Dose response to vitamin D supplementation among postmenopausal African American women¹–³

Sonia A Talwar, John F Aloia, Simcha Pollack, and James K Yeh

ABSTRACT

Background: Reports on the dose response to vitamin D are conflicting, and most data were derived from white men and women.

Objective: The objective was to determine the response of serum 25-hydroxyvitamin D [25(OH)D] to oral vitamin D₃ supplementation in an African American population.

Design: Healthy black postmenopausal women (n = 208) participated in a vitamin D₃ supplementation trial for a period of 3 y. Analyses were done in the vitamin D supplementation arm (n = 104) to quantify the response in serum 25-hydroxyvitamin D concentrations at a steady state vitamin D input. The participants received 20 μg/d (800 IU) oral vitamin D₃ for the initial 2 y and 50 μg/d (2000 IU) for the third year.

Results: Supplementation with 20 μg/d (800 IU/d) vitamin D₃ raised the mean serum 25(OH)D concentration from a baseline of 46.9 ± 20.6 nmol/L to 71.4 ± 21.5 nmol/L at 3 mo. The mean (±SD) concentration of serum 25(OH)D was 87.3 ± 27.0 nmol/L 3 mo after supplementation increased to 50 μg/d (2000 IU/d). All participants achieved a serum 25(OH)D concentration >35 nmol/L. 95% achieved a concentration >50 nmol/L, but only 60% achieved a concentration >75 nmol/L. All patients had concentrations <153 nmol/L. On the basis of our findings, an algorithm for prescribing vitamin D so that patients reach optimal serum concentrations was developed. The algorithm suggests a dose of 70 μg (2800 IU/d) for those with a concentration >45 nmol/L and a dose of 100 μg (4000 IU/d) for those with a concentration <45 nmol/L.

Conclusions: Supplementation with 50 μg/d (2000 IU/d) oral vitamin D₃ is sufficient to raise serum 25-hydroxyvitamin D concentrations to >50 nmol/L in almost all postmenopausal African American women. However, higher doses were needed to achieve concentrations >75 nmol/L in many women in this population. Am J Clin Nutr 2007;86:1657–62.

KEY WORDS Ethnicity, vitamin D, 25-hydroxyvitamin D, osteoporosis, vitamin D deficiency, African Americans

INTRODUCTION

Clinicians often measure serum 25-hydroxyvitamin D [25(OH)D] to determine vitamin D status. Although concentrations <20 nmol/L are well known to cause clinical osteomalacia and rickets, concentrations between 20 and 75 nmol/L (vitamin D insufficiency) have more recently been suggested to have an adverse influence on the skeleton (1, 2). Vitamin D insufficiency in the elderly is associated with low bone mass due to secondary hyperparathyroidism and, as a result, a higher incidence of fractures (2–4). It has also been appreciated that sufficient vitamin D may be just as important for other nonskeletal effects, such as the improvement of the immune system and the prevention of certain cancers (5).

Up to 42% of African American women and 4.2% of white women of childbearing age have serum 25(OH)D concentrations <62.5 nmol/L during the summer (6). The prevalence is expected to be much higher during the winter. Experts in the field are now disputing the vitamin D requirements set forth as adequate intakes in 1997 by the Panel on Calcium and Related Nutrients. There is an emerging consensus that 25(OH)D concentrations >75 nmol/L may be optimal for bone health and extraskeletal effects (7–12). Heaney (13) recently described that an oral intake of ≥55 μg/d (2200 IU/d) may be required in addition to the prevailing intake of vitamin D to raise 25(OH)D concentrations to near 80 nmol/L or higher. Blacks produce less vitamin D₃ than do whites in response to usual levels of sun exposure and have lower serum 25(OH)D concentrations in winter and summer (14, 15). Weaver and Fleet (16) estimated that blacks need 46–62 μg/d of vitamin D₃ supplements. However, this assumption is based on a solitary study performed in white adults (17). Thus far, there is a lack of sufficient evidence to make ethnically specific recommendations.

We analyzed the dose response of vitamin D supplementation in a cohort of postmenopausal African American women receiving daily vitamin D₃ supplementation for a period of 3 y in a double-blind, placebo-controlled longitudinal trial conducted at our center from 1998 to 2004 (18). The aim of this report was to quantify the response of serum 25-hydroxyvitamin D concentrations to a steady state vitamin D input.

