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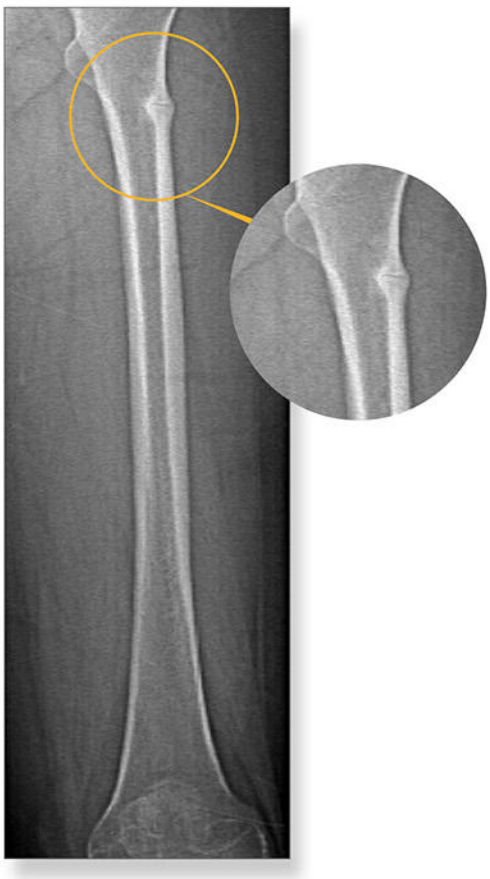

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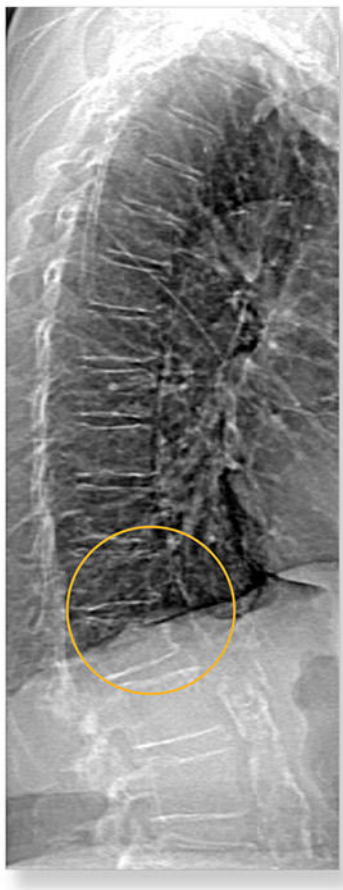

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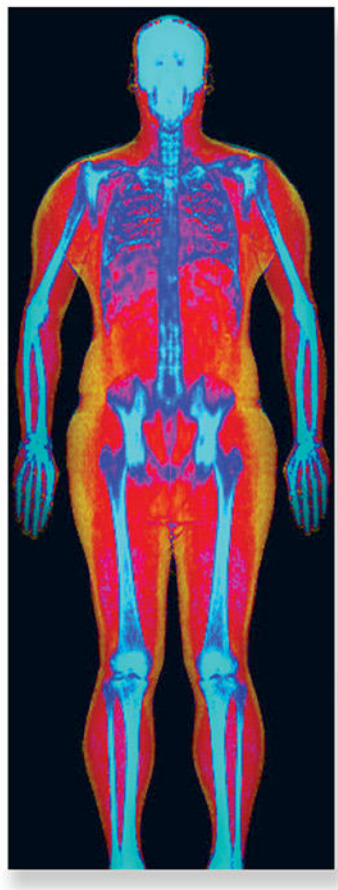

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ORIGINAL ARTICLE

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Vitamin D Supplementation in Elderly Black Women Does Not Prevent Bone Loss: A Randomized Controlled Trial

