Evaluation of Ergocalciferol or Cholecalciferol Dosing, 1,600 IU Daily or 50,000 IU Monthly in Older Adults

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Context: Whether ergocalciferol (D_2) and cholecalciferol (D_3) are equally effective to increase and maintain serum 25-hydroxyvitamin D [25(OH)D] concentration is controversial.

Objective: The aim of the study was to evaluate the effect of daily and once monthly dosing of D_2 or D_3 on circulating 25(OH)D and serum and urinary calcium.

Design, Setting and Participants: In a university clinical research setting, 64 community dwelling adults age 65+ were randomly assigned to receive daily (1,600 IU) or once-monthly (50,000 IU) D_2 or D_3 for 1 yr.

Main Outcome Measures: Serum 25(OH)D, serum calcium, and 24-h urinary calcium were measured at months 0, 1, 2, 3, 6, 9, and 12. Serum PTH, bone-specific alkaline phosphatase, and N-telopeptide were measured at months 0, 3, 6, and 12.

Results: Serum 25(OH)D was less than 30 ng/ml in 40% of subjects at baseline; after 12 months of vitamin D dosing, levels in 19% of subjects (n = 12, seven receiving daily doses and five monthly doses) remained low, despite compliance of more than 91%. D_2 dosing increased 25(OH)D_2 but produced a decline ($P < 0.0001$) in 25(OH)D_3. Substantial between-individual variation in 25(OH)D response was observed for both D_2 and D_3. The highest 25(OH)D observed was 72.5 ng/ml. Vitamin D administration did not alter serum calcium, PTH, bone-specific alkaline phosphatase, N-telopeptide, or 24-h urine calcium.

Conclusions: Overall, D_3 is slightly, but significantly, more effective than D_2 to increase serum 25(OH)D. One year of D_2 or D_3 dosing (1,600 IU daily or 50,000 IU monthly) does not produce toxicity, and 25(OH)D levels of less than 30 ng/ml persist in approximately 20% of individuals. Substantial between-individual response to administered vitamin D_2 or D_3 is observed. (***J Clin Endocrinol Metab*** **96: 981–988, 2011)**

Low vitamin D status is extremely common worldwide and adversely affects musculoskeletal health (1, 2). Additionally, low vitamin D status is increasingly associated with increased risk for other nonmusculoskeletal chronic diseases (3–6). Because current indoor lifestyle, clothing choices, and sun avoidance/sunscreen use severely limit sun exposure-dependent vitamin D production, vitamin D supplementation is often necessary. Therefore, identification of optimal approaches to provide supplementation and correct low vitamin D status is required.

Two chemically distinct forms of vitamin D exist; vitamin D_3 (cholecalciferol) is a 27-carbon molecule, whereas vitamin D_2 (ergocalciferol) contains 28 carbons and differs from vitamin D_3 by the presence of an additional methyl group and a double bond between carbons 22 and 23. Vitamin D_3 is produced from 7-dehydrocho-

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Abbreviations: BSAP, Bone-specific alkaline phosphatase; CI, confidence interval; CV, coefficient of variation; NTx, N-telopeptide; 25(OH)D, 25-hydroxyvitamin D.

TABLE 1. Participant demographic data at screening

Group	Age (yr)	Males	Females	BMI (kg/m^2)	Ca (mg/dl)	Albumin (mg/dl)	Creatinine (mg/dl)	25(OH)D (ng/dl)
Monthly D_2	71.3 (1.4)	5	11	25.0 (1.0)	9.4 (0.1)	4.1 (0.1)	0.9 (0.1)	32.4 (2.4)
Monthly D_3	73.7 (1.4)	6	10	26.1 (0.9)	9.5 (0.1)	4.2 (0.1)	0.9 (0.1)	34.8 (2.3)
Daily D_2	72.1 (1.6)	7	9	27.1 (0.8)	9.4 (0.1)	4.2 (0.1)	1.0 (0.1)	35.0 (2.4)
Daily D_3	74.0 (1.9)	5	11	28.1 (1.0)	9.3 (0.1)	4.2 (0.1)	1.0 (0.1)	30.1 (2.7)

Data are expressed as mean (SEM). No between-treatment group differences were present at baseline. BMI, Body mass index.

lesterol when human skin is exposed to UV B radiation (7). Food and/or supplement intake may provide either vitamin D_2 or D_3. Although chemical differences exist between these two forms, it remains controversial whether vitamin D_2 and vitamin D_3 are equally effective at increasing circulating 25-hydroxyvitamin D [25(OH)D] and/or have equivalent physiological effects. Indeed, a recent report finds similar effects from administering either D_2 or D_3 on circulating 25(OH)D levels (8) supporting their equivalence, whereas other publications find vitamin D_2 less "potent" at maintaining serum 25(OH)D than is vitamin D_3 (9–12). Nevertheless, these two forms of vitamin D are currently considered equal and interchangeable, as evidenced by the observation that supplements containing equal amounts of "vitamin D" may contain either vitamin D_2 or vitamin D_3.