SUBJECTS AND METHODS

Participants

Two hundred eight healthy postmenopausal African American women not receiving hormone replacement therapy were recruited from the Long Island community. One hundred four participants were randomly assigned to receive daily vitamin D supplements and 104 received placebo. All of the participants

¹ From the Bone Mineral Research Center, Winthrop University Hospital, Mineola, NY.
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³ Reprints not available. Address correspondence to JF Aloia, 222 Station Plaza North, Suite 510, Mineola, NY 11501. E-mail: jaloia@winthrop.org. Received October 26, 2006. Accepted for publication July 20, 2007.

provided written informed consent, and the trial was approved by the Institutional Review Board of Winthrop University Hospital. All of the procedures followed were in accordance with the ethical standards of our Institutional Review Board on human experimentation in accordance with the Helsinki Declaration of 1975 as revised in 1983. African American ancestry of the participants was assessed by self-declaration that both parents and ≥3 out of 4 grandparents were African American. Exclusion criteria included previous treatment with bone active agents and any medication or illness that affects skeletal metabolism.

Postmenopausal status was confirmed on the basis of serum follicle-stimulating hormone concentrations >23 mIU/L. A medical history and physical examination were conducted by a physician on site in all subjects. Exclusion criteria included previous treatment with bisphosphonates or fluoride; use of estrogens, calcitonin, glucocorticoids, androgens, phosphate, anabolic steroids, or >400 IU/d vitamin D 6 mo before entry; history of previous hip fracture; uncontrolled diabetes, anemia, or thyroid disease; history of current liver, renal, neurologic, or malignant disease; malabsorption or alcoholism; history of hypercalciuria, nephrolithiasis, or active sarcoidosis; smoking >10 cigarettes a day; unexplained weight loss; use of medications known to interfere with calcium or vitamin D absorption or metabolism, such as anticonvulsants; severe osteoarthritis or scoliosis that would interfere with bone density assessment of the spine or hip; and participation in weight training or elite athletic training.

Study design

The participants were randomly assigned with the use of a computer-generated sequence to receive either 20 μg/d (800 IU/d) oral vitamin D3 or a matched placebo. At the completion of 24 mo of supplementation, the dose of vitamin D3 was raised to 50 μg/d (2000 IU/d) in the vitamin D group, and the study continued for an additional year. Calcium intake was assessed with a food-frequency questionnaire at each visit, and supplements were provided as calcium carbonate. Other laboratory measurements made but not analyzed in this study included serum chemistries, calcium, serum parathyroid hormone, 1,25-dihydroxyvitamin D, osteocalcin, and cross-laps (18). Body fat was measured every 6 mo by dual-energy X-ray absorptiometry.

Outcome variables

A fasting blood sample was collected for analysis of serum 25(OH)D at baseline and at 3, 6, 12, 18, 24, 27, 30, and 36 mo. These samples were collected throughout the year but during the same month at the annual visits to avoid seasonal effects. Serum 25(OH)D was measured by radioimmunoassay (RIA) with the use of a kit manufactured by DiaSorin Inc (Stillwater, MN) (19). The intraassay CV was 4.1%, and the interassay CV was 7.0%. Our laboratory participates in DEQAS, an international quality assurance program to ensure accuracy in the measurement of serum 25(OH)D (20). Other laboratory measurements made but not analyzed in this study included serum chemistries, calcium, serum parathyroid hormone, 1,25-dihydroxyvitamin D, osteocalcin, and cross-laps (18). Body fat was measured every 6 mo by using dual-energy X-ray absorptiometry.

Statistical analysis

Multiple linear regression was used to model vitamin D response as a function of predictor variables, including dose, baseline values, season, body mass index, and percentage body fat. Slope at a specific time point was defined as the change in serum 25(OH)D from baseline divided by the dose assigned during the preceding 3 mo. Within-subject change in slope was analyzed with the paired t test. Pearson correlation was used to quantify the linear association between variables. Continuous change across time between the active and placebo groups were analyzed by using a mixed-model analysis of variance framework implemented in PROC MIXED (version 9.1; SAS Institute, Cary, NC). The analysis of correlated data arising from repeated measurements used Generalized Estimating Equations (GEEs) implemented in the SAS Procedure GENMOD. A 2-tailed P value <0.05 was deemed statistically significant. Results are expressed as means ± SD. Analyses were done both with all available data and with the use of only subjects with complete data. Because no differences in the results were found, only the results with the use of all available data are reported (ie, an intent-to-treat analysis). Similarly, nonparametric analyses and data transformation were applied, but, because they did not lead to different results, only the parametric analyses of the raw data are reported.

