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Effects of Vitamin D Supplementation in Older African American Women

J. Christopher Gallagher,* Munro Peacock, Vinod Yalamanchili, and Lynette M. Smith

Bone Metabolism Unit (J.C.G., V.Y.), Creighton University School of Medicine, Omaha, Nebraska 68131; Department of Endocrinology (M.P.), Indiana University School of Medicine, Indianapolis, Indiana 46202; and Department of Biostatistics (L.M.S.), College of Public Health, University of Nebraska Medical Center, Omaha, Nebraska 68198

*Corresponding author.

Address all correspondence and requests for reprints to: Dr J. C. Gallagher, MD, Bone Metabolism Unit, Creighton University School of Medicine, 601 North 30th Street, Suite 6718, Omaha, Nebraska 68131. E-mail: jcg@creighton.edu.

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Abstract

Context:

Serum 25-hydroxyvitamin D (25OHD) is lower in women with darker skin color. Is it due to lower skin production, lower absorption, or different metabolism of vitamin D?

Objectives:

The objective of the study was to measure the effect of vitamin D3 on serum 25OHD and serum PTH in older African American women with vitamin D insufficiency and the serum 25OHD 20 ng/mL or less (<50 nmol/L). The results can be used to estimate the Recommended Dietary Allowance (RDA).

Design and Setting:

This was a randomized, double-blind placebo trial at Creighton University Medical Center and Indiana University Medical Center.

Participants:

Participants were 110 healthy older African American women.

Interventions:

The intervention consisted of participants randomly assigned to placebo, vitamin D3 400, 800, 1600, 2400, 3200, 4000, or 4800 IU daily; calcium supplements were given to maintain total calcium intake of 1200–1400 mg/d.

Main Outcome Measurements:

Change in serum 25OHD and serum PTH levels at 12 months was measured.

Results:

Mean baseline serum 25OHD was 13 ng/mL (33 nmol/L). On 4800 IU, serum 25OHD averaged 50 ng/mL (125 nmol/L) compared with 47 ng/mL (117 nmol/L) in Caucasian women. Serum PTH at 12 months decreased significantly (P = .008) when related to serum 25OHD but not dose. Hypercalcemia

occurred in 7% and hypercalciuria in 15%. Events were unrelated to vitamin D dose.

Conclusion:

Vitamin D3 800 IU increased serum 25OHD greater than 20 ng/mL (>50 nmol/L) in 97.5% of the African American women just as it did in the Caucasian women, and therefore, the RDA is the same for both groups. Because absorption and metabolism of oral vitamin D absorption is similar in both groups, lower levels of serum 25OHD in African Americans must be due to lower production of vitamin D in skin.

In clinical studies serum 25-hydroxyvitamin D (25OHD) has been used as a biomarker of vitamin D insufficiency or deficiency. Vitamin D is a nutrient that is derived from sources other than food and up to 80% of vitamin D may be derived from sunlight due to skin production of vitamin D.

In a recent publication of the Institute of Medicine, it was pointed out that there were insufficient data to estimate the recommended dietary allowance (RDA) for other ethnic groups (1). The basic definitions encompassing nutrient recommendation for vitamin D include the RDA that meets the needs of most (97.5%) of the population, the estimated average requirement (EAR) that meets the needs of 50% of the population, and the tolerable upper intake level, an intake that does not produce risk of adverse effects in most individuals.

One of the issues noted by the Institute of Medicine (IOM) was the lack of dose-response studies in ethnic populations (1). In a recent study from our group, we studied the dose-response effect of vitamin D_3 in doses ranging from 400 to 4800 IU/d on serum 25OHD in Caucasian women and showed that 600–800 of vitamin D daily met the RDA based on achieving a serum 25OHD level of 20 ng/mL (2). In parallel to the Caucasian study, we conducted a similar trial in African American women that proceeded more slowly and was completed later. Although it is known that serum 25OHD levels are lower in African American women (3, 4), this was attributed to decreased formation of vitamin D in darker skin (5).

The main objectives of this trial were to study the effect of increasing doses of vitamin D_3 on serum 25OHD and serum PTH in older African American women with vitamin D insufficiency, ie, serum 25OHD 20 ng/mL (≤50 nmol/L). Because secondary hyperparathyroidism is associated with vitamin D insufficiency (6), the effect of vitamin D on serum PTH was another outcome. Finally, the results would provide data that could determine the RDA and EAR for vitamin D based on the response of serum 25OHD to vitamin D.

Materials and Methods

Study design and participants

Vitamin D supplementation in Older Subjects (ViDOS) was a 1-year, randomized, prospective, placebo-controlled clinical trial aimed at establishing the dose of vitamin D_3 required to increase serum 25OHD levels and normalize serum PTH in 97.5% of study subjects in older Caucasian and African American women who were all postmenopausal. One hundred ten African American postmenopausal healthy women (79 from Indiana and 31 from Omaha, Nebraska) who met the inclusion and exclusion criteria were entered into study.

The inclusion criteria were postmenopausal women, an age range of 57–90 years, and vitamin D insufficiency with serum 25OHD of 20 ng/mL or less. Exclusion criteria were as follows: significant comorbidities; history of cancer except skin cancer within the last 10 years; terminal illness; previous hip fracture; hemiplegia; uncontrolled type 1 diabetes ± significant proteinuria or fasting blood glucose greater than 140 mg in type 2 diabetes; active kidney stone disease or kidney stones more than 2 times

in lifetime; chronic renal failure (serum creatinine >1.4 mg/dL); evidence of chronic liver disease including alcoholism; physical conditions like rheumatoid arthritis, osteoarthritis, and heart failure severe enough to prevent reasonable physical activity; having severe vitamin D deficiency; serum 25OHD <5 ng/mL (<12.5 nmol/L) or > 20 ng/mL (>50 nmol/L); body mass index (BMI) greater than 45 kg/m^2; serum calcium <10.3 mg/dL (>2.57 mmol/L) or 0.3 mg/dL (>0.075 mmol/L) more than the upper limit of normal on 2 baseline tests; 24-hour urine calcium greater than 290 mg/dL (7.25 mmol) on 2 baseline tests; and bone mineral density T-score less than −3 on spine or hip specific to race. Participants were also excluded if they were on bisphosphonates for more than 3 months in the past; had been taking fluoride, PTH, or derivatives, eg, teriparatide in the last 6 months; had previous treatment within the last 6 months with calcitonin or estrogen, chronic high-dose corticosteroid therapy (>10 mg/d) for more than 6 months; were currently on anticonvulsants (phenytoin, phenobarbital), high-dose thiazide therapy (>37.5 mg/d), and any drugs interfering with vitamin D metabolism; or the subjects were not able to give informed consent.