Regardless, poor adherence with daily dosing of medications and supplements is widely appreciated. Thus, intermittent use of high-dose vitamin D treatment is a potentially attractive option. In some areas of the world, the only such high-dose option available by prescription is vitamin D_2. How to clinically monitor such intermittent dosing regimens has received little evaluation. However, intermittent high-dose oral vitamin D dosing leads to a prompt increase in circulating 25(OH)D, peaking within days, followed by a gradual decline. Although such a peak/trough effect is intuitively obvious, we have observed that clinicians rarely consider measurement of trough 25(OH)D concentration when using intermittent high-dose vitamin D.

The purposes of this 1-yr, randomized, double-blind, placebo-controlled prospective trial in adults age 65 and over were to evaluate the effect of vitamin D_2 or D_3, 1,600 IU daily *vs.* 50,000 IU monthly, on the serum 25(OH)D concentration and serum and urinary calcium concentration, while concurrently investigating the potential importance of measuring trough 25(OH)D values.

Subjects and Methods

Study participants

Community dwelling men and women 65 yr of age and older were recruited to participate in this study. Inclusion criteria included willingness to avoid use of nonstudy vitamin D supplementation in total daily doses above 400 IU and to use sunscreen of SPF 15 or higher when sun exposure for at least 15 min was expected. Exclusion criteria consisted of hypercalcemia (>10.5 mg/dl), serum 25(OH)D ≤ 10 or ≥ 60 ng/ml, 24-h urine calcium greater than 250 mg (females) or greater than 300 mg (males), known risk factors for hypercalcemia (*e.g.* malignancy or granulomatous disease), renal failure (calculated creatinine clearance ≤25 ml/min), known malabsorption syndromes (*e.g.* celiac disease, radiation enteritis, active inflammatory bowel disease), treatment with medications that interfere with vitamin D metabolism (*e.g.* phenobarbital, phenytoin), and current or prior use of medications affecting bone turnover. This study was reviewed and approved by the University of Wisconsin Health Sciences Human Subjects Committee. Signed informed consent was obtained from all participants.

Study design

All study volunteers were randomly assigned to receive vitamin D_2 or vitamin D_3 either daily (1,600 IU) or once monthly

TABLE 2. Serum 25(OH)D concentration for all groups at all study time points

	25(OH)D (ng/ml)				25(OH)D (ng/ml)	
	D_3 (1600 IU daily)	D_2 (1600 IU daily)	Change from baseline; ratio D_3/D_2	*P*	D_3 (50,000 IU monthly)	D_2 (50,000 IU monthly)
Base	29.9 (2.5)	32.0 (2.1)			36.3 (2.1)	31.1 (2.2)
1 month	34.4 (1.8)	32.9 (2.0)	1.13 (1.02–1.24)	0.01	38.5 (2.2)	32.5 (1.8)
2 months	35.9 (1.9)	34.5 (1.7)	1.11 (0.98–1.26)	0.10	40.2 (2.4)	32.8 (2.2)
3 months	37.5 (1.9)	33.8 (1.8)	1.19 (1.03–1.37)	0.02	41.7 (2.4)	32.8 (2.1)
6 months	40.3 (2.4)	36.8 (2.0)	1.17 (1.00–1.37)	0.05	42.3 (2.5)	34.1 (2.1)
9 months	39.5 (2.4)	36.9 (2.1)	1.14 (0.97–1.34)	0.11	44.0 (2.8)	35.1 (2.4)
12 months	39.0 (2.4)	38.1 (2.0)	1.09 (1.00–1.29)	0.32	45.2 (3.3)	34.7 (2.3)
Pooled			1.14 (1.00–1.29)	0.05		

25(OH)D data are reported as mean (SEM). Change from baseline ratio represents change in total 25(OH)D for D_3 group/change in total 25(OH)D for D_2 group (95% CI).

