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Reduction of parathyroid hormone with vitamin D supplementation in blacks: a randomized controlled trial

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Abstract

Background: Response of parathyroid hormone (PTH) to vitamin D supplementation is determined by the baseline PTH level and change in vitamin D status. Conflicting reports in Blacks exist on the PTH response to vitamin D to supplementation.

Methods: During 3 winters from 2007 to 2010, 328 healthy Blacks (median age, 51 years) living in Boston, MA were randomized into a 4-arm, double-blind trial for 3 months of placebo, 1000, 2000, or 4000 IU of vitamin D3. PTH was measured in 254 participants at baseline and at the end of vitamin D supplementation period.

Results: The differences in PTH between baseline and 3 months were 3.93 pg/mL for those receiving placebo, -3.37 pg/mL for those receiving 1000 IU/d, -6.76 pg/mL for those receiving 2000 IU/d, and -8.99 pg/mL for those receiving 4000 IU/d (-2.98 pg/mL for each additional 1000 IU/d of vitamin D3; $p < 0.001$).

Conclusion: We found a significant decrease in PTH with increasing doses of vitamin D supplementation up to intakes of 4000 IU/d in Blacks.

Trial registration: Clinical Trials.gov: NCT00585637

Keywords: Vitamin D, Parathyroid hormone, Blacks, Supplementation

Background

Blacks have significantly lower circulating 25-hydroxyvitamin D [25(OH)D] and higher serum parathyroid hormone [PTH] concentrations than Whites [1, 2]. Observational and intervention studies have shown that vitamin D deficiency and high serum PTH are associated with increased risk of skeletal disease [3, 4]. Paradoxically, Blacks have a lower risk of osteoporotic fractures partly because of skeletal resistance to PTH among other factors [5]. Recent studies have identified an association of high PTH with increased morbidity and mortality independent of bone disease [6]. In one study, elevated plasma PTH (>50 pg/mL) accounted for 20 % of the population-attributable risk proportion for cardiovascular mortality [7]. A consensus conference on primary hyperparathyroidism suggested that large populations of vitamin D-replete cohorts are necessary to establish reference intervals for PTH assays [8]. Furthermore, there has been recent debate about what constitutes vitamin D deficiency and sufficiency [9]. The most recent compilation of data suggest 25(OH)D level of 20 ng/mL (50 nmol/L) is adequate for the population. However, the 2011 Institute of Medicine (IOM) report concluded that there is currently only sufficient evidence to provide health guidelines for skeletal health. For extra skeletal outcomes, including cancer, cardiovascular disease (CVD), diabetes mellitus (DM) and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality and insufficient to inform nutritional requirements [10, 11]. The U.S. Preventive Services Task Force (USPSTF) concluded that the current evidence is insufficient to assess the balance of the benefits and

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harms of screening for vitamin D deficiency in asymptomatic adults [12]. Therefore, more data are needed to assess the need for vitamin D supplementation for non-skeletal outcomes and to identify potential threshold effects for non-skeletal outcomes given the current controversy about the role of PTH [13–16] and vitamin D in disease pathogenesis. Thus, understanding the role of vitamin D supplementation on PTH homeostasis is important.

The threshold for vitamin D sufficiency has been defined by some as the lowest serum concentration of 25(OH)D that maximally suppresses PTH secretion [17]. Several studies have reported varying individualized responses of Vitamin D supplementation on serum level of PTH [18, 19]. Yet, these studies did not include a sufficient number of Blacks. Therefore, we conducted an ancillary analysis of the dose–response effect of 3 doses of vitamin D3 and placebo on PTH levels within a blinded randomized clinical trial (RCT) to show how PTH responds to different doses of vitamin D3.

Methods

The parent study was a prospective, randomized, double blind, placebo-controlled trial of oral vitamin D supplementation in healthy Blacks (Clinical Trials.gov: NCT00585637). The protocol has been described in detail previously [20]. The primary goal of the trial was to examine the effect of daily supplementation of 1000 international units (IU), 2000 IU, and 4000 IU of vitamin D3 and placebo on plasma 25(OH)D levels. All participants provided written informed consent. The project was approved by the Institutional Review Boards of Harvard School of Public Health and the Dana-Farber Cancer Institute. All procedures were followed in accordance with the institutional guidelines.