Recruitment was obtained from the local population by advertising the study in local newspapers, church bulletins, and social groups.

Randomization and interventions

African American women who met the eligibility criteria were randomly assigned to 1 of the 8 dose groups at the Creighton center or the Indiana center. The study design was double blind, ie, all staff that assessed outcomes was blinded to the treatment and only the statistician had access to the treatment code. The randomization method was randomized blocks, stratified by screening serum 25OHD level less than 15 vs 15 ng/mL or greater (<37.4 vs ≥37.4 nmol/L). The study statistician generated the randomization list with SAS software (SAS Institute Inc, Cary, North Carolina). Screening occurred throughout the year from January 2008 to January 2010.

Vitamin D_3, 400-, 800-, 1600-, 2400-, 3200-, 4000-, and 4800-IU capsules and matching placebo capsules were custom manufactured for the study (Douglas Labs, Pittsburgh, Pennsylvania). The actual vitamin D_3 concentrations in the capsules were measured independently in Dr Hector DeLuca's laboratory located at the University of Wisconsin (Madison, Wisconsin) every 6 months over 3 years. There was no significant change in potency over the time period. The actual content of vitamin D_3 was 503 IU in 400 IU, 910 in 800 IU, 1532 in 1600 IU, 2592 in 2400 IU, 2947 in 3200 IU, 4209 in 4000 IU, and 4937 in 4800 IU capsules, respectively. Every participant took 1 vitamin D_3 capsule in the morning after breakfast. A prestudy, 7-day dietary record was obtained to estimate calcium intake, and based on the results, calcium supplements (Citracal; Bayer Health Care, Morristown, New Jersey) were given to maintain a total calcium intake of 1200–1400 mg/d, and subjects were advised to take calcium tablets in divided doses. A central medication log maintained a record of all study drugs dispensed to the subjects. At the 3-, 6-, 9-, and 12-month visits, compliance was calculated by counting the pills returned and dispensing new study pills. At the same time, information was collected on concomitant medications and over-the-counter supplements. Subjects were not allowed to take other vitamin D supplements during study, and those who wanted to take multivitamins were provided free multivitamins without vitamin D (Kirkman multivitamin without vitamins A and D; Kirkman, Oregon, Washington).

At baseline subjects underwent a medical history; previously validated questionnaires were used for smoking history, alcohol use, caffeine intake, depression scale, sun exposure, physical activity, and fall and fracture history/incidence. Fasting blood samples were collected at all visits (baseline, 3, 6, 9, and 12 months between 0700 and 1000 h) and allowed to clot and then centrifuged at 4°C for 15 minutes at 2056 × g to separate serum. All samples were stored frozen at −70°C until analysis. A comprehensive panel including serum calcium, creatinine, complete blood count, and lipid profile was performed at baseline and 12 months. A basic metabolic panel was done at 3, 6, and 9 months. Serum 25OHD, serum

PTH and serum N-telopeptides were done at baseline and 6 and 12 months. In addition, 24-hour urine was collected at baseline and every 3 month for measurement of calcium and creatinine. Serum and urine chemistries were measured either at Creighton University Clinical Chemistry Laboratory or at the Indiana Medical Center using standard auto analyzer methodology. Indiana had a slightly higher (+0.2 mg/dL) upper normal range for serum calcium.

Serum 25OHD at screening is measured by RIA after an acetonitrile extraction in the bone metabolism laboratory using kits manufactured by Diasorin, Inc (Stillwater, Minnesota). Screening at Indiana University was performed at Indiana in Dr Peacock's laboratory using the Diasorin Liaison assay. All the Indiana blood samples collected at screening and 6 and 12 months were repeated in the Creighton Bone Metabolism Laboratory using the Diasorin RIA, and it is those values that are presented in this paper. The minimum detection range reported from Diasorin and in our laboratory is 5 ng/mL. The interassay variation is 9.8% and the intraassay variation is 9.2% in our laboratory.

The bone metabolism laboratory participates in the vitamin D External Quality Assessment Scheme (7), which is an international program for monitoring the accuracy and precision of 25OHD assays; our results were within ±1 SD of the all-laboratory trimmed mean. Serum intact PTH was measured by the Diasorin immunoradiometric assay. The limit for serum PTH detection range in our laboratory is 1.0 pg/mL. The interassay variation is 4.1% and the intraassay variation is 2.9%.

Dietary intake of calcium and vitamin D at baseline was collected in Omaha from 7-day food diaries assessed by a trained dietitian. At Indiana 4-day dietary records collected information only on calcium intake.

Outcomes

Primary outcomes of this study were serum 25OHD and serum PTH levels after 12 months. The dose-response effect of vitamin D_3 400, 800, 1600, 2400, 3200, 4000, and 4800 IU/d plus calcium was compared with a placebo plus calcium control group. Serum 25OHD and serum PTH were measured at baseline and 6 and 12 months. The results of secondary outcomes will follow in subsequent papers.

Adverse events information was collected at each visit and graded by intensity (ie, mild, moderate, severe) and relation to treatment.

For study purposes, hypercalcemia was defined as a fasting serum calcium that was greater than 0.3 mg/dL above the upper limit of the normal range, which is greater than 10.5 mg/dL in Omaha and greater than 10.8 mg/dL in Indiana at any visit. If hypercalcemia was noted, then fasting serum calcium was repeated within 2 weeks. If the repeat value was confirmed as high, calcium supplements were stopped and serum calcium repeated within a week. If serum calcium still remained high, then the study drug was discontinued.