(50,000 IU). Matching daily and monthly placebos were used to blind study participants and research staff regarding treatment group assignments. The vitamin D_2 and vitamin D_3 preparations were in capsule form, produced by Tischon, Corp. (Salisbury, MD), and validated in the laboratory of Dr. H. DeLuca to contain the following: 50,000 IU vitamin D_3 = 56,000 ± 2%; 50,000 IU vitamin D_2 = 54,500 ± 2%; 1,600 IU vitamin D_3 = 1,664 ± 2%; and 1,600 IU vitamin D_2 = 1,712 ± 6%. After a screening visit, volunteers returned at baseline and months 1, 2, 3, 6, 9, and 12, at which time we obtained fasting serum specimens between 0700 and 1100 h and 24-h urine collections were returned. Additional fasting serum specimens were collected at 3 and 7 d after the baseline and at 3-month visits. "Trough" 25(OH)D measurements were collected immediately before the witnessed monthly dose administration at months 1, 2, 3, 6, and 9. All subjects receiving monthly vitamin D took this on an empty stomach at baseline and months 1, 2, 3, 6, and 9. This was done to ensure that the blood draws 3 and 7 d later were performed at consistent times after dose and that the trough 25(OH)D values were not confounded by inappropriate dosing. At all other times, study participants were advised to take the vitamin D with meals. Compliance was assessed by pill count at all study visits.

Outcome measures

The primary study endpoint was serum 25(OH)D as determined by reverse phase HPLC using methodology previously described (13). The laboratory performing 25(OH)D measurements participates in, and meets proficiency standards of, DEQAS (the vitamin D External Quality Assessment Scheme). The limit of quantitation for this assay is 3 ng/ml for $25(OH)D_2$ and $25(OH)D_3$; values below this were entered as zero. The intraassay coefficient of variation (CV) for this assay ranges from 1.9% at a 25(OH)D concentration of 61.5 ng/ml to 6.3% at a 25(OH)D concentration of 14.3 ng/ml. The interassay CV is 3.2% at a 25(OH)D concentration of 59.8 ng/ml and 3.9% at a 25(OH)D concentration of 14.3 ng/ml. Serum 25(OH)D concentration at all time points for a given individual was determined in a single HPLC run to minimize assay variability.

Secondary outcome measures included serum calcium and 24-h urine calcium as measured in routine clinical manner using a Roche Integra autoanalyzer (Meriter Laboratories, Madison, WI). In this laboratory, the normal range for serum calcium is 8.5–10.6 mg, and the normal range for 24-h urinary calcium is 100–320 mg. Other endpoints of skeletal relevance were evaluated using commercially available kits to measure bone-specific alkaline phosphatase (BSAP) by immunoassay (Metra BAP; Quidel Corporation, San Diego, CA), N-telopeptide (NTx) by competitive-inhibition ELISA (Osteomark, Seattle, WA) and PTH by ELISA (Immunodiagnostic Systems, Fountain Hills, AZ). Intra- and interassay CVs for these analytes in our laboratory for BSAP, NTx, and PTH are 7.5/5.1/5% and 4.5/7.9/7%, respectively. To minimize variability, serum aliquots from all time points for each individual were run with the same assay kit.

Statistical analysis

Baseline comparisons were analyzed using an unpaired *t* test. Serum 25(OH)D measurements at month 1, 2, 3, 6, 9, and 12 follow-up visits were log-transformed before analysis. A mixed effects linear regression model was applied to assess the effects of vitamin D supplement (D_2, D_3), dosing (daily, monthly), and their interaction, both overall and by visit with adjustment for baseline. In the absence of a significant interaction term, main effects of vitamin D supplement and dosing are reported, and analyses of combined daily and monthly dosing arms are presented. Models included log-transformed serum 25(OH)D at baseline as a covariate and used an unstructured variance-covariance matrix for the repeated outcome measurements. Analyses were performed using PROC MIXED in SAS software, version 9 (SAS Institute Inc., Cary, NC). Secondary endpoints, *e.g.* change in serum and urine calcium over time, were evaluated using similar repeated measures ANOVA models in Statview software (Abacus, Cary, NC).

Results

Demographic data

Sixty-four community dwelling adults [23 men/41 women; age, mean (range), 77 (65–88) yr; and body mass index, mean (range), 26.6 (17.4 to 37.4) kg/m^2] were enrolled in this study. One of these volunteers was Asian, two were Black, and the remaining 61 were Caucasian. No between-group differences were present at baseline (Table 1). Calcium supplementation use was reported by 41%, with a mean intake of 844 mg daily. One individual in the monthly D_3 group discontinued the study after 1 month