Recruitment and exclusion criteria

Participants were 30 to 80 years old, understood written and spoken English and self-identified as Black or African-American [21–23]. Enrollment during the late autumn and winter months minimized the influence of sun exposure on vitamin D levels. A total of 328 individuals living in the Boston area were enrolled into the parent trial (Fig. 1). Exclusion criteria included pregnancy, renal disease, preexisting parathyroid, thyroid, or calcium metabolism disorders, sarcoidosis, requirement for calcium channel blockers, type I diabetes, active malignancies (other than non-melanoma skin cancer), and plan for extended travel to a sunny region during supplementation phase of the study. Primary care physicians of all enrolled participants were required to provide documentation that the participant had no prior history of hypercalcemia.

Randomization and treatment

Participants were randomly assigned to one of four treatment arms: placebo, 1000 IU (25 mcg)/day, 2000 IU (50 mcg)/day, or 4000 IU (100 mcg)/day of vitamin D (as cholecalciferol). Treatment consisted of tablets that, in addition to placebo or vitamin D, also contained 200 mg of calcium carbonate. The tablets were formulated and manufactured by Pharmavite LLC (Mission Hill, California). Study medications were started during early winter (November or December) and were taken orally once a day for 3 months (completed in February or March) to minimize any effect of ultraviolet exposure in New England. Study statisticians generated the random allocation sequence. All participants, providers, and study staff were blinded.

Endpoints and follow up

The primary end point of the study was change in serum PTH from baseline to the 3-month end of randomized supplementation. Dietary intake of calcium and vitamin D was estimated by using a modified Food Frequency Questionnaire (FFQ) at baseline and 3 months.

Safety and compliance

Participants were followed for toxicity and compliance every 2 weeks by phone and every 4 weeks in person during supplementation. Study staff ascertained absence of symptoms (such as muscle aches, excessive thirst, frequent urination, and nausea). In addition, serum calcium was measured in all subjects who were taking hydrochlorothiazide (HCTZ:84 participants) at 4 to 6 weeks following study initiation and again at 12 weeks. An additional subset of randomly selected control participants (44 participants), who were not taking HCTZ, also underwent calcium assays at 3 months. Serum total calcium was analyzed using standard auto analyzer methodology. Any participant with serum calcium >10.5 mg/dL at the first calcium measurement was immediately discontinued from the study and the primary care physician was notified. If participants had elevated calcium at month 3 (end of supplementation period), they remained in the study. Electronic pill-dispenser systems and pill counts were used to track compliance.

Plasma vitamin D and PTH levels

Blood samples collected at baseline and 3 months were separated and plasma was stored in liquid nitrogen in the Dana-Farber Cancer Institute Clinical Research Laboratory. In this ancillary analysis, PTH was measured in 254 participants because of lack of stored blood samples for the others. Although the lower number reduces our power and statistical precision, the unavailability of sample is unlikely to cause a bias. All plasma samples were sent as a single batch to the laboratory of Dr. Bruce Hollis

