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Biochemical and Clinical Deficiency is Uncommon in African Immigrants despite a High Prevalence of Low Vitamin D: The Africans in America Study

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Abstract

Purpose—The Endocrine Society and Institute of Medicine (IOM) have concluded from studies in largely white populations that 25(OH)D is necessary for bone health. However, their definition of vitamin D insufficiency differs. The Endocrine Society recommends a 25(OH)D threshold of <30ng/mL. The IOM uses a lower threshold of 25(OH)D <20ng/mL. As African ancestry is associated with decreased 25(OH)D but increased bone mineral density (BMD), the applicability of these thresholds to Africans is unknown. Therefore, we examined in African immigrants the relationship of 25(OH)D to parathyroid hormone (PTH) and BMD.

Methods—One-hundred-eighty-six African immigrants (69% male, age 38±10 (mean±SD) range 20–64y) living in metropolitan Washington, DC were enrolled. BMD was determined from whole-body DXA scans. Decreased BMD required T-scores ≤−1.0. The threshold for low 25(OH)D was the concentration of 25(OH)D at which PTH became suppressed. This is known as the inflection point. Biochemical deficiency required low 25(OH)D and PTH>65 pg/mL. Clinical deficiency required low 25(OH)D and T-scores ≤−1.0.

Results—25(OH)D<30ng/mL and <20ng/mL occurred in 83% and 46% of African immigrants, respectively. PTH inversely correlated with 25(OH)D ($r = -0.31$, $P=0.002$). The inflection point

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occurred at a 25(OH)D concentration of 20ng/mL. Biochemical and clinical deficiency occurred in only 8% and 3% of immigrants, respectively.

Conclusion—As PTH became suppressed at 25(OH)D of 20ng/mL, the 25(OH)D<20ng/mL threshold for insufficiency may apply to African immigrants. However, ~50% of African immigrants have 25(OH)D<20ng/mL, but only <10% had evidence of deficiency. The value of providing vitamin D supplementation to the large number of African immigrants with 25(OH)D<20 ng/mL and no detectable evidence of deficiency needs to be determined.

Keywords

Vitamin D; Parathyroid Hormone; African immigrants; Bone Mineral Density

INTRODUCTION

As degree of African ancestry increases, vitamin D levels decline and bone mineral density (BMD) increases(1–3). Therefore, vitamin D requirements for the maintenance of bone health may differ by race and could be even lower in Africans than African-Americans.

Clearly, determining vitamin D requirements is challenging. In fact, the Endocrine Society and the Institute of Medicine (IOM) disagree on the definition of vitamin D insufficiency. The Endocrine Society recommends a threshold of 25(OH)D<30 ng/mL (to convert to nmol/L multiply by 2.5), whereas the IOM supports a threshold of <20 ng/mL(4, 5). However, these recommendations were based on studies in largely white cohorts and therefore may not be relevant to African descent populations. The challenge in making evidence-based recommendations for African descent populations is the paucity of data. For example, we reviewed the racial composition of 31 clinical investigations cited in the IOM report and found a combined total of 238,511 participants, 86% white, and only 7% African descent and 7% other (Supplemental Table 1).

Furthermore, for African immigrants to the United States no data exists on the relationship of 25(OH)D to BMD. The official position papers on vitamin D and health by the IOM, Endocrine Society and the United States Preventive Services Task Force (USPSTF) do not cite any references on African immigrants (4–6). In fact, to our knowledge, there is only one publication on 25(OH)D levels in African immigrants in the United States. It is an assessment of 25(OH)D levels in 71 veiled Somali women living in Seattle, Washington(7). Thus, there is no evidence-based data to guide evaluation of vitamin D status in African immigrants. Yet, this information is essential for informing policy and for providing optimal healthcare to one of the most rapidly growing immigrant populations in the United States. Since 1970, the African immigrant population in the United States has doubled every decade, growing to 1.6 million in 2012 and representing 4% of the foreign born adults(8).

In the evaluation of 25(OH)D status, the concentration of 25(OH)D at which PTH becomes suppressed, also called the inflection point, is used to define low 25(OH)D level(9, 10). Biochemical deficiency is defined as the combination of low 25(OH)D levels and elevated PTH levels; whereas clinical deficiency is defined as the combination of low 25(OH)D levels and decreased BMD (4, 5, 9–11).

Beyond 25(OH)D levels, bioavailable-25(OH)D is gaining attention as a marker of vitamin D sufficiency (12, 13). Bioavailable-25(OH)D is the fraction of total 25(OH)D which is clinically active and has two components: (25(OH)D bound to albumin) and free 25(OH)D. Total 25(OH)D has three components and is the sum of (25(OH)D bound to vitamin D binding protein (VDBP)) and (25(OH)D bound to albumin) and free 25(OH)D. Notwithstanding the debate about the accuracy of the measurement of VDBP, it has been suggested that the bioavailable-25(OH)D is a better indicator of vitamin D sufficiency than 25(OH)D(12–14). However, no data in African immigrants is available on the relationship of bioavailable-25(OH)D to BMD or PTH.