Hypercalciuria was defined as 24-hour urine calcium greater than 400 mg (10 mmol) at any of the follow-up visits (this was based on the limit established for Caucasians). If hypercalciuria greater than 400 mg developed during the treatment period, 24-hour urine calcium was repeated within 2 weeks. If hypercalciuria persisted, then calcium supplements were discontinued and dietary calcium was rechecked. A repeat 24-hour urine was performed in 2–4 weeks, and if elevation persisted, then the study drug was discontinued. In a post hoc analysis, we used the baseline 24-hour urine calcium for African Americans to define their upper limit of 270 mg.

Statistical analysis

The study was powered to detect differences between the dose groups in 12-month serum 25OHD; a sample size calculation was not performed for PTH. For details of the power calculations, see our previous paper (2); the estimate was that 20 subjects randomized to each dose group would provide greater than 90% power to detect a difference between dose groups in a 1-way ANOVA model. NCSS

Trial and PASS software (Number Cruncher Statistical Systems, Kaysville, Utah) was used for the sample size calculation (8).

Analysis was done using a modified intent-to-treat procedure that included all subjects randomized. For subjects who dropped out or were removed from the study, their data were included in the modified intent-to-treat analysis if available.

Subject characteristics at baseline are summarized by dose group. Mixed-effects models were used to estimate dose-response curves for serum 25OHD and PTH. Dose and time (baseline, 6 and 12 months) were included as fixed effects, and the subject was included as a random effect. Quadratic terms were explored for dose as well as dose-by-time interactions. Dose was divided by 1000 to prevent numeric overflow in the model estimation. We also determined the dose that meets the RDA and EAR for serum 25OHD. This can be interpreted as the dose at which 97.5% of individuals will have a serum 25OHD greater than 30 ng/mL (75 nmol/L) or 20 ng/mL (50 nmol/L); 1000 bootstrapped samples were used to determine the 95% prediction limits for 12-month serum 25OHD levels. The dose at which subjects reach the RDA is the dose at which the 95% prediction lower limit is above the serum 25OHD threshold of interest. The estimate of the average requirement (EAR), the dose at which serum 25OHD is greater than the threshold in 50% of the subjects, was also found. The dose used in the analysis was the estimated dose and not the analyzed dose. Recalculation of the dose response curves using the actual measured vitamin D content vs the stated or estimated doses is not significantly different.

Multivariate mixed-effects models were examined for serum 25OHD and PTH, adjusting for known covariates based on clinical experience: age, BMI category, calcium intake, smoking status, alcohol use, average caffeine intake, serum creatinine, and season. We also compared the effect of race on outcome, including data from African American and Caucasian subjects (from reference 2) using a mixed-effects model to test for race and dose interactions. SAS software (SAS Institute) was used for the statistical analysis. R version 2.11.0 was used to create graphical displays. $P < .05$ is considered statistically significant.

Reports were sent to the Data and Safety Monitoring Board approximately every 6 months to monitor accrual and safety data including adverse events and serum and urine calcium data. No interim monitoring of the primary outcome was conducted.

Results

One hundred ten African American women (79 from Indiana and 31 from Omaha, Nebraska) were randomized; there were 19 withdrawals, leading to 83% eligible subjects completing the study (Figure 1). Initially subjects were randomized to 1 of 8 groups, but because of low enrollment, the number of groups was reduced to 5 and 79 subjects were randomized to 1 of 5 groups. Baseline characteristics for the 5 groups are shown in Table 1; however, data for all 8 groups are shown on the figures. The baseline characteristics show the fasting serum glucose was high and the percent of women with a fasting glucose greater than 100 mg was 47%. Mean BMI of 32.7 kg/m^2 was also high, so it is likely that many women had metabolic syndrome.

Mean compliance for calcium in Omaha was 79% and for Indiana was 70%. Mean compliance for vitamin D in Omaha was 91% and for Indiana was 81%.

Serum 25OHD

A mixed-effects model was used to estimate the dose-response curve of serum 25OHD. Model fit was examined with residual plots and the model was determined to fit well. The interaction between dose^2 and time was not significant ($P = .79$) and neither was the dose^2 term ($P = .60$), so these terms were excluded from the model. There was a significant interaction between dose and time, indicating a linear relationship between serum 25OHD and the dose that differs between at least 2 of the time points ($P <$

.0001). The slopes did not differ significantly between the 6- and 12-month curves ($P = .51$), nor did the intercepts ($P = .27$). The dose-response curves for the 6- and 12-month serum 25OHD were almost identical. The estimated dose-response curve at 12 months for serum 25OHD nanograms per milliliter is 25.54 ± 4.81dose/1000 (Figure 2). The analysis was repeated using the actual measured doses of vitamin D, and the results were the same (Supplemental Figure 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

The mixed-effects model was used to determine the 95% prediction limits for the 12-month serum 25OHD levels (1 outlier subject was excluded to get more accurate predictions). The lower prediction limit was used to determine where 97.5% of individuals have predicted serum 25OHD greater than 20 ng/mL (50 nmol/L) (as recommended by the IOM), and we found that an individual would require a dose of 800 IU/d to obtain that RDA (a dose of 1600 IU is required to obtain a RDA level of 30 ng/mL or 75 nmol/L). To estimate the dose that obtains the EAR, we want 50% of new individuals to obtain a serum 25OHD level greater than 20 ng/mL (50 nmol/L), a dose between 0 and 400 IU/d is required. At a dose of 800 IU, the median predicted value would be greater than 30 ng/mL (75 nmol/L) for a new individual.

Effect of race

We considered all the data from the ViDOS study including both the Caucasian and African American subjects in 1 model, conducting the originally planned analysis for a race-by-dose interaction. The analysis of Caucasian data in its entirety is reported elsewhere (2). The mixed-effects model showed that none of the interactions between race × dose, race × dose^2, race × time × dose, or race × time × dose^2 were statistically significant (all $P > .10$). There was a marginal interaction between racetime ($P = .075$), but after adjusting for BMI, the racetime interaction was no longer significant ($P = .17$). Therefore, we can conclude that the effect of dose on serum 25OHD does not depend on race. Figure 3 shows the result of the Caucasian analysis at 12 months, with 95% prediction limits superimposed on the African American data. From this plot we can see that the African American results are similar to the Caucasian models. We show the Caucasian data and African American models on the same graphs separately by BMI groups, and again the results are similar between Caucasian and African American subjects (Supplemental Figures 2 and 3).