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ABSTRACT

Black Americans have lower levels of serum 25(OH)D but superior bone health compared to white Americans. There is controversy over whether they should be screened for vitamin D deficiency and have higher vitamin D requirements than recommended by the Institute of Medicine (IOM). The purpose of this trial was to determine whether Vitamin D supplementation in elderly black women prevents bone loss. A total of 260 healthy black American women, 60 years of age and older were recruited to take part in a two-arm, double-dummy 3-year randomized controlled trial (RCT) of vitamin D_3 versus placebo. The study was conducted in an ambulatory clinical research center. Vitamin D_3 dose was adjusted to maintain serum 25(OH)D above 75 nmol/L. Bone mineral density (BMD) and serum were measured for parathyroid hormone (PTH), C-terminal crosslink telopeptide (CTX), and bone-specific alkaline phosphatase (BSAP) every 6 months. Baseline serum 25(OH)D_3 was 54.8 ± 16.8 nmol/L. There was no group $\times$ time interaction effect for any BMD measurement. For all BMD measurements, except for total body and spine, there was a statistically significant negative effect of time ($p < 0.001$). An equivalency analysis showed that the treatment group was equivalent to the control group. Serum PTH and BSAP declined, with a greater decline of PTH in the treatment group. The rate of bone loss with serum 25(OH)D above 75 nmol/L is comparable to the rate of loss with serum 25(OH)D at the Recommended Dietary Allowance (RDA) of 50 nmol/L. Black Americans should have the same exposure to vitamin D as white Americans. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; DISEASES AND DISORDERS OF/RELATED TO BONE; CLINICAL TRIALS; BIOCHEMICAL MARKERS OF BONE TURNOVER; BONE MODELING AND REMODELING; PTH/VIT D/FGF23; CELL/TISSUE SIGNALING; ENDOCRINE PATHWAYS; DXA; ANALYSIS/QUANTITATION OF BONE

Introduction

In 2011, the Institute of Medicine (IOM) issued a report that established the Recommended Dietary Allowance (RDA) for vitamin D at 600 IU for adults and 800 IU/day for the elderly (>70 years).[1–3] The RDA-associated serum 25(OH)D (the accepted biomarker of vitamin D exposure) is 50 nmol/L (20 ng/mL). The IOM report recognized the limited availability of data for subpopulations, such as black Americans. It concluded that there was no evidence to recommend a different RDA for various races or ethnic groups. It has been noted that black Americans have lower serum 25(OH)D yet have higher bone mass and less fractures than white Americans. This has been referred to as the vitamin D "paradox."[4]

Shortly thereafter, the Endocrine Society published a guideline for those at risk for vitamin D deficiency.[5] They considered black Americans a vulnerable population since they had lower serum 25(OHD levels. They recommended that black Americans be screened with a serum 25(OH)D measurement and supplemented with a higher intake of vitamin D than recommended by the IOM. Their goal was to achieve serum 25 (OH)D concentrations above 75 nmol/L.

Vitamin D_3 supplementation of 800 IU/day, 1000 IU/day, and 2000 IU/day does not reduce bone loss in postmenopausal black American women compared to placebo.[6,7] However, it has been suggested that these intakes or a serum 25(OH)D of 50 nmol/L (the value associated with the RDA) may not be high enough to produce the desired effects of vitamin D.[5,8–10] We measured the influence of vitamin D on bone density loss in black American women in a randomized clinical trial (RCT). Dosage of vitamin D_3 was adjusted to sustain a serum 25(OH)D level above 75 nmol/L (30 ng/mL). The primary question asked

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Public clinical trial registration: http://clinicaltrials.gov/show/NCT01153568. Vitamin D and Osteoporosis Prevention in Elderly African American Women: A 4-year Randomized, Double-blind, Placebo-controlled Study to Investigate the Effect of Vitamin D Status in Elderly African American Women.
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was the following: Does maintenance of serum 25(OH)D above 75 nmol/L prevent bone density loss from the total femur compared to placebo?

Subjects and Methods

The physical performance, osteoporosis prevention, and vitamin D in older African Americans (PODA) study is a prospective, randomized, double-blind, placebo-controlled, 3-year clinical trial of vitamin D_3 supplementation in black American women older than 60 years of age. Baseline demographics and laboratory values have been reported in detail.[11] Participants were self-declared as black. Written informed consent was obtained from each participant and the trial was approved by the Winthrop IRB and monitored by a Data Safety Monitoring Board appointed by the National Institute of Aging. The trial was registered at www.clinicaltrials.gov as NCT011533568.

Healthy participants were recruited from the Long Island community by direct mail, e-mail to hospital employees, and presentations at black churches and events. The study was conducted in an ambulatory Clinical Research Center of an academic health center. After screening, those who consented and qualified were randomly allocated to one of two groups: vitamin D_3 supplementation or placebo. Inclusion criteria were healthy ambulatory women who were self-declared as black Americans, with serum 25(OH)D greater than 20 nmol/L and less than 65 nmol/L. Block randomization with a block size of four was performed at baseline using a computer generated (SAS Proc Plan; SAS Institute, Inc., Cary, NC, USA) randomization list. We recruited 260 participants. In the original study design, power was determined based on previous studies and a differential BMD rate of change of 0.18% or greater per year.

