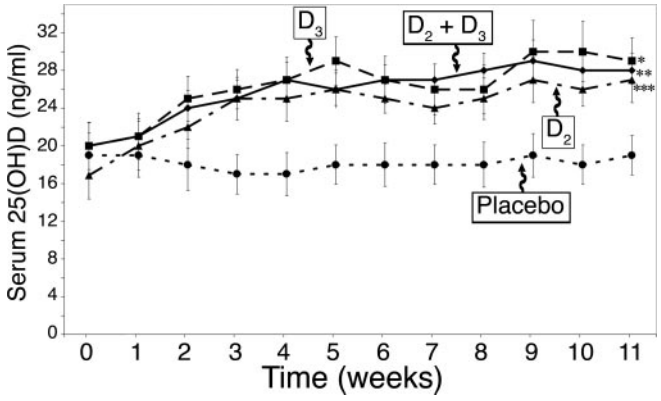

FIG. 1. Mean (± SEM) serum 25(OH)D levels after oral administration of vitamin D_2 and/or vitamin D_3. Healthy adults recruited at the end of the winter received placebo (●; n = 14), 1000 IU vitamin D_3 (D_3, ■; n = 20), 1000 IU vitamin D_2 (D_2, ▲; n = 16), or 500 IU vitamin D_2 and 500 IU vitamin D_3 [D_2 and D_3, ♦; 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 D_3 and placebo; **, $P = 0.041$ comparing 25(OH)D over time between 500 IU vitamin D_3 plus 500 IU vitamin D_2 and placebo; ***, $P = 0.023$ comparing 25(OH)D over time between vitamin D_2 and placebo.