The mixed-effects models of the dose response described above were adjusted for clinically important covariates. Final covariates included in the model were age, BMI, total calcium intake (diet + supplements), smoking status, alcohol use, serum creatinine, and season. Interactions between dose and covariates were explored and nonsignificant interactions were excluded. Total calcium intake and the interaction between BMI and dose are significant covariates in the multivariate model. While holding other covariates fixed in the multivariate model, a 1000-mg increase in total calcium intake results in a 3.8-ng/mL increase in serum 25OHD ($P = .011$). At the 12-month time point, in the group of BMI less than 30 kg/m^2, if dose of vitamin D is increased by 1000 IU, then serum 25OHD is increased on average by 5.2 ng/mL. At the 12-month time point, in the group of BMI of 30 kg/m^2 or more, if dose of vitamin D is increased by 1000 IU, then serum 25OHD is increased on average by 4.1 ng/mL. The slope of the dose-response curve is 1.14 ng/mL greater in the group of BMI less than 30 kg/m^2 than the group of BMI of 30 kg/m^2 or more [95% confidence interval (CI) 0.14–2.15 ng/mL, $P = .026$].

PTH results

One hundred nine subjects had serum PTH levels at baseline, 95 at 6 months, and 91 at 12 months. The residual plots for the PTH model indicated PTH on the log10 scale had a better fit. In the mixed-effects model for PTH, the dose × time interaction was not significant, indicating the effect of dose on PTH does not differ with time ($P = .36$). The interaction was excluded from the model, and we found that $\log_{10}$ PTH differs significantly over time ($P < .0001$) but does not differ significantly with dose ($P = .75$) (Figure 4). We reanalyzed the data using the actual measured amounts of vitamin D, and the results

were the same (Supplemental Figure 4). PTH levels were on average 6.4 ng/L higher at baseline than at 12 months. There was no difference in PTH levels between 6 and 12 months (P = .26). The estimated dose-response curve at 12 months for $\log_{10}$ serum PTH is 1.50–0.0039 × dose/1000, with the slope showing a nonsignificant decrease in $\log_{10}$ serum PTH as dose increases. When looking at the multivariate mixed effects model for PTH, the results are similar to those in the unadjusted model but with a significant effect of serum creatinine on PTH; a 1-mg/dL in serum creatinine results in a 0.20 $\log_{10}$ increase in PTH (95% CI 0.03–0.36, P = .20).

We also examined the model looking at serum PTH with time and serum 25OHD as predictors in a mixed-effects model. Serum 25OHD is a significant predictor of serum PTH but not time (P = .46). A 1-ng/mL increase in serum 25OHD resulted in a −0.0036 decrease in $\log_{10}$ PTH (95% CI −0.0057 to −0.0015, P = .0008). This result is similar to that in Caucasians, and the regression lines are parallel but not significant (P = .85) (Figure 5). The results for serum 25OHD and serum PTH were similar in the analysis with only the 5 doses completely enrolled (data not shown). To summarize, there was no significant effect of vitamin D dose on serum PTH; however, there was a significant reduction in serum PTH with increasing serum 25OHD.

Safety and adverse events

There was 1 serious adverse event, a cerebral hemorrhage, in a subject on 1600 IU and was thought to be unrelated to treatment. Minor adverse events were equally distributed within the dose groups. Hypercalcemia defined as serum calcium above the upper normal limit occurred in 7% of women subjects, with a total of 12 events. There was no correlation between vitamin D dose and hypercalcemia. The incidence of hypercalciuria was15% based on an upper normal limit for 24-hour urine calcium of 270 mg. There was no correlation between the vitamin D dose and hypercalciuria. There was no effect of thiazides on the incidence of hypercalcemia or hypercalciuria.

There were no significant changes among groups in serum creatinine, blood urea nitrogen, liver enzymes, or glucose.

Discussion

The primary finding of this first randomized, controlled, dose-response study of vitamin D in older African American women was that the increase in serum 25OHD after vitamin D supplementation in African American women was similar to that seen in the Caucasian women, and there were no significant differences between serum 25OHD levels at any dose (no interaction between race and dose). In Caucasians the response followed a quadratic curve and might have been the same in African Americans had there been more subjects in 8 dose groups rather than 5. There was considerable variability in the serum 25OHD response to vitamin D that in part can be attributed to differences in BMI.

There have been few long-term dose-response studies in African American women. In a bone loss study by Aloia et al (9), African American women were randomized to placebo or vitamin D 800 IU for 2 years, and then the dose was increased to 2000 IU for a third year. Mean serum 25OHD at baseline was 18 ng/mL and increased to 28 ng/mL on 800 IU and to 35 ng/mL on 2000 IU, and these reported levels are similar to those seen in this study (10). In another 6-month study of Caucasian and African American women and a small number of men aged 45–52 years, an algorithm was used to adjust subjects' 25OHD levels to greater than 30 ng/mL with escalating doses of vitamin D 2000–4000 IU/d (11). They found wide variability in response to dosing and no difference in serum 25OHD between Caucasian and African Americans. Part of the variability can be attributed to differences in body weight. We had shown previously in Caucasian women that women with normal BMI less than 25 kg/m^2 had higher serum levels of 25OHD compared with women with a BMI greater than 25 kg/m^2 (2). There were no African American women with a BMI less than 25 kg/m^2, so a direct comparison cannot be

made, but serum 25OHD levels in African Americans with a BMI greater than 25 kg/m^2 are similar to those in Caucasian women with a BMI greater than 25 kg/m^2.

Other factors that have been shown to affect serum 25OHD levels are genes involved in vitamin D metabolism, particularly genes that affect metabolism of vitamin D, CYP2R1 enzyme that converts vitamin D to 25OHD in the liver, and CYP24A1 enzyme that converts 25OHD to 24,24-dihydroxyvitamin D (12). Two other genes are *GC*, which produces the transport protein for vitamin D and its metabolites, and the gene controlling 7-dehydrocholesterol formation in skin. The latter has been linked to lower serum 25OHD, but there is no information yet on whether this gene is different in people with darker skin color but may be very relevant because darker skin is associated with lower serum 25OHD.