Optimal dosing algorithm development

The results from multiple regressions and other analyses were used to identify variables to be included in an empiric algorithm for prescribing vitamin D. Variables that were considered for inclusion were dose, age, amount of body fat, basal serum 25(OH)D concentration, and time of year that a patient’s vitamin D was measured. Because these data included only black women, race and sex were not included. Only dose, basal concentration, and season were found to predict vitamin D response. Data found by Vieth (21) suggest that the 25(OH)D response to each 1 μg vitamin D/d is approximately constant for doses >35 μg/d. We therefore approached the problem of finding the optimal vitamin D dose by multiplying a patient’s observed slope on 50 μg/d by a wide range of possible doses. This projected response is then added to the basal value to obtain a projected endpoint on that dose. (We did not adjust for season because the projection was made for the same time period during which the slope was measured; thus, the slope already includes the effects of season.) We had the computer search through a wide range of possible doses from 35 to 150 μg/d and calculated the projected vitamin D levels for each patient if everyone would be taking the same dose. We defined an optimal dose as one at which the concentrations of all patients are projected to remain <250 nmol/L, whereas ≥90% exceeded 75 nmol/L. A dose of 95 μg/d satisfied those criteria, but some patients were projected to be too close to 250 nmol/L. For safety purposes we tried another class of dosing rule that was based on the reasoning that not all patients need take the same dose. Patients whose basal value was below a to-be-determined threshold would be given a higher dose, whereas those with a basal value above that threshold would be given a lower dose, ie, after a single basal 25(OH)D vitamin D concentration measurement is made (Dobs), a high dose (DoseH) is prescribed if the Dobs is below a to-be-determined threshold (T) and a lower dose (DoseL) if the Dobs is above it. Potentially, these 3 variables (T,
Dose1 and Dose2) could vary as a function of a patient’s covariates (characteristics), such as age or weight, but we did not find this to be the case. The combinations of T, Dose1, and Dose2 that satisfied the criteria that all patients are projected to have concentrations <250 nmol/L (for safety) and that ≥90% of the population would achieve ≥75 nmol/L (for efficacy) was found by an SAS computer program by searching all possible combinations of T, Dose1, and Dose2. The nature of this algorithm does not allow for the estimation of parameters and their CIs.

RESULTS

Baseline characteristics of the vitamin D group are shown in Table 1. Thirteen percent of the women were taking calcium and vitamin supplements before entry into the study.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group (n = 104)</th>
<th>Vitamin D group (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.2 ± 6.3²</td>
<td>59.9 ± 6.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.4 ± 6.1</td>
<td>162.7 ± 6.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.2 ± 12.6</td>
<td>78.0 ± 13.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 4</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>Current user: 7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Ever: 40</td>
<td>35</td>
</tr>
<tr>
<td>Dietary vitamin D intake (µg/d)</td>
<td>4.6 ± 4.2</td>
<td>4.6 ± 4.8</td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>756 ± 541</td>
<td>762 ± 623</td>
</tr>
<tr>
<td>25(OH)D (nmol/L)</td>
<td>43.2 ± 16.8</td>
<td>46.9 ± 20.6</td>
</tr>
<tr>
<td>1,25(OH)2D (pmol/L)</td>
<td>118.8 ± 39.2</td>
<td>121.8 ± 39.6</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>42.4 ± 18.4</td>
<td>44.2 ± 19.3</td>
</tr>
</tbody>
</table>

The data are from reference 18. 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone. There were no significant differences between groups by independent t test.

² ± SD (all such values).