Participants returned for follow-up visits every 3 months with bone density and biochemical measurements at baseline and every 6 months for 36 months.

Participants were given either a single capsule of vitamin D_3 or matching placebo (depending on allocation) to take once daily. The initial dose was based on serum 25(OH)D. Every 3 months, the vitamin D_3 dose was adjusted to the nearest 30 μg to maintain serum 25(OH)D above 75 nmol/L. The dose assignments were made in real time by the research pharmacist in consultation with the Data Coordinating Center. As doses for the active patients were titrated up or down, the blind was maintained by randomly adjusting the placebo doses to match the distribution of changes in the active patients who were at the same point in the study.

The study drug was manufactured by Alcrea Health (Pittsburgh, PA, USA) in two batches. Vitamin D_3 was available in doses of 60, 90, and 120 μg (2400, 3600, and 4800 IU, respectively). The capsules were analyzed in batches for their actual content at an independent laboratory. Calcium supplements ($CaCO_3$) were provided, if needed, based on dietary recall to achieve a total dietary intake of 1200 mg/day in all participants.

Measurement of serum 25(OH)D was performed in a commercial laboratory using a immunochemiluminometric assay on a DiaSorin Liaison instrument to achieve rapid turnaround (Labcorp, Burlington, NC, USA). Serum samples were stored at –40°C and assayed at baseline and annually for vitamin D metabolite by the Department of Laboratory Medicine at the University of Washington (Seattle, WA, USA; PMID: 22968104, 21768219). Concentrations of 25(OH)D_3 were standardized to NIST SRM 972a (PMID: 27091017, 22141317). The coefficient of variation (CV) of 25(OH)D_3 measurement is 3.54% to 4.41%.

Measurement of serum intact PTH was performed by Immulite 2000 Analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). The CV is 1.34%. Serum bone-specific alkaline phosphatase (BSAP) and serum C-telopeptide of type-1 collagen (CTX) were measured by a one-step enzyme-linked immunosorbent assay (ELISA), Micro Vue BAP (Quidel Corp., San Diego, CA, USA). Serum bone alkaline phosphatase was measured by Micro Vue BAP. The intraassay CV was 5% and the interassay CV was 6%. The kit for serum CTX was manufactured by Nordic Bioscience Diagnostics A/S (Herlev, Denmark). The intraassay CV of the CTX assay was 5.4%, and the interassay CV was 6.5%. Serum and urinary calcium were measured by O-Cresolphthalein complex using automated equipment Dimension-RXL (Dade, DE, USA).

The primary specified endpoint for this study was change in BMD of the total femur. Other bone density measurements included: BMD of the trochanter and femoral neck, anteroposterior (AP) spine, total body, and nondominant radius. BMD was measured at baseline and every 6 months on a Hologic Discovery A instrument, Marlborough, MA. Previous center-specific studies of precision determined the least significant difference (LSC = 2.77 times the root mean-square standard deviation) to be 0.018 g/cm^2 (or a 2% decline) for total femur, the primary outcome of this study. A decline in total femur BMD from baseline that is past the LSC is considered statistically significant at the 0.05 level.

Statistical methods

Any participant that was randomized and received at least one dose of study medication was included in the intention to treat population. Descriptive statistics for continuous variables are reported as mean values with standard deviation (SD) or median values with interquartile range (IQR) depending on the skew of the data and whether normality may be assumed; for categorical variables, values are reported as frequency and proportions. Yearly percent changes from baseline for all BMD outcomes are presented along with 95% confidence intervals, stratified by treatment group. Correlations between continuous variables were examined via Spearman correlation coefficients and presented with 95% confidence intervals obtained via Fisher's Z transformation. Differences between treatment groups with respect to BMD outcomes were assessed via linear models using generalized estimating equations (GEEs) and an autoregressive correlation structure to account for within-patient correlation between BMD measurements taken over time. In the initial primary analysis, each BMD measurement was regressed onto baseline BMD level, time, and the interaction between treatment group and time to determine whether a statistically significant treatment effect was observed with respect to BMD changes over time. The original study hypothesis was that the actively treated group would have a slower rate of BMD loss over the 3-year study period.