There was a small positive association between the total calcium intake and serum 25OHD level; the multivariate model showed a total calcium intake of 1000 mg was associated with an increase in serum 25OHD of 3.8 ng/mL. A similar result was reported in a study giving a calcium supplement of 1000 mg daily, and the authors suggested that calcium may slow the metabolism of 25OHD (13).

It is known that in Caucasian women low serum 25OHD levels can cause secondary hyperparathyroidism and at serum 25OHD levels below 20 ng/mL increase bone resorption (6). In this study we found that secondary hyperparathyroidism associated with low serum 25OHD occurs similarly in African American women. After vitamin D supplementation, there was a decrease in serum PTH, although there was no clear dose effect, but once the data were analyzed in terms of the final serum 25OHD level, we found a significant inverse correlation indistinguishable from the response in Caucasian women. A previous study of African American women was shown to have higher serum PTH at higher serum 25OHD levels compared with Caucasian women, although this was not seen in our study (14).

This study was designed to provide information about the RDA for African American women. Our end point was based only on the vitamin D response effect on serum 25OHD. The results in this paper show that a vitamin D dose of 800 IU/d increases serum 25OHD greater than 20 ng/mL in 97.5% of the African American women. These results are identical with those reported in our study of Caucasian women (2) and are in line with the recommendations of the IOM committee (1). Recently the IOM, in assessing the available evidence, was unable to find any clinical data other than meta-analysis of fracture studies that supports a serum 25OHD greater than 20 ng/mL in Caucasian women (15–18).

There are almost no data on clinical studies of vitamin D in African Americans that give guidance on an optimum level of serum 25OHD in African Americans. A 3-year trial of vitamin D on bone loss that started with a vitamin D dose of 800 IU/d for 2 years and then increased the dose to 2000 IU/d in the third year showed an increase in serum 25OHD from 17 ng/mL to 35 ng/mL, but there was no difference in the rate of bone loss between placebo and either vitamin D dose 800 or 2000 IU of vitamin D after 3 years (8). In a cohort fracture study of African American and Caucasian women, it was shown that there was an increase in nonvertebral fractures in the African American group when serum 25OHD level exceeded 20 ng/mL, in contrast to the Caucasian group that showed a decrease in fractures (19). Thus, RDAs based on clinical end points may be different according to ethnicity.

With regard to the safety of vitamin D and calcium, our results show that the effects on serum and urine calcium results show some differences between Caucasian and African American women. In Caucasian women we reported that the incidence of hypercalciuria greater than 300 mg occurred in 33% of women (2) compared with 9% in this study of African Americans. The incidence of hypercalcemia was similar between the races but less severe in African American women, that is, there were fewer high values. Their mean calcium intake adjusted for compliance was 1098 mg/d that is lower than that in the Caucasian group, a mean of 1270 mg/d (2), and this might account for part of the difference.

The strengths of this study were the study design with adequate power to detect differences in terms of final serum 25OHD across a range of dose groups from 400 to 4800 IU daily. This is the first multiple-dose response randomized controlled trial conducted in African Americans. There are some limitations of the current study. The sample sizes are relatively small for each dose group. Furthermore, because this study was conducted in healthy older women, the results may not apply to other ethnic groups or those with disease. The highest dose of vitamin D used in ViDOS was 4800 IU/d, and the effect of higher doses on the dose response curve are not known. Also, because of the algorithm used to manage hypercalcemia, the incidence of hypercalcemia may be underestimated.

Serum 25OHD levels are lower in African Americans compared with Caucasians (3). In a North American study of 966 African Americans and 1602 Caucasians aged 74 years, the mean serum 25OHD was 21 ng/mL in African Americans compared with 29 ng/mL in Caucasians. Fifty-four percent of values were less than 20 ng/mL in African American compared with 18% in Caucasians, and there were fewer values greater than 30 ng/mL in African Americans, 16%, compared with 44% in Caucasians (4).

When the dose response of vitamin D on serum 25OHD in African American women is compared with that of Caucasian women, the increase in serum 25OHD after vitamin D supplementation is similar. Vitamin D 800 IU daily increased serum 25OHD 20 ng/mL (>50 nmol/L) in 97.5% of African American women, similar to results reported by us in Caucasian women (2), suggesting that the RDA for vitamin D is the same as that proposed by the IOM (1). The implication therefore is that the absorption and metabolism of vitamin D are similar in African American and Caucasian women. Although serum levels of serum 25OHD are usually much lower in African Americans, it is most likely because of decreased formation of vitamin D in skin.

Supplementary Material

Supplemental Data:

Acknowledgments

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Footnotes

Abbreviations:

BMI body mass index
CI confidence interval
EAR estimated average requirement
IOM Institute of Medicine
25OHD 25-hydroxyvitamin D
RDA recommended dietary allowance
ViDOS Vitamin D supplementation in Older Subjects.

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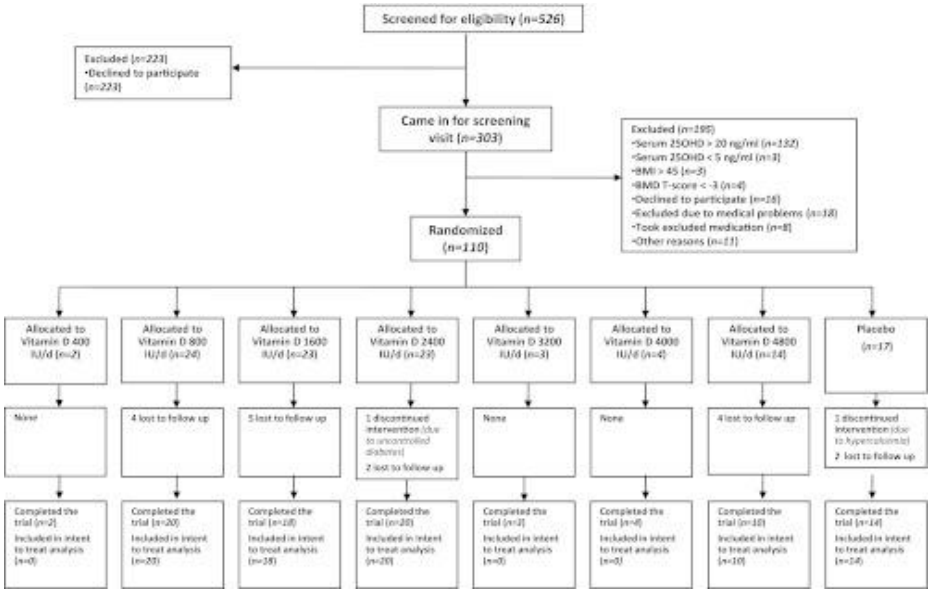
Figures and Tables

Figure 1.