Therefore, our primary goals were to determine in African immigrants (a) 25(OH)D levels, (b) the 25(OH)D inflection point and (c) the prevalence of biochemical and clinical deficiency. Our secondary goal was to assess the clinical value of bioavailable-25(OH)D by examining the relationship of bioavailable-25(OH)D to PTH and BMD.

MATERIALS AND METHODS

The Africans in America cohort enrolls immigrants from sub-Saharan Africa, who are living in the metropolitan Washington, DC area (latitude 38°53'N). As described previously, enrollees in the cohort are undergoing assessment of insulin resistance, beta-cell function and glucose tolerance status(15–17). In this report, we focus on the studies specifically performed to evaluate vitamin D status.

Of 197 African immigrants enrolled, 11 were excluded. Nine were taking vitamin D supplements, one person was found to have primary hyperparathyroidism and one person reported having granulomatous disease. Therefore, vitamin D status was evaluated in 186 African immigrants (69% male, age 38 ± 10 (mean $\pm$ SD) range 20–64y, BMI 27.7 ± 4.5 , range 18.2–41.2 kg/m²). The African region of origin of the participants was: 54% West, 21% Central and 25% East (Supplemental Table 2 lists the countries in each region). None of the women wore veils. Recruitment was achieved by newspaper advertisements, flyers and the NIH website. Participants self-identified as healthy. The absence of anemia, liver, renal, and thyroid disease was confirmed by routine laboratory tests. The study was approved by the NIDDK Institutional Review Board ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00484861) Identifier: NCT00484861). All participants gave written informed consent.

Analytic Measures

25(OH)D was measured by the LiasonX chemiluminescence immunoassay, with an interassay coefficient of variation (CV) of 2.2% (Diasorin, Stillwater, MN). VDBP was available in 181 consecutively enrolled participants and measured by commercial enzyme-linked immunosorbent monoclonal assay (R&D Systems, Minneapolis, MN). The inter-assay and intra-assay CV for VDBP measurement was 5.1–7.4% and 5.7–6.2%, respectively. Albumin and alkaline phosphatase were measured on the Roche Cobas 6000 Analyzer (Roche Diagnostics, Indianapolis, IN). Ionized calcium and intact PTH were available in 106 consecutively enrolled participants. Ionized calcium levels were measured by the ABL837 calcium ion-selective electrode instrument (Radiometer, Westlake, OH).

Intact PTH was measured by electrochemiluminescence immunoassay on the Roche Cobas e601 analyzer with an inter-assay CV of 3.7%.

Whole Body Bone Mineral Density

BMD was obtained from whole body dual-energy X-ray absorptiometry (DXA) scans (Hologic Discovery, Bedford, MA)(18, 19). T-scores present BMD relative to same sex individuals at peak bone mass, which is between age 20 and 29 years of age(20). T-scores can be presented as sex-specific only or race and sex-specific. For this study, white and African-American sex-specific T-scores were calculated with NHANES 1999–2004 as the reference population(21). As recommended by the International Society for Clinical Densitometry (ISCD), white T-scores were used to determine fracture risk (20). Therefore, osteopenia was defined as white T-scores between -1.0 and -2.5 and osteoporosis as white T-scores ≤ -2.5 . African-American T-scores were used to determine race-based differences in BMD.

Low 25(OH)D Levels and Deficiency

Low 25(OH)D was defined as the 25(OH)D concentration at which PTH became suppressed (i.e. the inflection point).

Biochemical 25(OH)D deficiency was defined as the combination of $\text{PTH} > 65 \text{ pg/mL}$ and 25(OH)D below the inflection point.

Clinical 25(OH)D deficiency was defined as white T-scores ≤ -1.0 and 25(OH)D below the inflection point.

Bioavailable-25(OH)D

Bioavailable-25(OH)D was calculated as described by Powe et al.(13)(Supplementary Methods).

Statistical Analyses

For comparison of continuous variables, one-way ANOVA with Bonferroni corrections were used. Chi-square was used for categorical variables. Pearson correlations were performed to examine associations between 25(OH)D, bioavailable-25(OH)D, BMD and PTH. Odds ratios were calculated to determine if low 25(OH)D levels occurred with T-scores of ≤ -1.0 . Seasonal variation in 25(OH)D and bioavailable-25(OH)D was evaluated with Kruskal-Wallis.