The proportion of patients exhibiting statistically real changes in our primary outcome of total femur BMD was assessed by computing the proportion of participants with a 36-week total femur BMD decline greater than the LSC. Time to target 25(OH)D_3 level was computed by assessing the first study visit where serum 25(OH)D_3 exceeded 75 nmol/L. All model and other p values presented are two-sided and p values <0.05 were considered statistically significant. SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

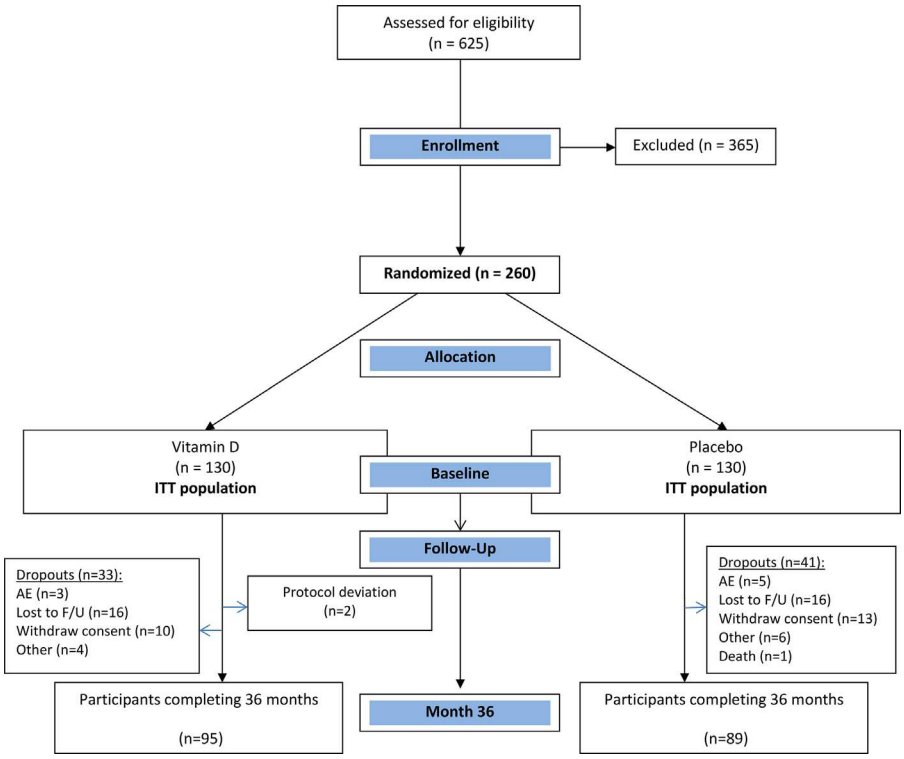

Fig. 1. Flow diagram for the study. 215 of the 365 exclusions were due to having a high 25(OH)D level. In both the placebo and vitamin D_3 group, none of the dropouts were due to a gastrointestinal complaint. One dropout in the vitamin D_3 group represents a subject found to have primary hyperparathyroidism at the 3-month visit. Dropouts designated as "other" were due to relocation out of the state or country, general health issues, and one subject who was withdrawn by the PI after having gastric bypass surgery, as this would affect vitamin D absorption.

Results

Flow diagram

A flow diagram for the study is given in Fig. 1. The first participant was randomized on December 8, 2010 and the last 36-month visit was June 13, 2016. In the placebo group, there were 41 dropouts. In the vitamin D group, there were 33 dropouts; one subject was found to have primary hyperparathyroidism. One subject in the placebo group died due to cardiorespiratory failure. Eighty-nine subjects in the placebo group and 95 subjects in the vitamin D group completed the 36-month study.

Baseline demographics and laboratory studies

The average age was 68.2 years and the BMI was 30 kg/m^2 (Table 1). There were no statistically significant differences between assigned groups. Serum 25(OH)D values reported were obtained from liquid chromatography–tandem mass spectrometry (LC-MS/MS).

Baseline values for serum 25(OH)D_3 are given in Table 1. Values (mean $\pm$ SE) for 12, 24, and 36 months in the active group were 108 ± 2.3, 113.8 ± 2.9, and 117 ± 2.9 nmol/L, respectively. Corresponding values for the placebo group were 48 ± 2.0, 49 ± 2.1, and 51 ± 2.7 nmol/L; 90% of the active group maintained serum 25(OH)D above 75 nmol/L. The mean dose of vitamin D_3 in the active arm was 3490 ± 1465 IU/day. Serum calcitriol increased by 10% at 36 months in the treatment group. Serum calcium did not change in either group. Overall compliance from pill count was 85% for the entire study.

Both PTH and BSAP decreased linearly in both groups with no interaction effects between treatment group and time. CTX was marginally associated with time in the active group ($p = 0.04$), but there was no difference between groups (Supporting Table 1).