Consort flow chart for study participants. BMD, bone mineral density.

Table 1.

Baseline Characteristics: Mean (SD)

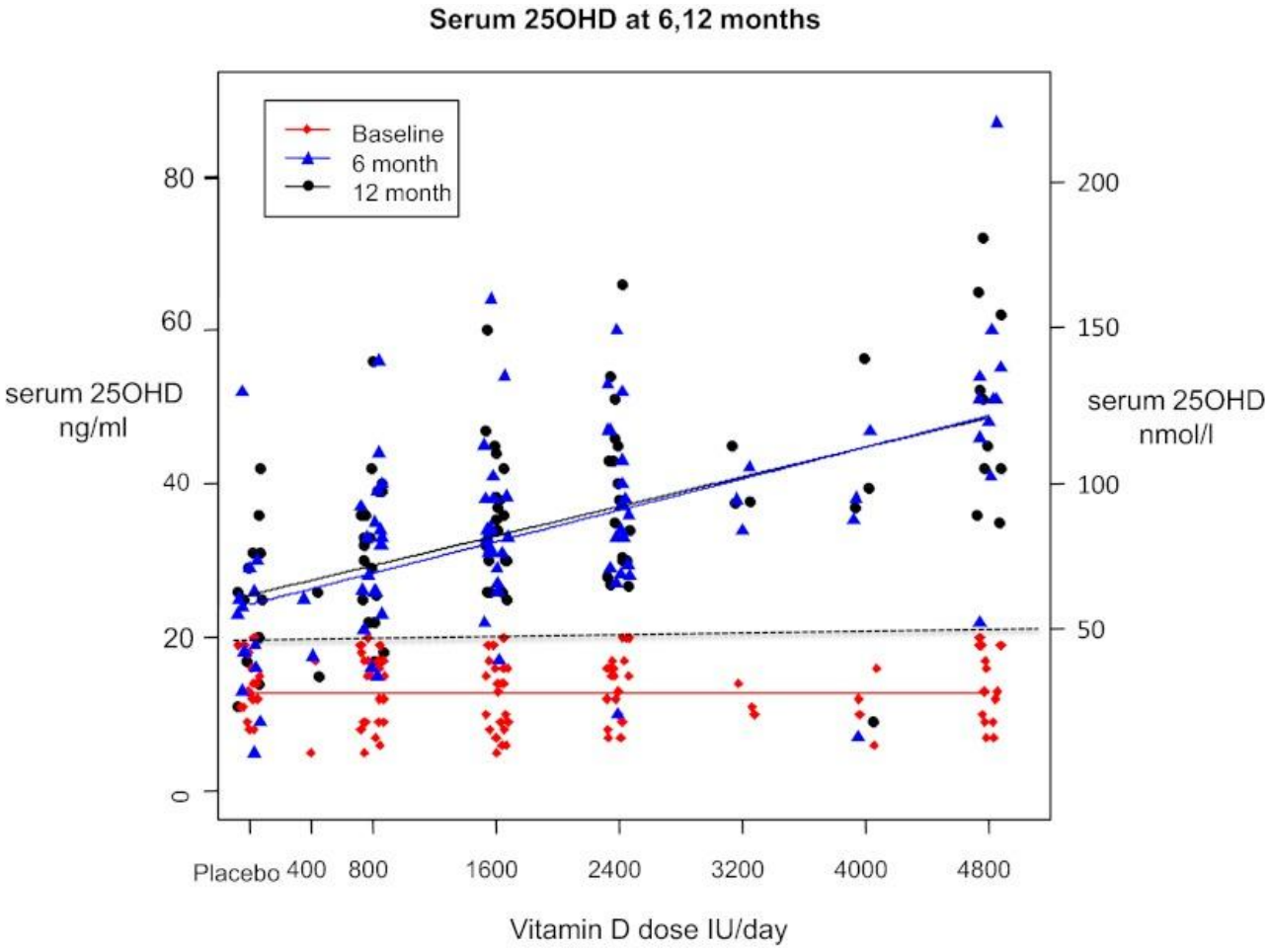
	All Subjects[a] (n = 110)	Dose Placebo (n = 17)	Dose 800 IU (n = 24)	Dose 1600 IU (n = 23)	Dose 2400 IU (n = 23)	Dose 4800 IU (n = 14)
Age, y	66.6 (7.5)	66.6 (6.9)	69.3 (8.9)	67.1 (6.2)	64.0 (6.5)	65.6 (6.5)
Weight, kg	85.4 (17.7)	81.6 (18.6)	85.1 (15.3)	83.0 (19.8)	87.9 (19.3)	93.2 (14.8)
BMI, kg/m^2	32.7 (7.0)	31.4 (6.1)	32.1 (5.4)	32.3 (9.6)	35.0 (7.4)	33.3 (5.5)
Serum calcium, mg/dL	9.4 (0.4)	9.3 (0.5)	9.4 (0.4)	9.4 (0.4)	9.4 (0.4)	9.4 (0.2)
24-Hour urine calcium, mg	85.8 (63.2)	91.1 (72.5)	78.7 (55.8)	63.9 (56.0)	97.0 (58.8)	97.5 (82.8)
Serum creatinine, mg/dL	0.90 (0.22)	0.96 (0.23)	0.96 (0.26)	0.89 (0.19)	0.82 (0.21)	0.90 (0.19)
Serum alkaline phosphatase, IU/L	79.4 (21.0)	81.0 (29.1)	81.9 (19.0)	79.7 (21.7)	77.3 (15.6)	77.3 (20.4)