In the vitamin D group, the concentration of serum 25(OH)D increased significantly (P < 0.0001) over the first 3 mo at the dose of 20 µg vitamin D3/d (Table 2 and Figure 1). The placebo group did not change its mean vitamin D concentration from baseline (time-by-group interaction: P < 0.0001). Over this same period, parathyroid hormone decreased significantly (P < 0.0001; Table 2). The response when assessed as the change in serum 25(OH)D concentrations per 1 µg vitamin D3 supplemented is equivalent to a slope of 1.1 ± 0.9 nmol · L⁻¹ · µg⁻¹. When the dose of vitamin D3 was raised from 20 to 50 µg/d during the final year of the study, the mean serum 25(OH)D concentration achieved after 3 mo at the higher dose was 87.3 ± 27.0 nmol/L. The mean 25(OH)D concentration, despite a 250% increase in dose, increased by 17.2 ± 22.2 nmol/L (22% increase). The slope was 0.76 ± 0.53 nmol · L⁻¹ · µg⁻¹ for the higher dose. The maximum increase in serum 25(OH)D was seen at 27 mo (3 mo after higher dose began); 60% of the participants achieved concentrations >75 nmol/L. At 36 mo, the mean serum

### Figure 1

Mean (±SD) changes from baseline in 25-hydroxyvitamin D [25(OH)D] concentrations in the vitamin D (solid line) group and the placebo group (dashed line) throughout the 36-mo study period. A significant group-by-time interaction was observed (P < 0.0001).
25(OH)D concentration waned to 73.9 ± 26.8 nmol/L, and only 50% of the participants achieved serum 25(OH)D concentrations >75 nmol/L at the end of the study.

In a multiple regression analysis, neither age, weight, body mass index, percentage body fat nor grams of body fat significantly influenced the response to vitamin D₃ supplementation. The 3-mo change per 1 µg vitamin D, ie, the response slope, was inversely dependent on the basal 25(OH)D concentration. The slope was also inversely dependent on the dose used for supplementation. The slope was not constant across the 2 doses: the higher dose of 50 µg produced a smaller change per 1 µg vitamin D in serum 25(OH)D (slope = 0.76 ± 0.5) than did the lower dose of 20 µg (slope = 1.1 ± 0.9) (paired t (53) = 2.8, P = 0.007).

The lower the baseline measure, the greater the vitamin D response. This was indicated by the negative correlation between baseline vitamin D and the change in vitamin D from baseline to specific time points. For example, among the active patients, the correlation between baseline and change was −0.38 (P = 0.0005) at 3 mo and was −0.35 (P = 0.007) at 27 mo. A very similar pattern of equally large negative correlation coefficients was observed among the placebo patients as well: the correlation between baseline and change at 3 mo was −0.26 (P = 0.017) and at 27 mo was −0.42 (P = 0.0009). This correlation was evident even when both measurements were taken in the same season 1 y apart, ie, at 12, 24, or 36 mo, which ruled out seasonal variation as an explanation for this association.

Effects of season

We noted empirically a pronounced peak in our serum 25(OH)D data during the months of June to September. At baseline, the pre- and postsummer periods were not statistically different with respect to the mean vitamin D concentration (37.3 ± 18.0 and 42.9 ± 16.8 nmol/L, respectively; P = 0.12), but were both statistically lower than during the summer period (50.5 ± 18.6 nmol/L). Pooling the 2 nonsummer periods for comparison with summer resulted in a mean difference of 10.4 nmol/L (the SE for the linear contrast was 2.5, t = 4.1, P = 0.0001). Age- and several weight-related variables were not seen to be significant factors associated with the change in vitamin D. Only basal vitamin D concentration and season are included as factors in the formula for prescribing vitamin D.

Results of computer search of optimal T, Dose₁, and Dose₂

Computer analysis of our data arrived at only one solution that satisfied our stated criteria. This solution suggests a dose of 70 µg for those with a concentration >45 nmol/L and a dose of 100 µg for those with a concentration <45 nmol/L. In an improvement over the dosing rule of “all patients take 95 µg/d” we found that the rule incorporating a threshold resulted in all patients projected to remain <220 nmol/L after 3 mo on the prescribed dose and 90% projected to achieve ≥75 nmol/L. Everyone was projected to reach 59 nmol/L. To guarantee that 97% of the subjects would have a concentration >75 nmol/L, a larger dose must be prescribed to result in 4 participants projected to have values of 25(OH)D >250 nmol/L.

Adherence

Vitamin D pill compliance after the randomization visit was 87%; ~96% of the subsequent visits were kept by our patients.