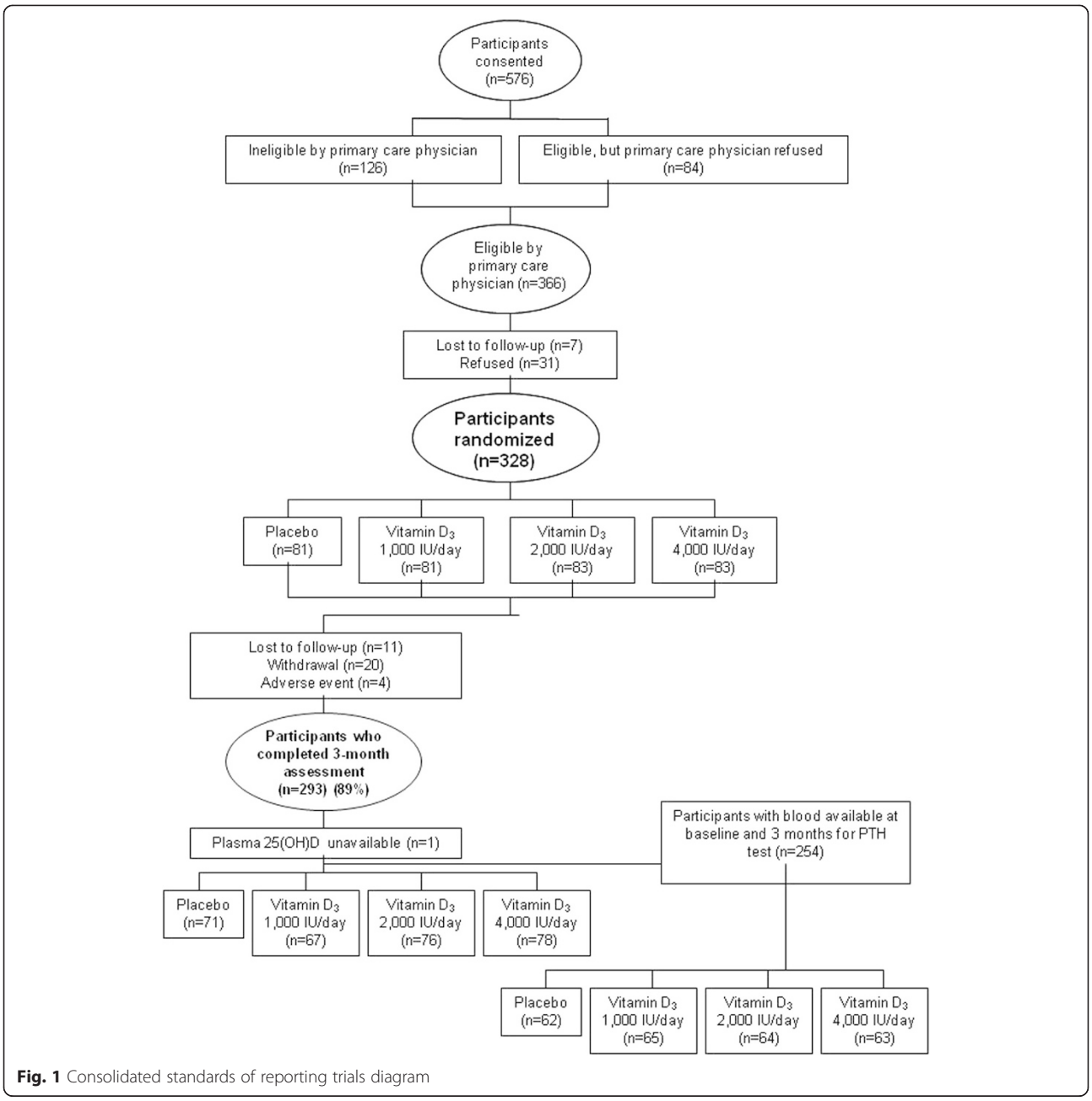

Fig. 1 Consolidated standards of reporting trials diagram

(Medical University of South Carolina, Charleston, SC), where 25(OH)D concentrations were measured using the Diasorin (DiaSorin, Inc.) radioimmunoassay [24]. The mean coefficient of variation of 25(OH)D measurements was 9 %. Samples for PTH assay were sent as a single batch to Heartland Assays (Ames, Iowa) and measured using the FDA approved DiaSorin intact PTH immunoradiometric assay (IRMA). The intra- and inter-assay CVs for this assay are 2.7 % and 4.3 % respectively. For Heartland Assays, the normal range of PTH is 13-54 pg/mL. For all assays, masked quality control samples were interspersed among the cases and all laboratory personnel were blinded. Of note, the normal range of PTH reported in laboratory manuals is 10-65 pg/mL [25, 26].

Statistical analysis

This trial has a statistical power of 80 % to detect differences in plasma 25(OH)D level of 5.3 ng/mL between treatment groups. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC with an intention-to-treat approach. Baseline characteristics of the study population were compared between supplementation arms using Chi-Square test for categorical variables and the Kruskal-Wallis test for continuous

variables. For our primary analysis, we used linear regression with the dose of vitamin D3 (per 1000 IU/day) as the independent variable and the 3-month change in PTH as the dependent variable.

We performed a number of a priori secondary analyses. We used linear regression to evaluate the change in PTH according to the change in plasma 25(OH)D levels. Second, we compared the mean change in PTH between placebo and all three vitamin D treatment groups combined. Third, we assessed the interaction effect of HCTZ use on the response of PTH to vitamin D supplementation. Fourth, we stratified participants based on baseline 25(OH)D (<20 ng/ml, ≥ 20 ng/ml) and compared PTH change(month 3-month 0), PTH at baseline, and PTH at 3 months. Finally, to assess whether the effect of supplementation with vitamin D on the primary endpoint, 3 month change in PTH, varied according to baseline 25(OH) D, we tested for interaction between treatment group and baseline 25 (OH) D levels.