To determine the inflection point, the level of 25(OH)D at which PTH becomes suppressed, a two part procedure was performed. First, locally weighted regression scatterplot smoothing (LOWESS) was performed with PTH vs. 25(OH)D. LOWESS is a nonparametric method used to fit a smooth curve to data(22). Second, multivariate adaptive regression splines (MARS) were used to identify the value of the inflection point detected by the smoothed data(23).

Statistical analyses were performed with STATA v13 (College Station, Texas). The Python open source package statsmodels (v. 0.6.1) was used for the LOWESS modeling with default parameters (statsmodels.api.nonparametric.lowess). The MATLAB open source package ARESLab (v. 1.5.1) was used for the MARS analysis. Results are presented as mean $\pm$ SD unless stated otherwise. $P < 0.05$ was considered statistically significant.

RESULTS

Population Characteristics

Demographic and social characteristics including duration of stay in the United States did not differ by African region of origin (Table 1). In addition, 25(OH)D levels did not differ between immigrants from West and Central Africa or Central and East Africa. However, immigrants from West Africa had higher 25(OH)D levels than immigrants from East Africa ($P=0.02$) (Table 1). Nonetheless, VDBP, albumin, calcium, alkaline phosphatase, PTH and percent of immigrants with 25(OH)D <20 ng/mL did not differ by African region of origin. Therefore, the entire cohort was evaluated as a single group.

Vitamin D levels

Mean 25(OH)D levels for the cohort were 21 ± 8 , range 4–48 ng/mL (Table 1). Eighty-three percent (155/186) of African immigrants had 25(OH)D <30 ng/mL and 46% (85/186) had 25(OH)D <20 ng/mL (Table 1).

Seasonal Variation

All of the African immigrants lived in the Washington, DC area and the concentration of 25(OH)D did not vary by season ($P=0.45$) (Figure 1). To ensure exposure to different seasons, the 9% (17/186) of immigrants who had been in the United States for less than two years were excluded and the comparison by season repeated. The repeat analyses showed no seasonal variation in 25(OH)D levels ($P=0.64$). Therefore, no adjustments for season were performed.

Parathyroid Hormone

Similar to the larger cohort, the 106 African immigrants who had PTH levels had a prevalence of 25(OH)D <30 ng/mL and <20 ng/mL of 84% (89/106) and 45% (48/106) respectively. PTH levels were 44.8 ± 16.2 pg/mL, range 20.2–101.8 pg/mL.

A significant inverse correlation was observed between PTH and 25(OH)D ($r=-0.31$, $P<0.01$) (Figure 2a). With LOWESS modeling (Figure 2b) followed by MARS analyses (Figure 2c), it was determined that the inflection point, which is the 25(OH)D concentration at which PTH became suppressed, was 20 ng/mL.

Twelve of the 106 African immigrants had PTH >65 pg/mL. The characteristics of these 12 immigrants are provided in Table 2. Eight of the 12 African immigrants with elevated PTH levels had 25(OH)D <20 ng/mL. Therefore, the prevalence of *biochemical 25(OH)D deficiency* was 8% (8/106). The 4% (4/106) of immigrants with PTH >65 pg/mL and 25(OH)D ≥ 20 ng/mL were categorized as PTH resistant.

Bone Mineral Density and Vitamin D

No correlation was found between BMD and 25(OH)D ($r=0.01$, $P=0.89$) (Figure 2).

Assessment of BMD by white T-scores—Six percent (11/177) of African immigrants (8 men, 3 women, age range 31 to 63y) had osteopenia with white T-scores between -1.0 and -2.2 (Figure 3). No African immigrants had white T-score ≤ -2.5 . Therefore, no one was classified as osteoporotic.

Of the 11 African immigrants with white T-scores ≤ -1.0 , only five immigrants had 25(OH)D concentrations <20 ng/mL. Therefore *clinical 25(OH)D deficiency*, occurred in 3% (5/177) of African immigrants (Figure 2).

Supporting the horizontal relationship between BMD and 25(OH)D, the odds ratio for 25(OH)D occurring with white T-scores ≤ -1.0 was: 1.04, 95% CI:0.30, 3.53, $P=0.96$ (Figure 3).

Assessment of BMD by African-American T-scores—Twenty-four percent (42/177) of African immigrants had African-American T-scores ≤ -1.0 . Specifically, 23% (40/177) (29 men, 11 women, age range 20 to 64y) had African-American T-scores between -1.0 and -2.5 and 1% (2/177) (1 man, 1 woman, age range 42–48y) had African-American T-scores ≤ -2.5 (Supplemental Figure 1).

Using 25(OH)D <20 ng/mL and African-American T-scores, the odds ratio for low vitamin D being associated with decreased BMD was: 1.03, 95% CI:0.52, 2.07, $P=0.93$.