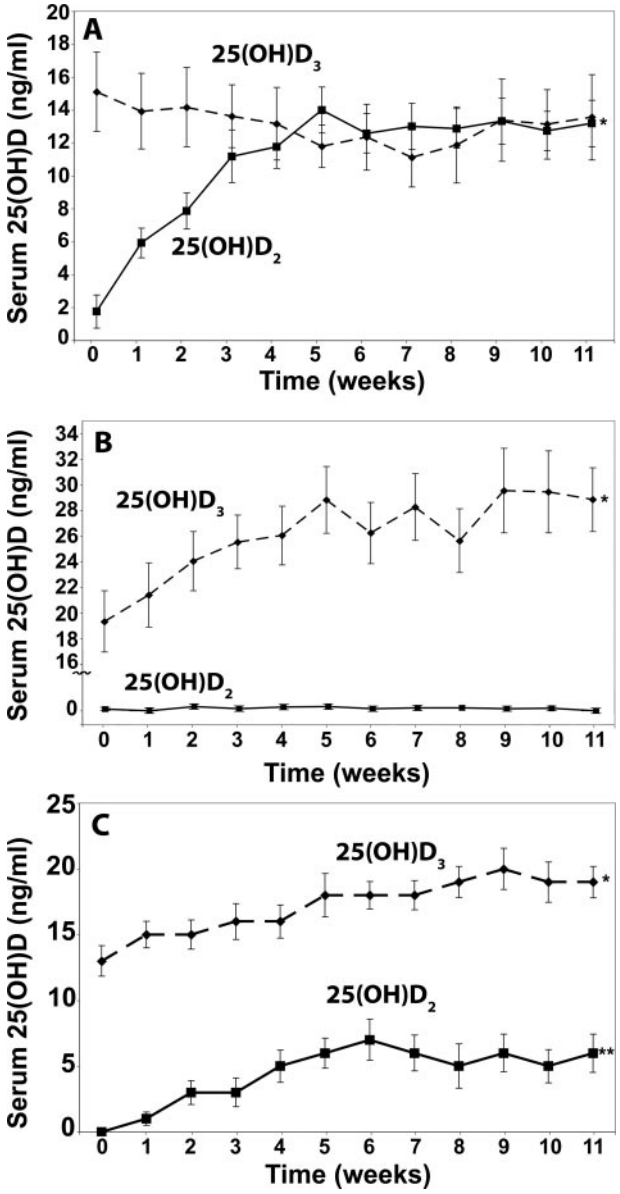

FIG. 2. Effect of vitamin D_2 or vitamin D_3 on serum $25(OH)D_2$ and $25(OH)D_3$ levels. Serum levels of $25(OH)D_2$ (■) and serum $25(OH)D_3$ (♦) were measured in healthy subjects receiving 1000 IU vitamin D_2 (A), 1000 IU vitamin D_3 (B), or 500 IU vitamin D_2 plus 500 IU vitamin D_3 (C) daily for 11 wk. Results are presented as means ± SEM over time. *, $P < 0.0001$ comparing $25(OH)D_2$ between baseline and 11 wk (A); *, $P < 0.0001$ comparing $25(OH)D_3$ between baseline and 11 wk (B); *, $P = 0.0014$ comparing between $25(OH)D_3$ and placebo group (C); **, $P = 0.0031$ comparing $25(OH)D_2$ and placebo group (C). Note serum $25(OH)D_2$ levels less than 4 ng/ml were obtained by subtracting the total $25(OH)D_3$ from the total 25(OH)D levels.

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 $25(OH)D_2$ and $25(OH)D_3$ also demonstrated a comparable increase in both levels in the group that received the combination of 500 IU vitamin D_2 (5.7 ± 4.5 ng/ml) and 500 IU vitamin D_3 (6.1 ± 4.3 ng/ml) (Fig. 2C).

Discussion

Many multivitamin preparations and some foods are fortified with vitamin D_2. Two recent observations have raised questions as to whether vitamin D_2 should be used either as a pharmaceutical agent or as a supplement because it appeared that vitamin D_2 not only was less effective than vitamin D_3 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 D_2 may not be bioequivalent to vitamin D_3 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 D_2 or 1000 IU vitamin D_3 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 D_3 group, 9.9 ng/ml for the vitamin D_2 group, and 8.2 ng/ml for the vitamin D_2 plus vitamin D_3 group, which is consistent with the observation that serum 25(OH)D levels increased by 1 ng/ml for every 100 IU vitamin D_3 (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 D_2 or vitamin D_3 is necessary to maintain serum 25(OH)D levels above 30 ng/ml when the sun provides no vitamin D_3.

Armas *et al.* (9) reported that a single dose of 50,000 IU vitamin D_2 was less effective than 50,000 IU vitamin D_3 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 D_2 had a significant reduction in serum 25(OH)D at the end of the study. We did not observe any negative influence of vitamin D_2 on either total 25(OH)D or $25(OH)D_3$ levels (Figs. 1 and 2). The maintenance of the serum $25(OH)D_3$ levels observed in this report (Fig. 1) was most likely due to the release of vitamin D_3 stored in the body fat because skin synthesis of vitamin D_3 does not occur during the winter in Boston (1). It is possible that a single pharmacological dose of vitamin D_2 enhanced the destruction of both vitamin D_2 and vitamin D_3 and their 25-hydroxy derivatives. However, when 50,000 IU vitamin D_2 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 D_2 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 D_3 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 D_2/d (increased 4.2 ± 2 ng/ml) is unclear at this time. The rise in serum $25(OH)D_3$ 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 D_2 was combined with vitamin D_3, there was no significant difference in the rise in 25(OH)D (Fig. 1). Furthermore, the group that received 1000 IU vitamin D_2 had no significant change in the level of $25(OH)D_3$, suggesting that vitamin D_2 at least at 1000 IU/d had no influence on the catabolism of vitamin D_3 or $25(OH)D_3$. Thus, 1000 IU vitamin D_2/d is as effective as vitamin D_3 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 D_2 and vitamin D_3 contributed equally to serum 25(OH)D levels in mothers and their neonates and elderly women, respectively. Furthermore, the concentrations of 1,25-dihydroxyvitamin D_2 and 1,25-dihydroxyvitamin D_3 were reported to be proportional to the distribution of $25(OH)D_2$ and $25(OH)D_3$ (19, 20), implying that the 25(OH)D-1-hydroxylase (CYP27B-1) recognized $25(OH)D_2$ equally as well as $25(OH)D_3$. Therefore, collectively, these data and our results suggest that vitamin D_2 is as effective as vitamin D_3 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 D_2 and vitamin D_3 are dissolved in influence either their bioavailability or catabolism. Our observations also suggest that 1000 IU vitamin D_2 or vitamin D_3 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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