Results

Baseline characteristics among the 328 eligible participants are shown in Table 1. The overall median age was 51 years with a median BMI of 31 kg/m^2. The only significant difference in baseline characteristics according to treatment assignment was that slightly more participants in the placebo and 1000 IU/day arms had a past history of cancer than those assigned to 2000 or 4000 IU/day. The compliance with study medication (measured by electronic pill dispenser system and pill counts) in the entire cohort was 96.6 % and did not differ significantly between arms. The 3-month follow-up plasma measurements were completed in 293 of the 328 participants (89 %). Of the 134/328(41 %) of participants

Table 1 Subject characteristics by supplementation arm[a,b,g]

Characteristic	Vitamin D3 Dose Assignment (IU)				
	PLACEBO	1,000	2,000	4,000	Overall
	(*n* = 81)	(*n* = 81)	(*n* = 83)	(*n* = 83)	
Age (y)	50.7 (44.1-58.0)[b]	51.1 (43.4-60.1)	50.3 (43.5-58.3)	51.3 (44.1-59.7)	51.0 (43.6-59.4)
Sex, No. (%)					
Male	27 (33.3)	22 (27.2)	28 (33.7)	29 (34.9)	106 (32.3)
Female	54 (66.7)	59 (72.8)	55 (66.3)	54 (65.1)	222 (67.7)
BMI (kg/m^2)	31.2 (26.5-35.9)	30.5 (27.0-37.5)	31.9 (26.2-36.9)	31.4 (27.4-35.7)	31.2 (26.8-36.3)
Biomarkers					
PTH (pg/mL)	36.75 (30.40-47.20)	35.40 (28.90-47.25)	36.40 (28.95-47.25)	37.40 (29.40-56.40)	36.9 (29.4-49.0)
25 (OHD) (ng/mL)	15.1 (10.4-23.6)	16.2 (11.0-22.7)	13.9 (9.5-22.3)	15.7 (11.0-23.3)	15.3 (10.4-22.8)
Smoking status, No. (%)					
Never	33 (40.7)	36 (44.4)	33 (39.8)	44 (53.0)	146 (44.5)
Past	20 (24.7)	16 (19.8)	27 (32.5)	20 (24.1)	83 (25.3)
Current	28 (34.6)	29 (35.8)	23 (27.7)	19 (22.9)	99 (30.2)
Frequency of exercise, (day/week)	3.0 (0.5-5.0)	3.0 (1.0-5.0)	3.0 (0-5.0)	3.0 (0-5.0)	3.0 (0-5.0)
Dietary vitamin D intake (IU)[c]	147.3 (71.4-262.8)	162.5 (92.6-295.5)	144.0 (58.0-265.1)	198.1(83.2-306.4)	167.5 (72.3-291.8)
Dietary calcium intake (mg)[c]	277.0 (171.7-632.3)	422.9 (226.1-795.9)	318.8 (172.7-637.4)	445.9 (198.6-780.4)	356.6 (188.6-693.8)
Regular multivitamin use,[d] No. (%)	10 (12)	18 (22)	15 (18)	22 (27)	65 (19.8)
Regular vitamin D supplement use,[d] No. (%)	8 (10)	6 (8)	2 (2)	8 (10)	24 (7.3)
HCTZ use, No. (%)	19	18	12	17	66 (20.1)
Post-menopausal hormone use,[e] No. (%)	0	0	0	1 (0.5)	1 (0.5)
Regular calcium supplement use,[d] No. (%)	7 (8.7)	9 (11.1)	7 (8.4)	9(10.8)	32 (9.8)
History of cancer,[f] No. (%)	6 (7.4)	6 (7.4)	0	3 (3.6)	15 (4.6)
History of hypertension, No. (%)	35 (43.2)	35 (43.2)	36 (43.3)	35 (42.1)	141 (43.0)

[a]There were no significant differences in subject characteristics across supplementation arms except where indicated
[b]Median; 25th, 75th percentiles in parentheses (all such values) except otherwise stated
[c]Refers to the intake during the preceding month of selected calcium-rich foods
[d]Defined as supplement use for 7 days/week during the preceding month
[e]Percentages were calculated from a total of 222 females
[f]Reported cancers include breast cancer, cervical cancer, uterine cancer, lung cancer, prostate cancer, and sarcoma
[g]PTH was measured in 254 individuals
Abbreviations: *BMI* body mass index, *PTH* parathyroid hormone, *25(OH)D-25* hydroxyvitamin D, *HCTZ* hydrochlorothiazide)

using anti-hypertensives, 84/134(63 %) participants were on a diuretic, HCTZ.