Bioavailable-25(OH)D

Bioavailable 25(OH)D concentrations for cohort were: 7 ± 4 , range 1–21 ng/mL and did not vary by African region of origin. However, bioavailable-25(OH)D tended to be higher in immigrants from West than East Africa ($P=0.09$) (Table 1). Bioavailable-25(OH)D did not vary across four seasons, ($P=0.66$) (Supplement Figure 2). There was a significant inverse correlation between PTH and bioavailable-25(OH)D ($r=-0.22$, $P=0.03$) (Supplemental Figure 3a). The concentration of bioavailable-25(OH)D at which PTH was suppressed was 11 ng/mL (Supplemental Figure 3b and 3c). In addition, there was no correlation with BMD ($r=0.03$, $P=0.70$), (Supplemental Figure 4).

DISCUSSION

In this first study of the relationship of vitamin D to bone health in African immigrants to the United States, we report that as PTH becomes suppressed at a 25(OH)D concentration of 20 ng/mL the definition of low vitamin D as 25(OH)D <20 ng/mL appears to be appropriate for African immigrants. Yet even using this threshold, nearly 50% of African immigrants would be classified as low, but only 8% had biochemical deficiency and 3% had clinical deficiency. The wide gap between the prevalence of low vitamin D and evidence of adverse consequences presents a dilemma about how widely to provide vitamin D supplementation. Finally, we found that in this study, 25(OH)D and bioavailable-25(OH)D levels provided equivalent physiological information about vitamin D status. Each of these findings is

discussed in sequence and related to reports in the literature about vitamin D in African-Americans and white populations.

Vitamin D Levels

Similar to reports in African-Americans, we found that 83% of African immigrants had 25(OH)D<30ng/mL and 46% had 25(OH)D levels <20ng/mL(18, 24). In comparison, the frequency of 25(OH)D <30 ng/mL and <20 ng/mL is lower in whites, specifically 70% and 30% respectively(18, 24).

Vitamin D Thresholds and Biochemical Deficiency

In the 106 immigrants who had PTH levels, we identified the inflection point for 25(OH)D as 20 ng/mL. In other studies, 25(OH)D inflection points have been reported to range from less than 20 ng/mL to as high as 40 ng/mL(11, 25, 26). In three studies specifically focused on African descent populations, we found reports of inflection points for 25(OH)D of 16, 19 and 20 ng/mL. For example, Aloia et al. evaluated 124 postmenopausal African-American women and identified an inflection point for 25(OH)D of 16 ng/mL(25). Emilion and Emilion studied 117 pre-menopausal African women living in Paris, and found a 25(OH)D inflection point of 19 ng/mL(26). Wright et al. reported that in 461 African-American men and women, aged 50 to 79, the 25(OH)D inflection point was 20 ng/mL(27). It is notable that these three investigations and our study of African immigrants enrolled men and women across a wide age range, yet each study found very similar inflection points for 25(OH)D.

Defining *biochemical deficiency* as PTH>65 pg/mL and 25(OH)D<20 ng/mL, 11% (12/106) had elevated PTH but only 8% (8/106) had biochemical deficiency (i.e. PTH>65 pg/mL and 25(OH)D<20 ng/mL) (Table 2). For the 4% (4/106) of immigrants with PTH>65 pg/mL levels and 25(OH)D ≥ 20 ng/mL, PTH resistance must be considered. PTH resistance is decreased skeletal sensitivity to the bone resorptive effects of PTH and has been invoked to explain both denser bones and decreased rate of osteoporotic fracture in African-Americans(28).

Among the eight immigrants with biochemical deficiency, only two had evidence of abnormality. A 50 year old man had slight hypocalcemia with an ionized calcium concentration of 1.11 mmol/L (normal 1.12 to 1.32). In addition, a 41 year old man had both elevated alkaline phosphatase level of 107 U/L (normal 35–105) and decreased BMD with a white T-score of –1.2. Nonetheless, all individuals with evidence of biochemical deficiency should be provided with vitamin D supplementation.

Vitamin D Thresholds and Clinical Deficiency

As reported in African-Americans (18), no relationship (i.e. correlation) was observed between BMD and 25(OH)D in African immigrants. In contrast, in whites low 25(OH)D strongly correlates with declining BMD and predicts increased fracture risk (18). Therefore, in predominantly white populations, vitamin D supplementation is considered to be an important tool for primary prevention(4, 5). In African-Americans, the paradoxical findings of low 25(OH)D levels, low fracture risk and high BMD, has led investigators from three key studies, the Women's Health Initiative, the National Osteoporosis Risk Assessment and

the Study of Osteoporotic Fractures, to suggest that the development of race-specific guidelines may be necessary(29–31). The underlying assumption is that African-Americans may need less 25(OH)D to maintain bone health than whites. Our work with African immigrants provides support for this view in another population of African descent.