Bone density measurements

For total femur BMD, the average 3-year absolute and percent decline in BMD from baseline in the placebo arm was –0.022 g/cm^2 and 2.5%, respectively compared to –0.016 g/cm^2 and 1.7% in the active treatment group (Fig. 2*A–D*); the difference in BMD loss over time between the two treatment arms was not statistically significant ($p = 0.08$). In each treatment group, the same proportion of participants declined past the total femur LSC by the 36 month visit (50% in each group) with an average decline from baseline in these patients of 0.039 g/cm^2 in the active group versus 0.041 g/cm^2 in the placebo group ($p = 0.55$). Similarly, across all BMD sites there were no statistically significant treatment effects, meaning that BMD changes over time were similar regardless of treatment. As a result, the final model for each BMD measurement consisted of baseline bone density levels and a main effect of time.

Given that this was a randomized clinical trial the primary a priori analysis presented is the estimation of the unadjusted treatment effect on total femur BMD at 3 years. As expected, there was broad baseline balance across treatment groups with respect to potential confounders (Table 1), thus adjustment for these variables in the model was deemed unnecessary.

Based on these final models, for all BMD measurements except for total body BMD and spine, there was a statistically

Table 1. Demographics and Baseline Characteristics

Characteristics	Active ($n = 128$)	Placebo ($n = 130$)	Overall ($n = 258$)	p
Demographics and behavioral, median (IQR)				
Age (years), median (IQR)	67.8 (65.3–71.2)	69.0 (65.4–73.4)	68.2 (65.4–72.5)	0.233
BMI (kg/m^2), median (IQR)	30.1 (26.4–34.4)	29.9 (26.8–33.9)	30.0 (26.5–34.0)	0.936
Calcium intake (mg), median (IQR)	814.0 (600.0–1142)	826.5 (628.0–1185)	826.5 (614.0–1157)	0.775
Bone density				
Total hip (g/cm^2), mean ± SD	0.919 ± 0.129	0.935 ± 0.134	0.927 ± 0.132	0.326
T-score total femur, mean ± SD	−0.716 ± 0.830	−0.613 ± 0.857	−0.664 ± 0.844	0.326
Femoral neck (g/cm^2), median (IQR)	0.767 (0.695–0.87)	0.805 (0.718–0.897)	0.785 (0.708–0.888)	0.112
Radius 1/3 (g/cm^2), mean ± SD	0.689 ± 0.067	0.692 ± 0.075	0.691 ± 0.071	0.707
Lumbar spine (g/cm^2), mean ± SD	1.006 ± 0.162	1.023 ± 0.171	1.014 ± 0.167	0.420
Total body (g/cm^2), median (IQR)	1.127 (1.068–1.214)	1.156 (1.07–1.243)	1.138 (1.07–1.228)	0.193
Laboratory				
25OHD$_3$ (ng/mL), mean ± SD	21.5 ± 6.5	22.2 ± 6.9	21.9 ± 6.7	0.402
PTH (pg/mL), median (IQR)	56.1 (41.7–73.6)	56.4 (39.5–73.8)	56.2 (40.3–73.7)	0.983
Serum Ca (mg/dL), median (IQR)	9.5 (9.2–9.8)	9.5 (9.3–9.8)	9.5 (9.3–9.8)	0.897
Serum P (mg/dL), median (IQR)	3.5 (3.2–3.8)	3.5 (3.2–3.8)	3.5 (3.2–3.8)	0.816
Serum Cr (mg/dL), median (IQR)	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.499
CTX (ng/mL), median (IQR)	0.52 (0.37–0.67)	0.50 (0.39–0.73)	0.51 (0.38–0.69)	0.289
BSAP (μg/L), median (IQR)	19.88 (16.7–26.1)	19.45 (15.4–23.3)	19.6 (16.2–24.4)	0.078

For continuous data, p values are from Wilcoxon rank-sum test for non-normally distributed variables and two independent samples t test for normally distributed variables. For categorical variables, p values are from Fisher's exact test. Normally distributed variables are presented as mean ± SD and not normally distributed variables are presented as median (IQR).

IQR = interquartile range (first quartile – third quartile); SD = standard deviation; 25OHD = serum 25-hydroxyvitamin D; CTX = cross-linked C-telopeptide; BSAP = bone specific alkaline phosphatase.

significant negative effect of time (all p values <0.001). For spine and whole-body BMD, there was a statistically significant positive effect ($p = 0.001$) such that as time on the study increased, BMD increased linearly, again regardless of treatment group. The average baseline spine BMD was 1.01 g/cm^2, which increased to 1.03 g/cm^2. The average whole-body BMD was 1.15 g/cm^2, which increased to 1.16 g/cm^2 at 36 months. This change in BMD of the spine and total body was very small.