Effect of vitamin D3 supplementation on plasma 25(OH) D

Among 328 participants, the median 25(OH)D level at baseline was 15.3 ng/mL. As previously published, baseline plasma 25(OH)D did not differ significantly between treatment arms ($P = 0.63$; Table 2) [27]. Circulating 25(OH)D levels at 3 months differed significantly by the vitamin D3 supplementation arm, with a median of 14.2, 28.1, 35.5, and 47.3 ng/mL for the placebo, 1000 IU/day, 2000 IU/day, and 4000 IU/day arms, respectively ($P < 0.001$). [Effect estimate ± SE: 7.7 ± 0.45 ng/mL for each 1000 IU vitamin D3; P-trend, 0.001]. Notably, plasma 25(OH)D decreased at 3 months among participants treated with placebo (Table 2).

Effect of vitamin D on PTH supplementation

The median [IQR] PTH level at baseline was 36.9 pg/mL [29.4, 49.0]. At baseline, secondary hyperparathyroidism (defined as PTH > 60 pg/mL) was present in 40 participants. Of participants with 25(OH)D < 20 ng/mL, 21.8 % had PTH ≥ 60 pg/mL compared to 6.8 % of participants with 25(OH)D ≥ 20 ng/mL. Plasma PTH did not differ significantly between treatment arms ($P > 0.05$; Table 1). Plasma PTH declined with vitamin D supplementation. After 3 months of vitamin D supplementation, participants with PTH ≥ 60 pg/mL were 4.6 % for 1000 IU/d, 4.7 % for 2000 IU/d, and 3.2 % for 4000 IU/d compared to 14.5 % for placebo; p for trend = 0.03.

We examined changes in serum PTH according to vitamin D supplementation in several ways. We determined the mean PTH for each arm and calculated the difference between baseline and 3 months follow up. Serum PTH levels at 3 months differed significantly by the vitamin D3 supplementation arm, with a mean of 3.9 pg/mL, -3.4 pg/mL, -6.8 pg/mL and -9.0 pg/mL for the placebo, 1000 IU/day, 2000 IU/day, and 4000 IU/day arms, respectively (-2.98 pg/mL for each additional 1000 IU/d of vitamin D3 $p < 0.001$). Using linear regression with the dose of vitamin D3 (per 1000 IU/day) as the independent variable and the $\log_{10}$ 3-month change in PTH as the dependent variable, we found a decrease of -0.07 (0.02) for each additional 1000 IU/d of vitamin D3 ($P < 0.001$). (See Additional file 1: Figures S1 and S2) Comparing all three doses (1000, 2000, 4000 IU/d) versus placebo, PTH decreased by -10.30 pg/mL ($p < 0.001$). Excluding the placebo group, a nonsignificant decrease in PTH occurred at 3 months (PTH: -1.75 pg/mL 95 % CI [-3.59-0.08]; $p = 0.06$, for each additional 1000 IU/d of vitamin D3) versus change in PTH at 3 months including the placebo group (-2.98 pg/mL 95 % CI [-4.41, -1.54]; $p < 0.001$).

Relationship between PTH and 25(OH)D

The relationship between PTH and circulating 25(OH)D was evaluated at baseline and at 3 months. Using a linear regression at baseline, a 1 ng/mL higher 25(OH)D was associated with a significant -0.30 pg/mL lower PTH ($p = 0.01$). At 3 months, a 1 ng/mL increase in 25(OH)D resulted in a significant -0.23 pg/mL decrease in PTH

Table 2 Effect of Vitamin D3 Supplementation on PTH (pg/mL) During the Treatment (Baseline to 3 months)[a]