Serum glucose, mg/dL[b]	106 (36.0)	101 (52.5)	111 (36.6)	109 (39.1)	103 (25.6)	109 (35.8)
Serum AST, IU/L[c]	24 (12.2)	27 (27.6)	23 (6.6)	24 (6.4)	23 (7.5)	23 (7.9)
Serum ALT, IU/L	20 (15.2)	25 (35.7)	18 (6.1)	20 (8.5)	21 (7.7)	22 (7.8)
Serum 25OHD level, ng/mL	13.2 (4.3)	13.6 (3.8)	13.5 (4.6)	12.5 (4.7)	13.8 (4.0)	13.6 (4.7)
Serum PTH, pg/mL	43.0 (19.9)	43.1 (17.6)	42.1 (23.0)	37.3 (16.3)	46.1 (24.5)	44.3 (16.8)
Diet calcium intake, mg/d	551 (221)	540 (190)	604 (282)	523 (197)	529 (231)	584 (210)
Current drug use						
Thiazide use	43 (39%)	10 (59%)	10 (42%)	11 (48%)	7 (30%)	4 (29%)
Diuretic use	6 (5%)	0 (0%)	3 (13%)	1 (4%)	0 (0%)	1 (7%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

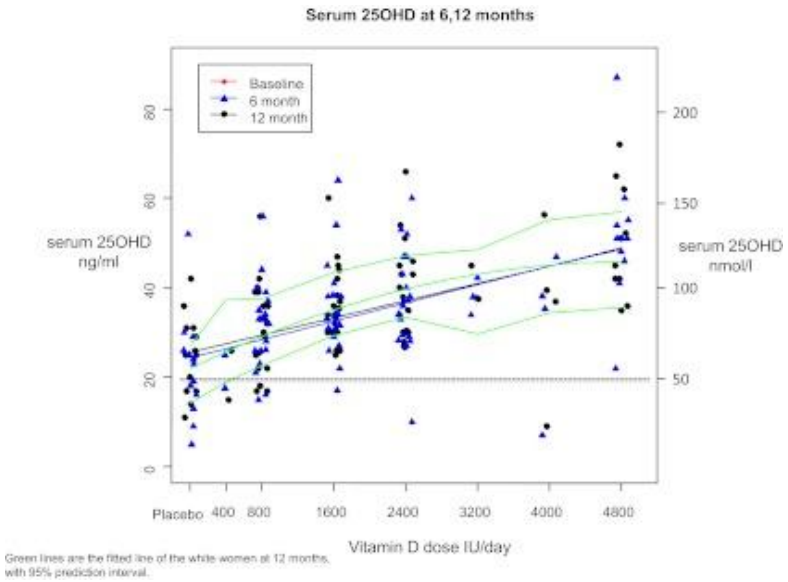
[a]Two subjects in the 400-IU group, 3 in the 3200-IU group and 4 in the 4000-IU group are included in the all-subjects column of the table but are not included as individual columns in the table due to small sample sizes.
[b]Serum glucose was higher in the Omaha group ($P = .019$).
[c]Serum AST was higher in the Indiana group ($P = .009$).

Figure 2.



Vitamin D dose response curve. Final and 6-month serum 25OHD levels (nanograms per milliliter and both nanomoles per liter) are presented according to the dose of vitamin D IU/d or placebo. Serum 25OHD at 6 and 12 months was significantly lower in the placebo group compared with all the vitamin D dose groups individually ($P < .05$). The blue line is the regression line for 6-month serum 25OHD values, and the black line is the corresponding regression line for the 12-month values The red diamonds represent the values at baseline for each group.

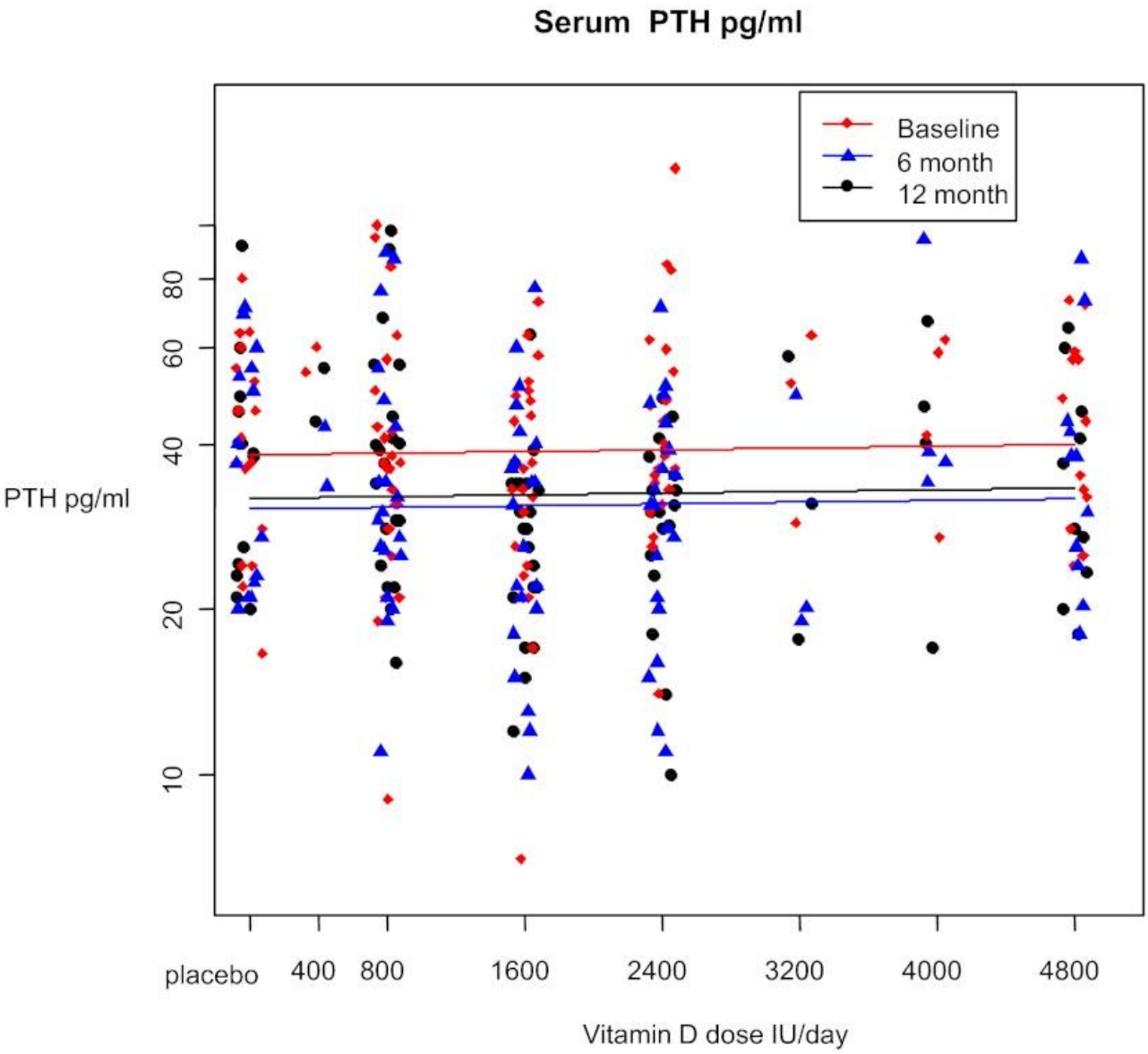
Figure 3.