TABLE 2. Continued

Change from baseline; ratio D_3/D_2	*P*	25(OH)D (ng/ml) D_3 (pooled daily and monthly dosing)	25(OH)D (ng/ml) D_2 (pooled daily and monthly dosing)	Change from baseline; ratio D_3/D_2	*P*
		33.0 (1.7)	31.5 (1.5)		
1.06 (0.96–1.16)	0.27	36.4 (1.4)	32.7 (1.3)	1.09 (1.02–1.17)	0.01
1.10 (0.97–1.25)	0.13	38.0 (1.5)	33.6 (1.4)	1.11 (1.01–1.21)	0.02
1.14 (0.99–1.32)	0.07	39.6 (1.6)	33.3 (1.4)	1.17 (1.05–1.29)	0.01
1.11 (0.94–1.30)	0.20	41.3 (1.7)	35.5 (1.5)	1.14 (1.02–1.27)	0.02
1.12 (0.95–1.32)	0.18	41.7 (1.8)	36.0 (1.6)	1.13 (1.01–1.27)	0.04
1.16 (0.97–1.38)	0.10	42.0 (2.1)	36.4 (1.6)	1.12 (0.99–1.27)	0.06
1.11 (0.98–1.38)	0.11			1.13 (1.03–1.23)	0.01

due to spousal illness. Compliance with study preparation was as follows: daily D_2, 95.4%; daily D_3, 91.6%; monthly D_2, 99.4%; and monthly D_3, 98.9%.

25(OH)D

At baseline, 40% (25 of 63) of participants had low vitamin D status (<30 ng/ml); after 12 months of vitamin D supplementation, status of 19% (12 of 63) remained low (data not shown). Of the 12 participants in whom 25(OH)D remained below 30 ng/ml at 1 yr, eight were receiving D_2 (four daily and four monthly), and four were receiving D_3 (three daily and one monthly). Inadequate compliance with vitamin D dosing seems unlikely to explain persistence of low vitamin D status in these individuals. Specifically, for those receiving daily vitamin D but remaining low, compliance with D_2 (n = 4) ranged from 90–98%, whereas for D_3 (n = 3) compliance was 41, 100, and 100%. For those receiving monthly vitamin D but remaining low, compliance was 100%.

Total 25(OH)D increased from baseline to the 12-month follow-up with all regimens [D_3 daily, 32%, 95% confidence interval (CI), 17 to 49%, $P < 0.0001$; D_3