	Vitamin D Dose, IU/d					
Parameter, mean (SE)	Placebo	1000	2000	4000	3 months Change[b]	*P*-Value
n (at baseline)	62	65	64	63		
Total PTH, pg/mL					−2.98 [-4.41,-1.53]	<0.0001
Baseline PTH, mean (SE)	39.40 (14.20)	41.15 (18.02)	42.21 (20.94)	42.96 (16.79)		
3 months PTH, mean (SE)	43.27 (18.21)	39.83 (15.56)	36.42 (15.69)	34.18 (12.75)		
Difference PTH[c], mean (SE)	3.93 (18.93)	−3.37 (17.84)	−6.76 (14.71)	−8.99 (12.36)		
25(OH)D, ng/mL						
Baseline 25(OH)D, mean(SE)	17.07 (1.03)	17.33 (1.00)	16.12 (0.98)	17.79 (0.98)	7.57 [6.69,8.46]	<0.0001
3 months 25(OH)D, mean (SE)	14.23 (0.96)	28.12 (1.11)	35.48 (1.21)	47.30 (1.22)		
Difference 25(OH)D[d], mean (SE)	−2.58 (0.66)	11.01 (1.22)	19.21 (1.21)	29.79 (1.29)		
Calcium, mg/dL						
1 month Calcium, mean (SE)	9.54 (0.08)	9.77 (0.13)	9.77 (0.13)	9.81 (0.12)		
3 months Calcium, mean (SE)	9.57 (0.09)	9.59 (0.10)	9.59 (0.10)	9.77 (0.07)		

[a]PTH, Parathyroid hormone; mean (SE), mean(Standard Error); IU, international unit. The numbers do not always sum to group totals due to missing information for some variables

[b]Month3 – Month0 change in PTH per 1000 IU/d of vitamin D supplementation, Mean (95 % Confidence Interval). Month3 – Month0 change in 25(OH)D per 1000 IU/d of vitamin D supplementation, Mean (95 % Confidence Interval)

[c]Difference PTH, Month 3-Month 0 difference in PTH

[d]Difference 25(OH)D, Month 3- Month 0 difference in 25(OH)D

($p = 0.0005$). These models showed a significant inverse relationship between 25(OH)D and PTH. No interaction between baseline 25(OH)D and vitamin D dose effect on change in PTH was observed (p for interaction = 0.15). When baseline 25(OH)D was stratified, we observed a significant decrease in PTH at 3 months among those with 25(OH)D <20 ng/mL (-3.76 pg/mL 95 % CI [-5.59,-1.92]; $p < 0.0001$; for each additional 1000 IU/d of vitamin D3) and a non-significant decrease among those with 25(OH)D ≥ 20 ng/mL (-1.56 pg/mL; 95 % CI [-3.79,0.66]; $p = 0.16$ for each additional 1000 IU/d of vitamin D3). Comparing baseline PTH level by 25(OH)D status (deficient versus nondeficient), 25(OH)D < 20 ng/mL: PTH mean (SD), 42.4 (19.9) pg/mL versus 39.7(14.0) pg/mL for 25(OH)D ≥ 20 ng/mL ($p = 0.24$). Comparing 3-month PTH level by 25(OH)D status, 25(OH)D < 20 ng/mL: PTH mean (SD), 38.1(17.7) pg/mL versus 38.9 (12.0) pg/mL for 25(OH)D ≥ 20 ng/mL ($p = 0.72$). No significant interaction between HCTZ use and change in PTH with vitamin D supplementation was observed (p for interaction = 0.59). Plasma PTH declined in HCTZ and non-HCTZ users (HCTZ:-4.2 pg/mL 95 % CI [-7.6,-0.85]; $p = 0.02$; for each additional 1000 IU/d of vitamin D3; non-HCTZ: -2.51 pg/mL 95 % CI [-4.07,-0.96]; $p = 0.002$).

Adverse effects

We previously reported the hypercalcemia events [28]. Briefly, after 1 month of the 12-week vitamin D supplementation period, 4 participants taking HCTZ experienced modestly elevated serum calcium levels, ranging from 10.7 to 11.0 mg/dL. At 3-months, only one HCTZ participant had elevated calcium (calcium = 11.2 mg/dL). There were no significant differences in calcium concentrations between treatment arms at 1 month ($P = 0.14$) and 3 months ($P = 0.52$).