Although obese participants were observed to have a higher total femur BMD at baseline compared to overweight participants (0.97 versus 0.90 g/cm^2), accounting for BMI in the primary model yielded no statistically significant differences in the estimated treatment effect. In other words, the decline in total femur BMD was similar regardless of treatment group or baseline BMI group.

The primary analysis presented was conducted as an intention to treat (ITT) analysis, thus our models included all valid data from all randomized participants whenever possible. A per protocol analysis was completed by analyzing only the $n = 184$ participants who completed the 3 year study. The results were highly consistent. There were $n = 76$ participants who did not complete the study for various reasons (see Fig. 1). On average, the group who did not complete the study was older than the group of $n = 184$ who completed the trial (70.5 versus 68.3 years; $p = 0.003$) and had higher serum PTH (67.96 versus 56.45 mg/dL; $p = 0.002$). No other statistically significant differences were observed between these two groups.

It was of interest to examine whether the two treatment arms may be considered equivalent with respect to total femur BMD levels over time. At 1, 2, and 3 years, study participants in the active group had an average BMD that was 0.0043 (95% CI, −0.001 to 0.009), 0.007 (95% CI, 0.002 to 0.013), and 0.007 (95% CI, 0.0000 to 0.014) g/cm^2 higher than participants in the control group, respectively. At each time point, the 90% confidence intervals for these changes are completely contained within the predefined equivalence margin of 0.018 g/cm^2; thus, the treatment group was considered equivalent to the control group with respect to total femur BMD changes.

Trial participants were stratified into one of two groups, regardless of initial treatment assignment based on whether they achieved a target serum 25(OH)D level of 75 nmol/L or greater by 12 months postrandomization. Average bone density levels were examined over time for months 18 through 36. Again, there was a statistically significant effect of time ($p < 0.001$) such that as time increased, femur BMD declined; however, there was no statistically significant difference between groups with respect to this trend ($p = 0.45$).

Adverse events

There were no serious adverse events thought to be related to vitamin D. Adverse events are given in Table 2 using MeDRA. There were 24 incidents of hypercalcemia (>10.5 mg/100 mL), nine in the placebo (nine participants) and 15 in the active group (11 participants) over 3 years. Based on previous studies in postmenopausal black American women, we used 0.222 as the definition of hypercalciuria for fasting urine calcium. There were 53 instances of hypercalciuria in 33 individuals (17 in the active group and 16 in the placebo group). There is no statistically significant difference in event rate for either group.

Discussion

Maintaining serum 25(OH)D$_3$ levels above 75 nmol/L as recommended by the Endocrine Society Guidelines does not prevent