Overall in our study, low BMD occurred across a wide range of 25(OH)D (9 to 35 ng/mL), (Figure 2). Furthermore, the odds ratio for 25(OH)D<20 ng/mL predicting T-score < -1.0 was not significant. Therefore, when low BMD does occur in African immigrants, reasons other than low vitamin D must also be considered. Nonetheless, for the 3% (5/177) of African immigrants who met the classic definition of *clinical deficiency*, vitamin D supplementation would be wise.

Interestingly, 24% of African immigrants had African-American T-scores -1.0 but only 6% had white T-scores -1.0 ($P<0.001$). The higher prevalence of low BMD using African-American rather than white T-scores, suggests that relative to white controls, BMD is higher in African immigrants than whites.

There may be genetic reasons for why people of African descent appear to be relatively exempt from the adverse effects of low vitamin D levels on bone health. Studies of African-Americans have revealed that as degree of African ancestry increases, vitamin D levels decrease but bone density increases(1–3). Bone structure may also be a factor. Nelson et al. has reported that African-American and Black South African women have thicker bone cortices and lower buckling ratio than white American and white South African women(32). Furthermore, even at the same BMD, the Study of Osteoporotic Fractures has revealed that African-Americans are less likely to experience a fracture than whites(31). Overall, in African descent populations higher BMD and enhanced bone structure may mitigate the potential for adverse effects of low total-25(OH)D levels on bone health.

Seasonal Variation

The Endocrine Society states that inadequate exposure to sunlight is a leading cause of low vitamin D levels(4). Therefore, African descent populations with low vitamin D levels, could potentially be treated with increased exposure to sunlight. However, cutaneous production of precursors to 25(OH)D represents a balance between exposure to sunlight and the melanin content of the skin; the former increases and the latter decreases cutaneous production of vitamin D precursors(33).

Seasonal variation in 25(OH)D levels occurs in whites and African-Americans, but the variation is less in African-Americans(34–36). This race difference in degree of seasonal variation is usually attributed to the effect of melanin(37). Yet, in African immigrants living in the Washington, DC metropolitan area (Latitude 38°53'N), we found that 25(OH)D did not vary by season(Figure 1). Presumably African immigrants have less genetic admixture than African-Americans and a higher cutaneous melanin content. In the absence of seasonal variation in 25(OH)D, increased exposure to sunlight is not likely to be a viable therapeutic option for vitamin D insufficiency in African immigrants.

Bioavailable-25(OH)D

In studies comparing African-Americans and whites, it has been proposed that bioavailable-25(OH)D levels were more informative about vitamin D status than 25(OH)D (12, 13). However, in our investigation in which only one race was studied and a monoclonal antibody for VDBP was used, the clinical insight provided by studying bioavailable-25(OH)D was equivalent to that obtained from 25(OH)D. For example, as occurred with 25(OH)D, bioavailable-D did not vary by season. In addition, neither 25(OH)D nor bioavailable-25(OH)D correlated with BMD. However, the inflection point for bioavailable-25(OH)D was 11 ng/mL compared to 20 ng/mL for 25(OH)D. As bioavailable-25(OH)D represents a fraction of the total 25(OH)D concentration, a lower inflection point would be expected.

Limitations

Limitations of this investigation include the cross-sectional design and the fact that PTH levels were available in only 106 of the 186 participants. However, for the identification of the 25(OH)D inflection point, our sample size is similar to other studies in which 25(OH)D levels were evaluated relative to PTH(25, 26). Another challenge is that we used whole body BMD instead of site-specific bone density. The advantage of whole body BMD is that it provides a single composite measure of bone density, which has been shown in data from NHANES 1999–2004 to correlate well with sub-regions such as the lumbar spine(18, 19). Another issue is the fact that this was a convenience sample. But it is worth noting that recruitment for our study was facilitated by the fact that in the Washington, DC metropolitan area African immigrants represent 15% of the foreign born population compared to 4% in the United States overall(8). Age is another consideration. In our study, mean age was 38 ± 10 , range 20 to 64y. If the participants were older, it is possible that a higher percentage might have had a detectable decrease in BMD. However, a value of this study is that it is a report of 25(OH)D levels in African immigrants in the age range from 20 to 64 years. In addition, seasonal variation was assessed across the population rather than in the same individuals in different seasons. Finally, this study did not enroll children, adolescents or lactating women and no veiled women requested to participate, so the results of this investigation cannot be extrapolated to these groups.