Discussion

Black Americans have significantly lower 25(OH)D and higher PTH concentrations than Whites [1, 2]. We evaluated the hypothesis that vitamin D supplementation reduces PTH in Blacks. PTH has been shown to be a sensitive biomarker of vitamin D activity in vivo [17]. At baseline, we found a significant inverse association between serum 25(OH)D and PTH similar to prior cross-sectional studies [2]. Vitamin D supplementation led to an increase in circulating 25(OH)D in this vitamin D-deficient Black population and a decrease in PTH in a dose-dependent manner confirming the presence of vitamin D deficiency based on PTH criteria. Vitamin D deficiency is defined as 25(OH)D less than 20 ng/mL by IOM, and it provides no formal guidelines regarding vitamin D screening [29]. The USPTF gives no recommendation for or against screening and treating asymptomatic individuals for vitamin D deficiency, because the evidence regarding the benefits and harms is insufficient [12].

Vitamin D supplementation had a strong and unequivocal effect in lowering PTH when baseline levels were <20 ng/mL but a weaker and non-significant decrease for 25(OH)D > 20 ng/mL. This finding suggests that a reduction in PTH is clear when 25(OH)D greater than or equal to 20 ng/mL is attained; a more modest lowering effect is possible with 25(OH)D levels higher than 20 ng/mL. A large cross-sectional analysis of 312,962 paired serum PTH and 25-OHD (no information provided about race/ethnicity) similarly found significant continuing declines in serum PTH levels beyond 20 and 30 ng/ml of 25(OH)D [30], but a larger study than ours would be required to test this definitively. In terms of vitamin D dose needed to maximally suppress PTH, an effect is clear with supplementation of at least 1000 IU/day (e.g., comparing all three doses (1000, 2000, 4000 IU/d) versus placebo, PTH decreased by -10.30 pg/mL ($p < 0.001$)). When excluding the placebo group, and thereby assessing the effect of vitamin D over a range of 1000 to 4000 IU, a nonsignificant decrease in PTH occurred (PTH: -1.75 pg/mL 95 % CI [-3.59-0.08]; $p = 0.06$, for each additional 1000 IU/d of vitamin D3). Thus, our results suggest that intakes higher than 1000 IU/d may be required to maximally suppress PTH in Blacks. Of note, in this population, we estimated 1640 IU vitamin D3/d was needed to raise the plasma 25(OH)D concentration to ≥ 20 ng/mL in ≥ 97.5 % of participants [27].

In agreement with our findings, a systematic review of clinical trials on the response of parathyroid hormone to vitamin D supplementation shows that PTH decreases linearly during vitamin D supplementation for any given 25(OH)D level [31]. Furthermore, the review suggests that longitudinal vitamin D supplementation studies on populations with wide range of mobility and age are needed to further elucidate their modifying effects and the inter-individual variation in responses of PTH to vitamin D supplementation [31].

The IOM Report [10, 11] and the Endocrine Society Clinical Practice Guideline [32] both agree that providing vitamin D for any reason other than bone health is not supported by current published literature. The main way in which the two reports differ is on the upper threshold for which vitamin D is safe. For the IOM, the upper threshold is 50 ng/mL but for the Endocrine Society it is 100 ng/mL [32]. The basis for their difference is driven by the interpretation of elevated PTH levels. Controversy remains on how these thresholds were selected [33]. Neither report recommends vitamin D supplementation when PTH levels are in the normal range. The IOM Committee concluded that the evidence that vitamin D or calcium reduced risk of nonskeletal chronic disease outcomes is inconsistent, inconclusive, and did

not meet criteria for establishing cause-and-effect relationship [10, 11]. Furthermore, the Endocrine Society states that there is not sufficient evidence to recommend screening individuals who are not at risk for deficiency to prescribe vitamin D to attain the noncalcemic benefit for cardiovascular protection [32].

Few studies have examined the relationship between vitamin D supplementation and PTH in Blacks. In a study of 127 postmenopausal Black women randomized to either placebo or 1000 IU of vitamin D supplementation with calcium supplement to bring daily calcium intake to 1000 mg, serum 25(OH)D increased by 100 % in supplement users from a baseline of 11.6 ng/mL and produced a significant decline in PTH at 3 months [34]. In another study of 198 White and African-American women, participants were randomly assigned to placebo or daily vitamin D supplementation and were given calcium to maintain total calcium intake of 1000-1200 mg/d. At 12 months, the investigators concluded that a vitamin D dose of 400 IU/d increased serum 25(OH)D to greater than 20 ng/mL in 97.5 % of Whites while 800 to 1600 IU/d was required to reach the same effect in African Americans [35]. They also found that that serum PTH reduced significantly in both races over time but the change was not dose dependent [35].