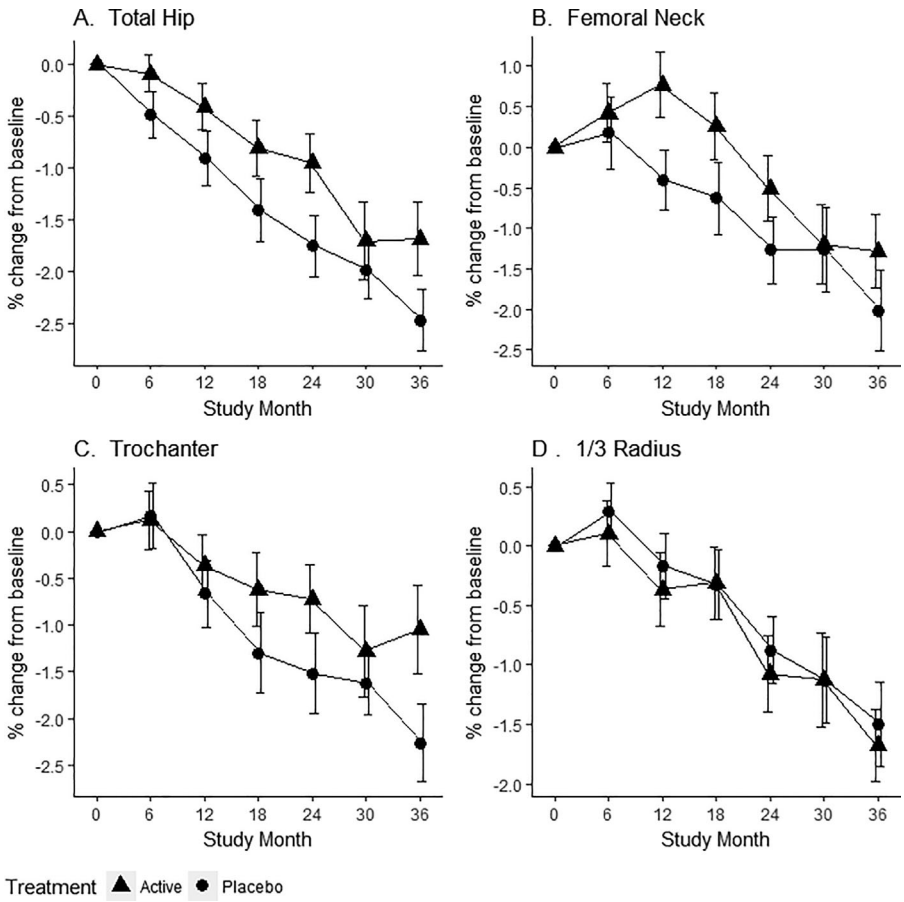

Fig. 2. Percent change in BMD from baseline over time stratified by treatment group. Group means (circle) ± 1 standard error at each study visit for: (*A*) total femur BMD, (*B*) femoral neck, (*C*) trochanter, and (*D*) 1/3 radius.

bone loss in elderly black American women. The rate of aging bone loss in the treatment group was not less than the placebo group, which had an average serum 25(OH)D_3 consistent with the RDA recommended by the IOM (50 nmol/L). Because the Dietary Reference Intakes (DRIs) for vitamin D are based solely on skeletal health, it may be concluded that elderly black American women should not be subjected to screening with serum 25(OH)D levels, and need not exceed the RDA for vitamin D intake.

There is a statistically significant relationship of serum 25(OH)D to BMD and involutional loss of BMD in white women. However, we previously conducted a 3-year RCT in 208 black American postmenopausal women who received 800 IU/day of vitamin D_3 for 2 years and 2000 IU for the last year.[6] In contrast to white Americans, there was no benefit in terms of bone loss in the treatment group at either dose. Baseline mean 25(OH)D_3 was 47 nmol/mL in this prior study. These findings were confirmed in a 2-year RCT of postmenopausal black American women ($n = 103$) with a much lower baseline 25(OH)D_3 (<25 nmol/mL).[7]

There was a small but statistically positive effect ($p = 0.001$) for spine and total body BMD in the current study. These changes were not clinically significant and could be due to extraskeletal calcification with aging.

The optimal value for the RDA-associated serum 25(OH)D level has been much debated.[8–10,12,13] Serum 25(OH)D levels are lower in black-Americans since childhood because of less absorption of ultraviolet rays due to their highly pigmented skin.[14–16] However, black Americans have a superior calcium economy to white Americans with higher PTH, calcitriol, and intestinal calcium absorption, and lower urine calcium excretion.[17–20] Bone mass is higher in black Americans starting from childhood. During adolescence black Americans achieve a higher peak bone mass that is retained throughout the lifespan.[21] Major osteoporotic fracture risk is one-half that of white Americans.[22,23] Thus, it is questionable that black Americans should be considered to be "at risk" and require higher intakes of vitamin D. Further, there is emerging evidence that high intakes of vitamin D may increase the risk of falls and fracture.[24,25] The increased risk occurs at lower concentrations of 25(OH)D in black Americans than in white Americans.[26] Finally, a recent systematic analysis carried out for the US Public Health Task Force resulted in a recommendation against using vitamin D supplements for prevention of falls and fractures in community dwelling adults who do not have osteoporosis or vitamin D deficiency.[27–29] This recommendation in part emanated from omitting studies that included subjects with vitamin D deficiency from consideration.

It could be argued based on their superior calcium economy that black Americans should have a lower RDA than white Americans. However, if this were entertained, the risk of rickets and osteomalacia would be increased greatly; 30% of black Americans have 25(OH)D concentrations below 30 nmol/L, compared to 5% of white Americans.[30] The 30-nmol/L value