Conclusion

In this evaluation of African immigrants to America, we report that PTH became suppressed at 25(OH)D concentration of 20 ng/mL. Therefore a threshold of <20 ng/mL appears to be an appropriate threshold to define low vitamin D in African immigrants. It is not clear, however, that a recommendation to provide vitamin D supplementation to all Africans immigrants with $25(\text{OH})\text{D} < 20$ ng/mL should be made. Although ~50% of African immigrants had $25(\text{OH})\text{D} < 20$ ng/mL, only 8% had biochemical deficiency and 3% had clinical deficiency. Definitely, vitamin D supplementation should be provided to the African immigrants with $25(\text{OH})\text{D} < 20$ ng/mL and either elevated PTH or decreased BMD. The clinical conundrum is whether vitamin D supplementation should be offered to the large number of African immigrants with $25(\text{OH})\text{D} < 20$ ng/mL and no evidence of bone disease. To avoid unnecessary treatment and potential risks from raising vitamin D levels(30, 38,

39), prospective studies are necessary to determine the need and safety of vitamin D supplementation in African immigrants to the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Chen Z, Qi L, Beck TJ, Robbins J, Wu G, Lewis CE, et al. Stronger bone correlates with African admixture in African-American women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2011; 26(9):2307–16. Epub 2011/05/19.
2. Ochs-Balcom HM, Preus L, Wactawski-Wende J, Nie J, Johnson NA, Zakharia F, et al. Association of DXA-derived bone mineral density and fat mass with African ancestry. *J Clin Endocrinol Metab*. 2013; 98(4):E713–7. Epub 2013/02/26. [PubMed: 23436924]
3. Signorello LB, Williams SM, Zheng W, Smith JR, Long J, Cai Q, et al. Blood vitamin d levels in relation to genetic estimation of African ancestry. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2010; 19(9):2325–31. Epub 2010/07/22.
4. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011; 96(7):1911–30. Epub 2011/06/08. [PubMed: 21646368]
5. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011; 96(1):53–8. Epub 2010/12/02. [PubMed: 21118827]
6. LeFevre ML. Screening for vitamin d deficiency in adults: u.s. Preventive services task force recommendation statement. *Ann Intern Med*. 2015; 162(2):133–40. Epub 2014/11/25. [PubMed: 25419853]
7. Reed SD, Laya MB, Melville J, Ismail SY, Mitchell CM, Ackerman DR. Prevalence of vitamin D insufficiency and clinical associations among veiled East African women in Washington State. *J Womens Health (Larchmt)*. 2007; 16(2):206–13. Epub 2007/03/29. [PubMed: 17388737]
8. Gambino, CP.; Trevelyan, EN.; Fitzwater, JT. *The Foreign-Born Population from Africa: 2008–2012*. 2014.
9. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J Clin Endocrinol Metab*. 2012; 97(4):1153–8. Epub 2012/03/24. [PubMed: 22442274]
10. Rosen CJ, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, et al. IOM committee members respond to Endocrine Society vitamin D guideline. *J Clin Endocrinol Metab*. 2012; 97(4):1146–52. Epub 2012/03/24. [PubMed: 22442278]
11. Ginde AA, Wolfe P, Camargo CA Jr. Schwartz RS. Defining vitamin D status by secondary hyperparathyroidism in the U.S. population. *Journal of endocrinological investigation*. 2012; 35(1):42–8. Epub 2011/05/25. [PubMed: 21606669]
12. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med*. 2013; 369(21):1991–2000. Epub 2013/11/22. [PubMed: 24256378]