Reduced bone turnover and reduced risk of osteoporotic fractures in Black women compared to White women [36, 37] have resulted in the suggestion of a lower cutpoint for normal serum 25(OH)D in Blacks. In contrast, the Women's Health Initiative (WHI) nested case–control study suggested that 25(OH)D greater than 20 ng/mL is associated with increased fractures in Blacks [38], but the cases had about 50 % more treated diabetes than the controls (11 % versus 16 %, difference between groups $p = 0.05$) and diagnosed diabetes is associated with greater risk of fractures in Blacks than Whites [39]. Furthermore, they could not test whether the association between low 25(OH)D levels and fracture was independent of BMD because only three WHI clinics measured BMD [38]. Interestingly, this WHI study found no association between PTH and fracture risk in any ethnic group [38]. Yet, recent studies have implicated low 25(OH)D in increased all-cause and cause-specific mortality in both Blacks and Whites [40–44].

Furthermore, although Blacks have been shown to be less sensitive to the effects of PTH on bone turnover [45], serum PTH levels have been shown to be an independent risk factor for cardiovascular events, cardiovascular mortality, and all-cause mortality, even in individuals with PTH within the normal or slightly elevated range [7, 46–49]. A community-based prospective study of 958 elderly men found that higher plasma levels of PTH were associated with higher risk for cardiovascular mortality independently of established cardiovascular risk factors and factors associated with mineral homeostasis. The results remained significant in participants with PTH within the normal range. Thus, PTH levels may portray prognostic information even in the absence of primary or secondary hyperparathyroidism [7]. In the health ABC study, elevated PTH (≥70 pg/mL) was associated with increased all-cause, CVD, and noncancer, non-CVD mortality in Black and White community-dwelling older adults [6].

Strengths of the study include the use of multiple doses of vitamin D supplementation during winter months and the use of an all Black cohort. Limitations of our study include the use of a population with low calcium intake. Thus, it may not be generalizable to populations with higher calcium intake. In addition, we studied only a short duration of supplementation with 3 doses of vitamin D3 (highest dose 4000 IU/d). Lastly, this study shows that vitamin D supplementation changes vitamin D and PTH levels, but it has no outcome measure as to long term effect on health of changing either vitamin D or PTH levels and this is a major limitation of the study design. However, our previous work showed that vitamin D supplementation in this cohort reduced blood pressure [20] without causing hypercalcemia even in HCTZ users [28].

Conclusions

This study highlights a dose-dependent decrease in PTH in Blacks with vitamin D supplementation confirming correction of low vitamin D, but whether reduction of PTH should be done or is safe to do is unproven. Identification of optimal levels of plasma 25(OH)D and PTH remain to be established.

Additional file

Additional file 1: Figure S1. Log Change of PTH (Month 3-Month 0) by Vitamin D Dose/day. **Figure S2.** Change in PTH (Month 3- Month 0) by Vitamin D Dose/day. (PDF 201 kb)

Abbreviations

PTH: Parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D; IOM: Institute of Medicine; WHI: Women's Health Initiative; CVD: Cardiovascular disease; DM: Diabetes mellitus; USPSTF: U.S. Preventive Services Task Force; RCT: Randomized clinical trial; FFQ: Food frequency questionnaire; IRMA: Immunoradiometric assay; HCTZ: Hydrochlorothiazide; BMI: Body mass index.

Competing interests

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Authors' contributions

PC: Data acquisition, data analysis, draft, review and editing of manuscript. PC takes responsibility for the integrity of the data and the accuracy of the data analysis. FA: Draft, review and editing of manuscript. KN: Review and editing of manuscript. JS: Review and editing of manuscript. BD: Study

design, data acquisition, data analysis, review and editing of manuscript. GB: Study design, review and editing of manuscript. AC: Review and editing of manuscript. BH: Review and editing of manuscript. KE: Study design, review and editing of manuscript. CF: Study design, review and editing of manuscript. EG: Study design, data analysis, review and editing of manuscript. All authors read and approved the final manuscript.

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