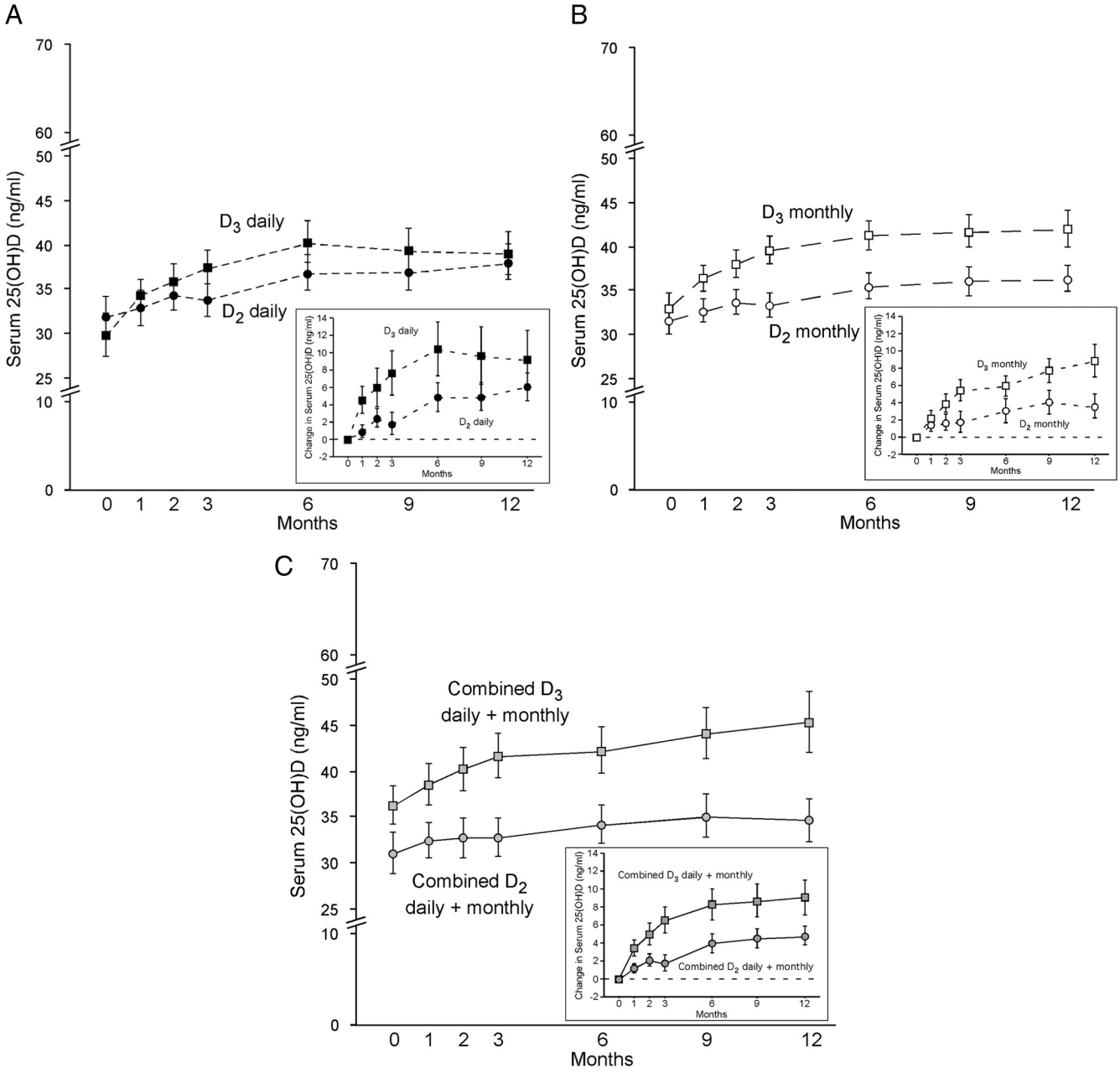

FIG. 1. Effect of vitamin D_2 or D_3 on serum 25(OH)D. The main figure presents mean 25(OH)D levels (SEM) at each follow-up visit; *inset* presents mean change from baseline (SEM). After 12 months of supplementation, serum 25(OH)D increased numerically to a greater extent with D_3 than D_2 with daily (9.2 *vs.* 6.1 ng/ml; $P = 0.05$; A) and monthly (8.9 *vs.* 3.6 ng/ml; $P = 0.11$; B) dosing. When the daily and monthly dosing groups are combined, a greater increase ($P = 0.01$) in 25(OH)D was observed (C) with D_3 (9.1 ng/ml) than with D_2 (4.8 ng/ml).

monthly, 29%, 95% CI, 14 to 46%, $P = 0.0002$; D_2 daily, 21%, 95% CI, 7 to 36%, $P = 0.003$; and D_2 monthly, 11%, 95% CI, −1 to 25%, $P = 0.08$]. Subjects receiving D_3 had significantly greater increases in 25(OH)D compared with those receiving D_2 (13%; 95% CI, 3 to 23%; $P = 0.01$). Similar increases were seen for both dosing frequencies (daily, 14%; 95% CI, 0 to 29%; $P = 0.05$; monthly, 11%; 95% CI, −2 to 27%; $P = 0.11$; interaction $P = 0.83$) and at all follow-up visits (7–13% at each visit; interaction $P = 0.36$) (Table 2). Frequency of dosing did not significantly impact 25(OH)D levels (daily *vs.* monthly, 5%; 95% CI, −4 to 15%; $P = 0.29$).

The absolute increase at 12 months with D_3 was greater than with D_2 for both daily (9.2 *vs.* 6.1 ng/ml, respectively; $P = 0.05$) and monthly (8.9 *vs.* 3.6 ng/ml, respectively; $P = 0.11$) dosing (Fig. 1, A and B). The average increase in serum 25(OH)D achieved per 100 IU of daily vitamin D_3 and D_2 was 0.58 and 0.38 ng/ml, respectively.

With monthly dosing, a significant increase in 25(OH)D was observed at 3 and 7 d after 50,000 IU of either D_2 or D_3. After the initial 50,000 IU dose, the mean increase at d 3 for vitamins D_3 and D_2 was 6.3 and 5.2 ng/ml, respectively. A similar increase was observed after the initial and month 3 doses (Fig. 2A). As might be expected, no change in 25(OH)D was observed 3 and 7 d after initiating daily dosing of 1,600 IU with either D_2 or D_3 (data not shown). That 50,000 IU of vitamin D_2 or D_3 produces only a modest (~1.5–2 ng/ml) increase in serum 25(OH)D 1 month later is depicted in Fig. 2B.

Substantial between-individual variability was noted for daily and monthly dosing with both D_2 and D_3. This variability is depicted by group (daily or monthly dosing of vitamin D_2 or D_3) in Fig. 3A. That this variability in 25(OH)D increase is not dependent solely upon the baseline concentration is depicted in Fig. 3B.

One year of vitamin D treatment did not produce toxic 25(OH)D levels. In fact, serum 25(OH)D exceeded 60 ng/ml in only three individuals; two women receiving daily or monthly vitamin D_3 had values of 60.1 to 66.7 ng/ml, whereas a value of 72.5 ng/ml was observed at 12 months in a man receiving monthly vitamin D_3.