Table 2. Adverse Events

System Organ Class (MedDra)	Placebo	Active treatment
Blood and lymphatic system disorders	2	2
Cardiac disorders	4	6
Congenital, familial and genetic disorders	0	1
Ear and labyrinth disorders	4	3
Endocrine disorders	2	2
Eye disorders	4	4
Gastrointestinal disorders	21	20
General disorders and administration site conditions	12	11
Hepatobiliary disorders	0	1
Immune system disorders	6	3
Infections and infestations	82	85
Injury, poisoning, and procedural complications	54	51
Investigations	20	12
Metabolism and nutrition disorders	15	12
Musculoskeletal and connective tissue disorders	57	49
Neoplasms benign, malignant and unspecified	9	9
Nervous system disorders	25	21
Psychiatric disorders	1	2
Renal and urinary disorders	7	3
Reproductive system and breast disorders	2	0
Respiratory, thoracic and mediastinal disorders	12	17
Skin and subcutaneous tissue disorders	8	6
Surgical and medical procedures	29	23
Vascular disorders	6	13

Number of participants with $\geq$1 event.

is the threshold for increased risk for a true deficiency state. Shifting the DRI distribution curve would increase the number of black Americans with serum 25(OH)D levels below the threshold for risk of deficiency ($<$30 nmol/L); ie, osteomalacia and rickets.

Despite the absence of influence of vitamin D on bone density in this study, there was an effect of calcium and vitamin D on PTH and bone turnover. BSAP declined in tandem in treatment and placebo groups, suggesting that this decline was simply an effect of calcium supplementation. PTH declined in both groups, presumably in part due to the increase in calcium intake, but there was a greater decrease in the vitamin D treatment group. The greater decrease in PTH is probably due to the additional effect of a genomic action of vitamin D on the parathyroid. The suppression of PTH by vitamin D has several other possible explanations. However, calcium absorption increases little, if at all, in the dose range studied.[31–36] Also, serum calcium was unchanged in this study. Serum 25(OH)D and 1,25 $(OH)_2D$ increased in the treatment group, so that it is plausible that it is an effect of one or both of these metabolites on the parathyroid glands that decreases PTH concentration.

When combined with calcium supplements, high-dose vitamin D results in a higher incidence of hypercalcemia and hypercalciuria than calcium supplements alone.[37] Unfortunately, we did not routinely measure 24-hour urine calcium in this study. Because black Americans conserve urine calcium more efficiently, it would be expected that they would be less likely than white Americans to develop hypercalciuria.

Two Cochrane meta-analyses reported an increased incidence of kidney stones from vitamin D. These analyses included the Women's Health Initiative (WHI), which had a low dose of vitamin D with a high calcium intake. This large study dominated the Cochrane meta-analyses. In a more recent meta-analyses by Kahwati and colleagues[29] no increased incidence of stones was found. However, the recent evidence report compiled for the US Preventive Services Task Force (USPSTF) (which included the WHI and two studies by Lappe and colleagues[38,39]) also found an increased risk for kidney stones in combined supplementation. High-dose vitamin D intake could conceivably increase the incidence of stones through the occurrence of hypercalciuria in susceptible individuals. We have previously shown an increase in urine calcium excretion with high intake of vitamin D and calcium supplementation greater than that seen with calcium supplements alone.[40]

Other adverse effects of high-dose vitamin D have been reported, including falls and fractures with very high doses of vitamin D (500,000 IU once a year).[25] As a result of promotion to the public of possible benefits of vitamin D, the prevalence of high intakes (4000 IU/day and higher) has grown from $<$0.1% prior to 2003, to 3.3% in 2014 in the general US population. It is noteworthy that in our study the majority of volunteers screened and excluded was due to high 25(OH)D. Our study was confined to elderly black American women and, therefore, should not be generalized to other groups. A strength of our study was the use of a specific serum 25(OH)D_3 goal of over 75 nmol/L with double-dummy adjustment of dose to successfully maintain this goal. In addition, our study was carried out over 3 years.

In conclusion, we showed that maintaining serum 25(OH)D_3 above 75 nmol/L did not affect aging bone loss in black American women. There is no known value to increasing vitamin D intake above the RDA in this subpopulation. However, we do not recommend lowering the RDA for black Americans because it might result in placing an unacceptable portion of them at risk for rickets or osteomalacia. Whether vitamin D recommendations should be influenced by proposed extraskeletal actions of vitamin D should be elucidated by several clinical trials soon to be completed.[41]

Disclosures

All authors state that they have no conflicts of interests.

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Authors' roles: JFA designed and supervised and wrote the manuscript; MM was responsible for medical supervision of the study participants. JFA designed the study; SI and MF, the study statisticians, were responsible for the data and statistical analyses and contributed to the writing of the manuscript. AS, SK, RD, AS, and GU were research fellows who were responsible for clinical care, data gathering, data presentation, and analysis and review of the manuscript. LR, the laboratory director, was responsible for the biochemical assays. None of the authors had a personal or financial conflict of interest.

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