13. Powe CE, Ricciardi C, Berg AH, Erdenesanaa D, Colterone G, Ankers E, et al. Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2011; 26(7):1609–16. Epub 2011/03/19.
14. Bouillon R, Jones K, Schoenmakers I. Vitamin D-binding protein and vitamin D in blacks and whites. *N Engl J Med*. 2014; 370(9):879. Epub 2014/02/28. [PubMed: 24571765]
15. O'Connor MY, Thoreson CK, Ricks M, Courville AB, Thomas F, Yao J, et al. Worse cardiometabolic health in african immigrant men than african american men: reconsideration of the healthy immigrant effect. *Metab Syndr Relat Disord*. 2014; 12(6):347–53. Epub 2014/05/13. [PubMed: 24814168]
16. Sumner AE, Thoreson CK, O'Connor MY, Ricks M, Chung ST, Tulloch-Reid MK, et al. Detection of Abnormal Glucose Tolerance in Africans Is Improved by Combining A1C With Fasting Glucose: The Africans in America Study. *Diabetes Care*. 2015; 38(2):213–9. Epub 2014/10/24. [PubMed: 25338926]
17. Ukegbu UJ, Castillo DC, Knight MG, Ricks M, Miller BV 3rd, Onumah BM, et al. Metabolic syndrome does not detect metabolic risk in African men living in the U.S. *Diabetes Care*. 2011; 34(10):2297–9. Epub 2011/08/30. [PubMed: 21873563]
18. Gutierrez OM, Farwell WR, Kermah D, Taylor EN. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. *Osteoporos Int*. 2011; 22(6):1745–53. Epub 2010/09/18. [PubMed: 20848081]
19. Looker AC, Melton LJ 3rd, Harris T, Borrud L, Shepherd J, McGowan J. Age, gender, and race/ethnic differences in total body and subregional bone density. *Osteoporos Int*. 2009; 20(7):1141–9. Epub 2008/12/03. [PubMed: 19048179]
20. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, et al. International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. *Bone*. 2008; 43(6):1115–21. Epub 2008/09/17. [PubMed: 18793764]
21. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. *PloS one*. 2009; 4(9):e7038. Epub 2009/09/16. [PubMed: 19753111]
22. Cleveland W, Devlin S. Locally weighted regression: an approach to regression analyses by local fitting. *J Am Stat Assoc*. 1988; 83(403):596–610.
23. Friedman JH, Roosen CB. An introduction to multivariate adaptive regression splines. *Statistical methods in medical research*. 1995; 4(3):197–217. Epub 1995/09/01. [PubMed: 8548103]
24. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch Intern Med*. 2009; 169(6):626–32. Epub 2009/03/25. [PubMed: 19307527]
25. Aloia JF, Talwar SA, Pollack S, Feuerman M, Yeh JK. Optimal vitamin D status and serum parathyroid hormone concentrations in African American women. *Am J Clin Nutr*. 2006; 84(3):602–9. Epub 2006/09/09. [PubMed: 16960175]
26. Emilion E, Emilion R. Estimation of the 25(OH) vitamin D threshold below which secondary hyperparathyroidism may occur among African migrant women in Paris. *Int J Vitam Nutr Res*. 2011; 81(4):218–24. Epub 2012/01/13. [PubMed: 22237770]
27. Wright NC, Chen L, Niu J, Neogi T, Javadi K, Nevitt MA, et al. Defining physiologically “normal” vitamin D in African Americans. *Osteoporos Int*. 2012; 23(9):2283–91. Epub 2011/12/23. [PubMed: 22189572]
28. Cosman F, Morgan DC, Nieves JW, Shen V, Luckey MM, Dempster DW, et al. Resistance to bone resorbing effects of PTH in black women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1997; 12(6):958–66. Epub 1997/06/01.
29. Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, et al. Osteoporosis and fracture risk in women of different ethnic groups. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2005; 20(2):185–94. Epub 2005/01/14.

30. Cauley JA, Danielson ME, Boudreau R, Barbour KE, Horwitz MJ, Bauer DC, et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: the Women's Health Initiative (WHI). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2011; 26(10):2378–88. Epub 2011/06/29.
31. Cauley JA, Lui LY, Ensrud KE, Zmuda JM, Stone KL, Hochberg MC, et al. Bone mineral density and the risk of incident nonspinal fractures in black and white women. *JAMA*. 2005; 293(17): 2102–8. Epub 2005/05/05. [PubMed: 15870413]
32. Nelson DA, Pettifor JM, Barondess DA, Cody DD, Uusi-Rasi K, Beck TJ. Comparison of cross-sectional geometry of the proximal femur in white and black women from Detroit and Johannesburg. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2004; 19(4):560–5. Epub 2004/03/10.
33. O'Connor MY, Thoreson CK, Ramsey NL, Ricks M, Sumner AE. The uncertain significance of low vitamin D levels in African descent populations: a review of the bone and cardiometabolic literature. *Progress in cardiovascular diseases*. 2013; 56(3):261–9. Epub 2013/11/26. [PubMed: 24267433]
34. Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr*. 1998; 67(6):1232–6. Epub 1998/06/13. [PubMed: 9625098]
35. Levis S, Gomez A, Jimenez C, Veras L, Ma F, Lai S, et al. Vitamin d deficiency and seasonal variation in an adult South Florida population. *J Clin Endocrinol Metab*. 2005; 90(3):1557–62. Epub 2005/01/07. [PubMed: 15634725]
36. Luque-Fernandez MA, Gelaye B, VanderWeele T, Ferre C, Siega-Riz AM, Holzman C, et al. Seasonal variation of 25-hydroxyvitamin D among non-Hispanic black and white pregnant women from three US pregnancy cohorts. *Paediatric and perinatal epidemiology*. 2014; 28(2):166–76. Epub 2013/12/21. [PubMed: 24354847]
37. Armas LA, Dowell S, Akhter M, Duthuluru S, Huerter C, Hollis BW, et al. Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol*. 2007; 57(4):588–93. Epub 2007/07/20. [PubMed: 17637484]
38. Amrein K, Quraishi SA, Litonjua AA, Gibbons FK, Pieber TR, Camargo CA Jr. et al. Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: a cohort study. *J Clin Endocrinol Metab*. 2014; 99(4):1461–9. Epub 2014/01/16. [PubMed: 24423347]
39. Sempos CT, Durazo-Arvizu RA, Dawson-Hughes B, Yetley EA, Looker AC, Schleicher RL, et al. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. *J Clin Endocrinol Metab*. 2013; 98(7): 3001–9. Epub 2013/05/15. [PubMed: 23666975]

Figure 1. Box and whisker plots of 25(OH)D by season

Winter: December through February; **Spring:** March through May; **Summer:** June through August; **Fall:** September through November.