Serum 25(OH)D_3 was measurable in all study participants at baseline. In contrast, 25(OH)D_2 was present in only 16 and generally at low concentration (mean, 10.2 ng/ml; range, 5.5–15.1 ng/ml). Although dosing with vitamin D_2, either daily or monthly, increases total 25(OH)D as noted above, both of these approaches led to a prompt and substantial ($P < 0.0001$) decrease in circulating 25(OH)D_3. In fact, the mean numerical reduction in 25(OH)D_3 is approximately 3-fold greater than the corresponding increase in total 25(OH)D (Fig. 4). Similarly, dosing with vitamin D_3 appeared to reduce circulating 25(OH)D_2; these data are not presented because only six people that received vitamin D_3 had measurable 25(OH)D_2 at baseline.

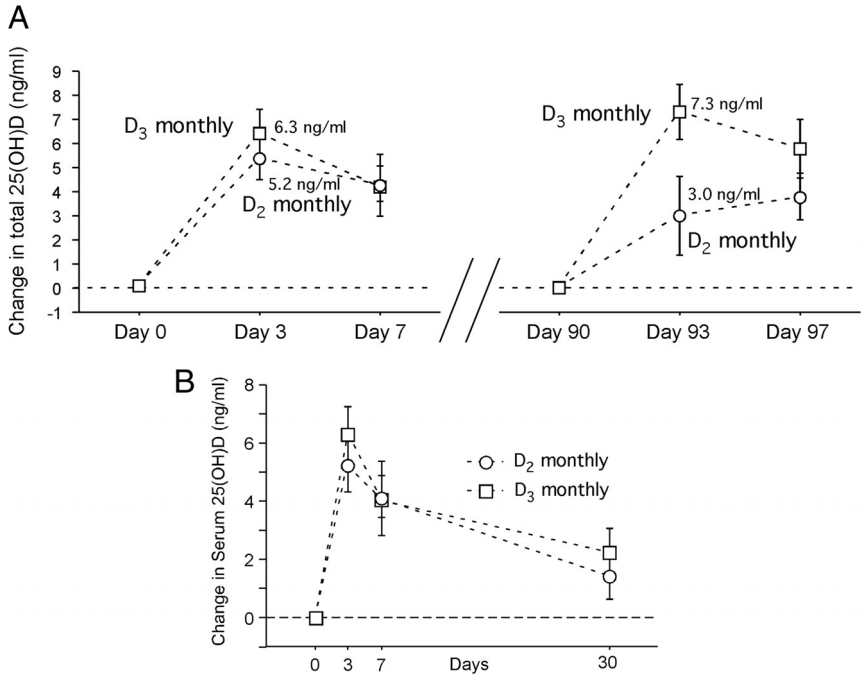

FIG. 2. Impact of monthly vitamin D dosing on 25(OH)D. Serum 25(OH)D increases promptly after 50,000 IU of either vitamin D_2 or D_3. This phenomenon is present not only after the first dose, but also after the third monthly dose with a quite comparable increase in mean 25(OH)D (A). As noted in panel B, the decline over 1 month is such that the serum 25(OH)D increased by only 1.4 ng/ml with vitamin D_2 and 2.2 ng/ml with vitamin D_3.

Serum and urine calcium

No individual developed hypercalcemia during the course of this study; the highest serum calcium observed was 10.6 mg/dl (laboratory upper limit of normal = 10.6 mg/dl). Serum calcium did not differ in any group, and no between-group differences were observed during the study (data not shown). Similarly, no change in 24-h urinary calcium excretion was observed in any treatment group, and no between-group difference was observed (Fig. 5).

PTH and bone turnover markers

No effect of vitamin D supplementation was observed on serum PTH for any of the individual groups, when the daily and monthly dosing groups were combined for vitamin D_3 and vitamin D_2 or when all study participants were combined (data not shown). Similarly, no effect of vitamin D supplementation