Daily calcium intake including supplements was 1349 ± 204 mg/d.

Adverse events

There were 8 serious adverse events in this subset of subjects, none of which was considered to be related to the study medication. Specific study-related adverse events included 6 isolated incidents of mild hypercalcemia in this group. The hypercalcemia resolved on repeat fasting sampling. Similarly, isolated episodes of elevated 24-h urinary calcium excretion (defined as >5 mg · kg⁻¹ · d⁻¹) were observed among 3 participants. Calcium supplements had to be discontinued in one participant because of persistent hypercalciuria, which resolved the abnormality. In the other 2 participants, the condition resolved spontaneously on repeat analysis of 24-h urine samples with no alteration in study supplements. Overall, there was a slight increase in serum calcium and urinary calcium excretion over 3 y with vitamin D supplementation. However, this increase was similar to the increase seen with calcium supplementation alone (placebo arm). In addition, the concentrations remained within the reference range for healthy adults in all participants. There were no episodes of nephrolithiasis. There was a slight increase in serum creatinine in both groups over 3 y that also remained within the reference range for healthy adults in all participants.

Twenty-four–hour urinary calcium adjusted for body weight (mg · d⁻¹ · kg⁻¹) was not statistically different between the vitamin D and placebo groups during the course of the study (Figure 2). Very few patients ever exceeded 5 mg · d⁻¹ · kg⁻¹ and, when retested, were found to be below the threshold of 5, except in one instance.

Although vitamin D did not seem to adversely affect the calcium economy, we did note a statistically positive correlation between serum calcium (measured across all active patients after baseline, when calcium supplementation began) and 25(OH)D (r = 0.22, n = 626 observations). Because the observations were not independent, a GEE analysis controlling for multiple observations per individual resulted in a P value <0.0001 for the association between serum calcium and 25(OH)D. Correlations with a similar magnitude were noted at individual time points.

FIGURE 2. Mean (±SD) urinary calcium excretion by weight in the vitamin D group (solid line) and the placebo group (dashed line) throughout the 36-mo study period. Calcium excretion remained stable throughout the study. No significant group-by-time interaction was observed.
The mean serum calcium concentration among those in the highest quartile of serum vitamin D was 0.25 mg/dL higher than that among those in the lowest quartile ($P < 0.0001$). This single change takes on more significance when it is contrasted with the small amount of overall variability in serum calcium. Because the SD across the study was 0.48 mg/dL, vitamin D shifts the population more than half an SD.

**DISCUSSION**

This study is the first report of dose responses to oral vitamin D$_3$ supplementation among African Americans. Our data show that the current recommended daily allowance of vitamin D$_3$ of 400–600 IU/d will not optimize vitamin D nutrition in this population. Furthermore, higher amounts than the recommended upper daily allowance of 50 µg/d (2000 IU/d) may be required to achieve concentrations of 25(OH)D $> 75$ nmol/L in most of the African American population. Our study showed that a dose of 50 µg/d can raise the population serum 25(OH)D concentration to an average of $\approx 75$ nmol/L. However, to raise the 25(OH)D concentration to $> 75$ nmol/L in all individuals, a dose of 70 µg (2800 IU/d) for those with a concentration $> 45$ nmol/L and a dose of 100 µg (4000 IU/d) for those with a concentration $< 45$ nmol/L are required in an African American population.

The response to vitamin D$_3$ supplementation in the literature yielded somewhat variable results. Barger-Lux et al (12) showed that in a relatively replete group of white subjects, 25 µg vitamin D$_3$/d resulted in an increase of 13 nmol/L from a mean of 67 to 80 nmol/L. This amount of supplementation left a significant proportion of the study group at suboptimal concentrations. The basal 25(OH)D concentration was negatively correlated with response, and the dose was inversely correlated with the response per 1 µg. Likewise, Heaney et al (17) treated a group of healthy volunteers with a basal 25(OH)D concentration of 72 nmol/L with either 25 or 250 µg/d vitamin D$_3$. They reported a dose response of 0.7 nmol/L per 1 µg oral vitamin D$_3$ supplemented. The mean 25(OH)D concentration was 84 nmol/L after 5 mo of supplementation with the 25-µg/d dose, which left many subjects with serum 25(OH)D concentrations $< 75$ nmol/L. In this relatively vitamin D–replete group of subjects, Heaney et al (17) suggest that $\approx 114$ µg/d would be required to achieve optimal 25(OH)D in most of the subjects. In another study, Vieth et al (23) showed that 25 µg/d raised the mean concentration of 25(OH)D from 47 nmol/L to only 68.7 nmol/L, whereas 100 µg/d raised it to 96 nmol/L. Eighty-eight percent of the participants receiving 100 µg/d achieved 25(OH)D concentrations $> 80$ nmol/L compared with only 35% of those receiving 25 µg/d (23). Although 100 µg/d resulted in optimum serum 25(OH)D concentrations in most of the subjects in Vieth et al’s study, it is likely that many of the subjects would not require this much vitamin D$_3$ to achieve optimal concentrations. Furthermore, the above data are applicable only to the white population. Other than our previous work, very little data regarding vitamin D dosing in African Americans is available in the literature (24).