Figure 2. PTH vs. 25(OH)D

a: PTH vs. 25(OH)D (n=106)

Solid lines represent simple regression. Dotted line is at PTH=65 pg/mL, the threshold for elevated PTH.

b: Locally weighted regression scatterplot smoothing (LOWESS) of data in Figure 2a.

c: Multivariate adaptive regression splines (MARS) analyses of smoothed data in Figure 2b.

Figure 3. BMD vs. 25(OH)D with white T-scores

a: BMD vs. 25(OH)D (n=177)

b: Men only (n=123)

c: Women only (n=54)

Table 1Demographic and Metabolic Characteristics^a

Variable	Total (n=186)	West (n=100)	Central (n=40)	East (n=46)	P-value ^b
Age (y)	38±10	39±11	38±10	37±7	0.29
Male (%)	69%	71%	68%	67%	0.87
BMI (kg/m ²)	27.7±4.5	27.4±4.3	28.9±5.2	27.3±3.9	0.13
Smoking Prevalence	6%	8%	0%	7%	0.19
Health Insurance	65%	61%	68%	70%	0.55
Exercise 30min, 3x/week	28%	30%	28%	26%	0.88
Years in America (y)	12±9	13±10	11±9	12±8	0.45
25(OH)D (ng/mL) ^c	21±8	23±9	20±7	19±7	0.02 ^d
Prevalence of 25(OH)D<20 (ng/mL)	46%	43%	40%	57%	0.22
Prevalence of 25(OH)D<30 (ng/mL)	83%	75%	90%	96%	<0.01
VDBP (µg/mL) ^e	82±60	83±61	77±51	87±67	0.75
Albumin (g/dL)	3.9±0.3	4.0±0.3	3.9±0.3	3.9±0.2	0.46
Bioavailable-25(OH)D (ng/mL) ^e	7±4	8±4	7±3	6±4	0.09
Calcium (mmol/L) ^f	1.18±0.05	1.18±0.05	1.19±0.04	1.18±0.05	0.55
Alkaline Phosphatase (U/L)	66±19	65±20	68±17	68±18	0.63
PTH (pg/mL) ^f	44.8±16.2	47.2±17.6	43.2±17.9	42.1±11.7	0.34

^aUnless noted otherwise, results presented as mean±SD^bComparisons by one-way ANOVA with Bonferroni corrections for continuous & chi-square for categorical variables^cTo convert to nmol/L multiply by 2.5^dNo significant difference between West and Central Africans or Central and East Africans ($P>0.05$). $P=0.02$ for difference between West and East Africans^eResults available for 181 consecutively enrolled participants^fResults available for 106 consecutively enrolled participants

Table 2

Characteristics of the African immigrants with Elevated PTH (by 25(OH)D)

No.	25(OH)D (ng/mL)	PTH ^a (pg/mL)	Sex	Age (years)	Calcium ^b (mmol/L)	Alkaline Phosphatase ^c (U/L)	T-score White Reference ^d	T-Score AA Reference ^d
1	4	101.8	M	46	1.17	97	0.3	-0.5
2	9	98.5	M	54	1.22	79	0.6	-0.2
3	11	74.4	M	50	1.11	91	2.2	1.3
4	13	67.4	M	39	1.13	54	1.3	0.5
5	13	79.3	M	44	1.15	69	0.0	-0.8
6	16	75.3	F	46	1.21	88	-0.2	-1.1
7	18	70.5	M	42	1.18	88	-0.3	-1.1
8	18	78.8	M	41	1.18	107	-1.2	-1.9
9	20	92.6	M	52	1.15	38	1.1	0.3
10	21	81.5	F	33	1.13	46	-0.4	-1.2
11	26	68.5	M	38	1.23	57	2.0	1.0
12	35	69.2	M	63	1.18	69	-1.0	-1.7

^aNormal range for PTH: 15–65 pg/mL

^bNormal range for Calcium: 1.12–1.32 mmol/L

^cNormal range for alkaline phosphatase: 35–105 U/L

^dNHANES 1999–2004(see reference 21)