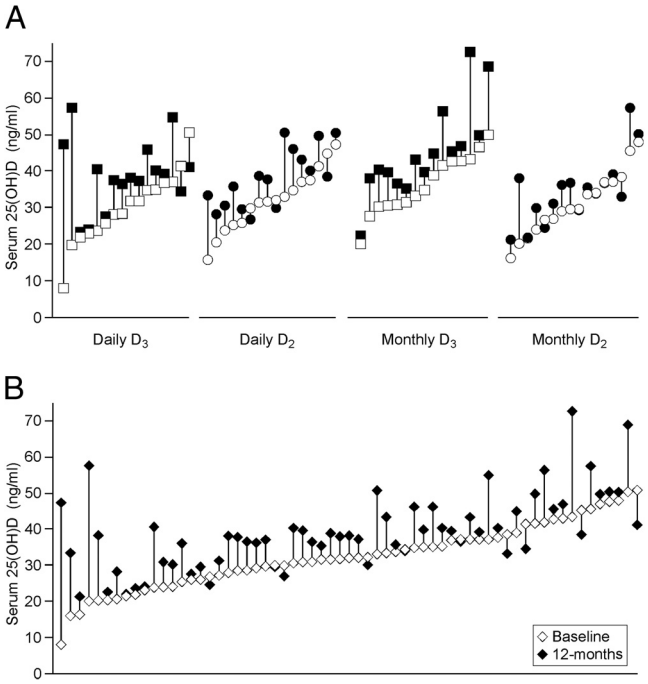

FIG. 3. Between-individual variability with daily and monthly vitamin D dosing. Variable responses in serum 25(OH)D to vitamin D dosing either daily or once-monthly is apparent for both vitamin D_2 and D_3, as well as for daily and monthly dosing (A). That the increase in 25(OH)D is not dependent solely on the 25(OH)D concentration at baseline is illustrated in panel B. In A and B, Baseline 25(OH)D value is represented by the *open symbol* and the 12-month value by the *closed symbol*.

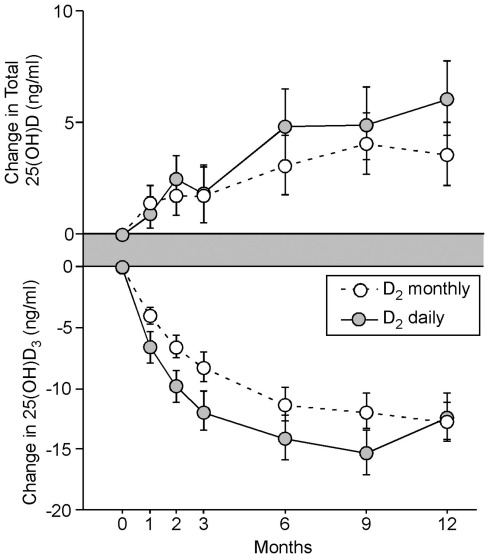

FIG. 4. Effect of D_2 dosing on circulating 25(OH)D_3 concentration. Ergocalciferol dosing, whether daily or monthly, produced a significant decline of approximately 12 ng/ml in circulating 25(OH)D_3 concentration ($P < 0.0001$).

was observed on BSAP or NTx for any of the vitamin D supplementation groups (data not shown).

Discussion

In this cohort of older adults, a substantial minority (~19%) did not have optimal vitamin D status after 12 months of dosing with 1,600 IU daily or 50,000 IU monthly. Thus, these relatively "high" doses do not ensure vitamin D adequacy even in a population with only a modest prevalence of vitamin D inadequacy (40%) at baseline. Inadequate compliance does not explain this result because all but one of the individuals who remained low were over 90% compliant with supplementation. Thus, the vitamin D required to ensure adequacy in all people is higher than 1,600 IU daily or the comparable amount (50,000 IU) once per month. That vitamin D doses greater than 1,600 IU daily are required to ensure adequacy in all individuals is consistent with a recent clinical observation using intermittent ergocalciferol (14).

In this study, vitamin D_3 produced a greater increment in serum 25(OH)D than vitamin D_2. These results are consistent with the majority of prior work (10, 12, 15–19). It seems feasible that vitamins D_2 and D_3 could have differing effects on 25(OH)D due to differences in metabolism. For example, the mitochondrial hydroxylase encoded by the CYP24A1 gene 25-hydroxylates vitamin D_3, whereas it 24-hydroxylates vitamin D_2 (20, 21). Moreover, the CYP3A4 hydroxylase is more effective in 24-hydroxylating vitamin D_2 than D_3 (22, 23). Whether these or other enzymatic variations produce the observed difference in 25(OH)D increase after supplementation with vitamins D_2 and D_3 remains to be determined. Additionally, as demonstrated in this study, vitamin D_2 dosing reduces circulating 25(OH)D_3. This finding, consistent with competition by substrate for the 25-hydroxylase enzyme, differs from a recently published study (8). It is unclear why such differing results are observed. Although the physiological importance, if any, of this 25(OH)D_3 reduction remains unknown, it seems plausible that this decline contributes to the less robust increase in total 25(OH)D observed with vitamin D_2 administration. Additionally, the absence of changes in physiological endpoints such as PTH and NTx when 25(OH)D_3 is replaced by 25(OH)D_2

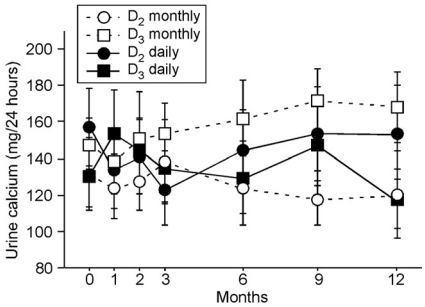

FIG. 5. Absence of effect of vitamin D supplementation on urine calcium. Twenty-four-hour urinary calcium excretion was unchanged ($P = 0.14$) in all groups over the 12 months of study.