Another finding of our study was that the basal serum 25(OH)D concentration is a predictor of the response to vitamin D$_3$ supplementation: higher increases are seen at lower basal 25(OH)D concentrations, a finding consistent with previous studies (12). However, we believe that this finding is a statistical artifact due to regression to the mean (25); therefore, we did not include this factor in our dose finding algorithm. On the other hand, a basal value is still useful because it determines the degree of insufficiency in an individual and the change required to attain optimal concentrations.

A comparison of our results on vitamin D responses with those in the literature among whites suggests that the response to oral vitamin D supplementation is not blunted in African Americans. If one presumes that the slope of the response to oral vitamin D$_3$ is 0.7 nmol/L per 1 µg oral vitamin D$_3$, supplemented, as reported by Heaney et al (26), then by inference, a dose of 50 µg vitamin D$_3$/d is expected to raise serum concentrations of 25(OH)D from $\approx 47$ nmol/L (our baseline) to 82 nmol/L in whites. In fact, the mean concentration achieved in our participants was 87 nmol/L at 27 mo. Application of the Barger-Lux formula for predicting the response to 1 µg vitamin D (12) to our initial dose of 20 µg yields a dose-response slope of 1.57. For the dose of 50 µg, the predicted slope is 1.16. The ratio of these 2 numbers is almost exactly the ratio of our observed slopes, which suggests structural similarities between blacks and whites in terms of their response. Heaney’s (13) recent recommendation of an oral intake of 55 µg/d (2200 IU/d) in addition to the prevailing recommended intake of vitamin D to raise 25(OH)D concentrations near 80 nmol/L is based on the population achieving a mean concentration of 80 nmol/L instead of each individual achieving an optimal concentration.

Our simplified one-measurement, one-dose adjustment algorithm gave satisfactory results. But given the individual variability in the responses to vitamin D, a better, more precise result would be expected if the concentration of 25(OH)D and the dose of vitamin D was adjusted a second time.

Application of this or similar algorithms to other populations may not be as effective. The effect of sunlight is lower in the African-American population, and our study was performed in a northern latitude. Thus, in light-skinned populations, or where sun exposure is greater, seasonal adjustments would be a greater consideration. It is also possible that age, percentage body fat, or some other measurable variable may influence the response among whites. Still, we are encouraged that a simplified dosing scheme can ultimately be developed for wide clinical application, and these data may be used to make recommendations for populations in whom the baseline 25(OH)D is known.

In our study, we found no influence of increasing the vitamin D intake on bone loss. African Americans differed from whites in that they have a more efficient calcium economy. Blacks conserve urinary calcium more efficiently and yet have relative resistance to the effects of parathyroid hormone on the skeleton (27, 28). Their bone mass is superior to whites, and their risk of fracture is lower. Thus, blacks have a lower requirement for calcium than do whites for a skeletal endpoint. The optimal calcium and vitamin D status in African Americans will be determined in the future by their extracalcemic effects in protecting against hypertension, obesity, diabetes, autoimmune diseases, and certain cancers (29–31).

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The authors’ responsibilities were as follows—SAT: helped design and write the manuscript and designed and supervised the study participants; JFA: helped design and write the manuscript and designed and supervised the study; SP (study statistician): responsible for the data and
statistical analyses and helped write the manuscript; and JKY (laboratory director): responsible for the biochemical assays. None of the authors had a personal or financial conflict of interest.

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