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 (D2) and cholecalciferol (D3) 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 D2 or D3 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) D2 or D3 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%. D2 dosing increased 25(OH)D2 but produced a decline (P < 0.0001) in 25(OH)D3. Substantial between-individual variation in 25(OH)D response was observed for both D2 and D3. 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, D3 is slightly, but significantly, more effective than D2 to increase serum 25(OH)D. One year of D2 or D3 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 D2 or D3 is observed. (J Clin Endocrinol Metab 96: 981–988, 2011)
l esterol when human skin is exposed to UV B radiation (7). Food and/or supplement intake may provide either vitamin D2 or D3. Although chemical differences exist between these two forms, it remains controversial whether vitamin D2 and vitamin D3 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 D2 or D3 on circulating 25(OH)D levels (8) supporting their equivalence, whereas other publications find vitamin D2 less “potent” at maintaining serum 25(OH)D than is vitamin D3 (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 D2 or vitamin D3. 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 intermittent use of high-dose vitamin D treatment is a potentially attractive option. In some areas of the world, the intermittent use of high-dose vitamin D treatment is a potentially attractive option. In some areas of the world, the intermittent use of high-dose vitamin D treatment is a potentially attractive option. In some areas of the world, the intermittent use of high-dose vitamin D treatment is a potentially attractive option.

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 D2 or D3, 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 D2 or vitamin D3 either daily (1,600 IU) or once monthly.

### Table 1. Participant demographic data at screening

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Males</th>
<th>Females</th>
<th>BMI (kg/m²)</th>
<th>Ca (mg/dl)</th>
<th>Albumin (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>25(OH)D (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly D2</td>
<td>71.3 (1.4)</td>
<td>5</td>
<td>11</td>
<td>25.0 (1.0)</td>
<td>9.4 (0.1)</td>
<td>4.1 (0.1)</td>
<td>0.9 (0.1)</td>
<td>32.4 (2.4)</td>
</tr>
<tr>
<td>Monthly D3</td>
<td>73.7 (1.4)</td>
<td>6</td>
<td>10</td>
<td>26.1 (0.9)</td>
<td>9.5 (0.1)</td>
<td>4.2 (0.1)</td>
<td>0.9 (0.1)</td>
<td>34.8 (2.3)</td>
</tr>
<tr>
<td>Daily D2</td>
<td>72.1 (1.6)</td>
<td>7</td>
<td>9</td>
<td>27.1 (0.8)</td>
<td>9.4 (0.1)</td>
<td>4.2 (0.1)</td>
<td>1.0 (0.1)</td>
<td>35.0 (2.4)</td>
</tr>
<tr>
<td>Daily D3</td>
<td>74.0 (1.9)</td>
<td>5</td>
<td>11</td>
<td>28.1 (1.0)</td>
<td>9.3 (0.1)</td>
<td>4.2 (0.1)</td>
<td>1.0 (0.1)</td>
<td>30.1 (2.7)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>25(OH)D (ng/ml)</th>
<th>D₂ (1600 IU daily)</th>
<th>D₃ (1600 IU daily)</th>
<th>Change from baseline; ratio D₃/D₂</th>
<th>P</th>
<th>D₂ (50,000 IU monthly)</th>
<th>D₃ (50,000 IU monthly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>29.9 (2.5)</td>
<td>32.0 (2.1)</td>
<td>1.13 (1.02–1.24)</td>
<td>0.01</td>
<td>36.3 (2.1)</td>
<td>31.1 (2.2)</td>
</tr>
<tr>
<td>1 month</td>
<td>34.4 (1.8)</td>
<td>32.9 (2.0)</td>
<td>1.11 (0.98–1.26)</td>
<td>0.10</td>
<td>38.5 (2.2)</td>
<td>32.5 (1.8)</td>
</tr>
<tr>
<td>2 months</td>
<td>35.9 (1.9)</td>
<td>34.5 (1.7)</td>
<td>1.19 (1.03–1.37)</td>
<td>0.15</td>
<td>40.2 (2.4)</td>
<td>32.8 (2.2)</td>
</tr>
<tr>
<td>3 months</td>
<td>37.5 (1.9)</td>
<td>33.8 (1.8)</td>
<td>1.17 (1.00–1.37)</td>
<td>0.05</td>
<td>41.7 (2.4)</td>
<td>32.8 (2.1)</td>
</tr>
<tr>
<td>6 months</td>
<td>40.3 (2.4)</td>
<td>36.8 (2.0)</td>
<td>1.14 (0.97–1.34)</td>
<td>0.11</td>
<td>42.3 (2.5)</td>
<td>34.1 (2.1)</td>
</tr>
<tr>
<td>9 months</td>
<td>39.5 (2.4)</td>
<td>36.9 (2.1)</td>
<td>1.09 (1.00–1.29)</td>
<td>0.32</td>
<td>44.0 (2.8)</td>
<td>35.1 (2.4)</td>
</tr>
<tr>
<td>12 months</td>
<td>39.0 (2.4)</td>
<td>38.1 (2.0)</td>
<td>1.14 (1.00–1.29)</td>
<td>0.05</td>
<td>45.2 (3.3)</td>
<td>34.7 (2.3)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25(OH)D data are reported as mean (SEM). Change from baseline ratio represents change in total 25(OH)D for D₃ group/change in total 25(OH)D for D₂ 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 D3 and vitamin D2 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 D3 = 56,000 ± 2%; 50,000 IU vitamin D2 = 54,500 ± 2%; 1,600 IU vitamin D3 = 1,664 ± 2%; and 1,600 IU vitamin D2 = 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)D2 and 25(OH)D3; values below this were entered as zero. The vitamin D2 and vitamin D3 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 D3 = 56,000 ± 2%; 50,000 IU vitamin D2 = 54,500 ± 2%; 1,600 IU vitamin D3 = 1,664 ± 2%; and 1,600 IU vitamin D2 = 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.

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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 8.5–11.0 mg, and the normal range for 24-h urinary calcium is 8.5–11.0 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 (Immunodiagnostics 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 (D2, D3), 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/m²] 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 D3 group discontinued the study after 1 month.
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$_3$

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**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.

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
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 different 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$_2$
(resulting from D₂ supplementation) supports the known biological efficacy of ergocalciferol.

It should be appreciated that some of the published work comparing the effect of vitamin D₂ and D₃ 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 D₂ and D₃. Although this study, and the majority of published work, finds D₃ more potent that D₂ at increasing 25(OH)D, it should be recognized that the historical view (24) supported by other recent work finds vitamins D₂ and D₃ 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 D₂ or D₃ 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 D₂ or D₃.

In this study, the increase in circulating 25(OH)D per 100 IU of daily vitamin D₃ 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 D₃ (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 D₃ 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 D₂ or D₃ 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 D₂ with D₃ on serum PTH concentration, vitamin D deficiency was not required for study participation. Whether D₂ and D₃ 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 D₂ and D₃ 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 D₃ is slightly, but significantly, more effective than vitamin D₂ 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.

Acknowledgments

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