African American data superimposed on the vitamin D response curve for Caucasians represented by the green

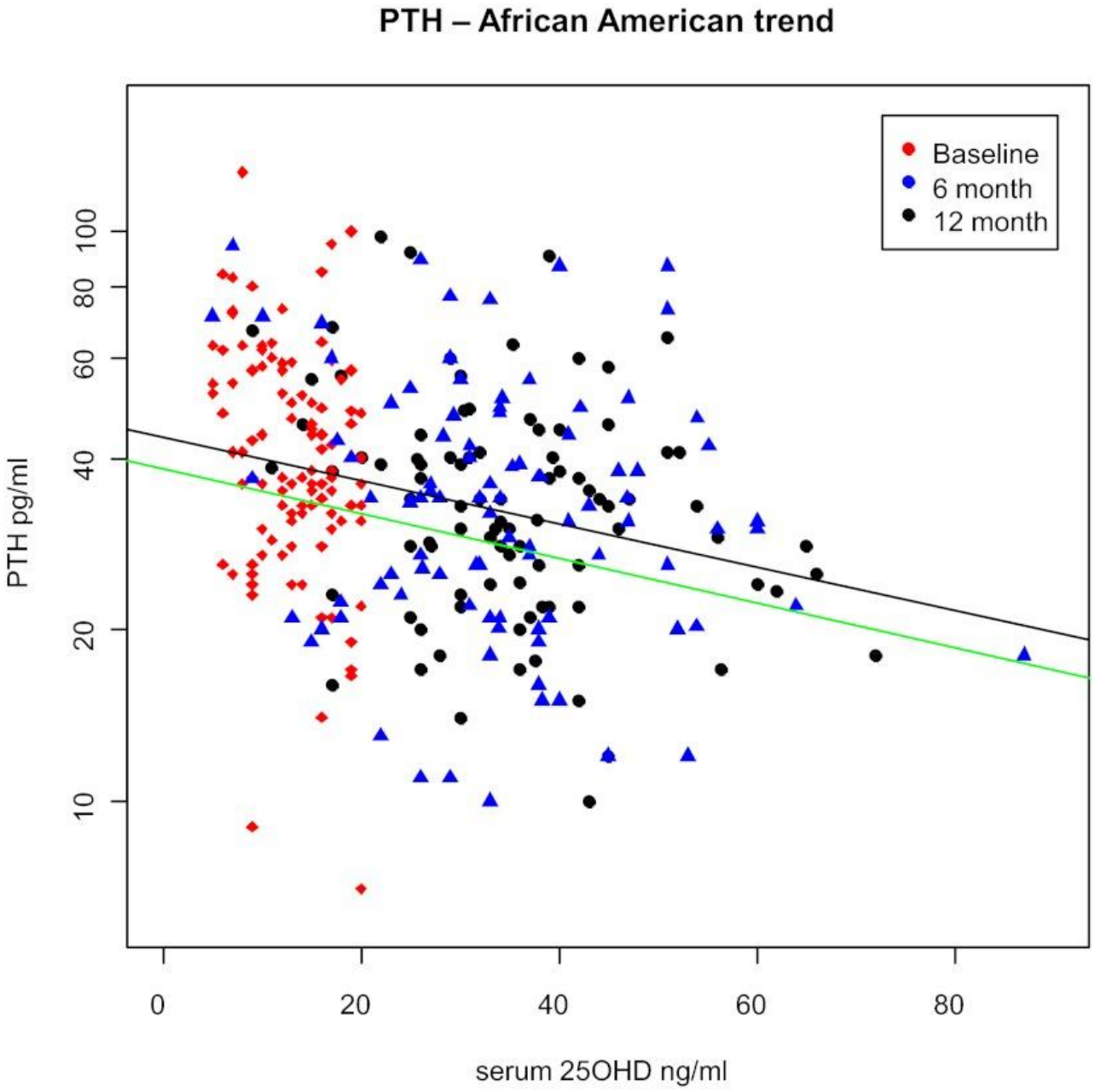
lines. The green lines are the 95% prediction intervals for the Caucasian data derived from a published report (2). The blue and black lines are the regression lines for 6- and 12-month serum 25OHD values.

Figure 4.



Effects of different doses of vitamin D or placebo on serum PTH levels (picograms per milliliter) at 12 months. There is no significant effect of dose on serum PTH. The regression lines are shown for baseline data (red), 6-month values (blue), and 12-month values (black).

Figure 5.



Effect of different doses of vitamin D on serum PTH (picograms per milliliter) at 12 months according to the serum 25OHD (nanograms per milliliter). There is a significant decrease in serum PTH with increasing serum 25OHD level (P = .008). The regression lines for African American values are shown as a black line; log PTH = 1.6387−0.00381serum 25OHD and the regression line for Caucasian values as a green line; log PTH = 1.5833−0.00392serum 25OHD (data for Caucasians is from reference 2).