(resulting from D_2 supplementation) supports the known biological efficacy of ergocalciferol.

It should be appreciated that some of the published work comparing the effect of vitamin D_2 and D_3 did not independently validate the vitamin D content of study preparations. This potentially may have confounded some of the prior literature, but it was not the case in this study where the study preparations contained virtually the same amount of vitamins D_2 and D_3. Although this study, and the majority of published work, finds D_3 more potent that D_2 at increasing 25(OH)D, it should be recognized that the historical view (24) supported by other recent work finds vitamins D_2 and D_3 equally effective (8, 25, 26). Possible explanations for these conflicting results include differences in age and race between the study populations. Although the data remain conflicting, it is clear that either D_2 or D_3 can be used to increase circulating 25(OH)D. Given the between-individual variability noted in this study and by others (27), measurement of 25(OH)D to ensure optimal status seems wise, whether one is using D_2 or D_3.

In this study, the increase in circulating 25(OH)D per 100 IU of daily vitamin D_3 supplemented was approximately 0.6 ng/ml. This is similar to a number of other reports in which serum 25(OH)D increases by approximately 0.6–0.7 ng/ml per 100 IU of daily D_3 (27–29). Recognizing that individuals with lower baseline levels of 25(OH)D may achieve a greater increment in 25(OH)D (30, 31), a reasonable clinical "rule of thumb" is that addition of 1000 IU vitamin D_3 daily should increase circulating 25(OH)D by approximately 6–7 ng/ml. Additionally, between-individual variability in response to equal doses of vitamin D prevents assurance that this magnitude of response will occur in a given individual. The causes of such differential response likely reflect differences in gastrointestinal absorption of vitamin D and subsequent differences in metabolism; however, the precise mechanism(s) remain to be defined. A clinical implication of these differences is that monitoring of 25(OH)D is required if a healthcare provider wishes to ensure that an individual patient achieves optimal vitamin D status. Alternatively, it seems logical that provision of very high doses of vitamin D would provide optimal vitamin D status; this work does not allow definition of what would constitute such "large" doses. It is clear from this study, however, that 50,000 IU of either D_2 or D_3 once per month does not ensure vitamin D adequacy in all individuals. Moreover, if one is monitoring the 25(OH)D concentration with intermittent large dosing, it is important to appreciate that substantial peak to trough differences exist (~4–7 ng/ml) with monthly dosing of 50,000 IU vitamin D. Given the approximate 3- to 4-wk half-life of 25(OH)D (32), an "optimal" 25(OH)D obtained soon after dosing could be "low" for much of the month.

Limitations of this work include relatively small sample size, evaluation of only older adults, and study of a largely Caucasian population. Additionally, because the study was not designed to compare the effect of D_2 with D_3 on serum PTH concentration, vitamin D deficiency was not required for study participation. Whether D_2 and D_3 have differing effects on PTH can thus not be addressed by these data and will require future study. Although our data suggest similar kinetics between daily and monthly dosing, we acknowledge the possibility that 25(OH)D kinetics may, in fact, differ between daily and monthly dosing approaches. However, such differences may not be of clinical relevance given the long half-life of 25(OH)D (~3 wk). The favorable pharmacokinetics of intermittent vitamin D dosing likely contribute to reports of equal effects on serum 25(OH)D with daily, weekly, and monthly dosing (33). This observation, in concert with reported suboptimal adherence with vitamin D supplementation (34, 35), emphasize the need for additional research to evaluate potential vitamin D dosing kinetic differences. Study strengths include independent validation of the vitamin D_2 and D_3 content in the supplements, use of a well-validated HPLC system to measure 25(OH)D, excellent study participant compliance with the preparations, and the relatively long study duration.

In conclusion, vitamin D supplementation with 1,600 IU daily or the equivalent amount once per month (50,000 IU) does not ensure a serum 25(OH)D concentration of more than 30 ng/ml in all people. Moreover, the 25(OH)D level at presentation does not allow accurate prediction of those who will attain a value above 30 ng/ml on treatment. Vitamin D_3 is slightly, but significantly, more effective than vitamin D_2 at increasing circulating 25(OH)D. The physiological importance of this, if any, remains to be determined. Substantial between-individual variability in response to equal doses of vitamin D exists; this warrants measurement of 25(OH)D concentration when vitamin D supplementation is used in clinical practice.

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