Published in final edited form as:

Endocr Pract. 2016 August ; 22(8): 911–919. doi:10.4158/EP151079.OR.

Association between 25-hydroxyvitamin D and Intact Parathyroid Hormone Levels across Latitude among Adults with African Ancestry

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Abstract

Objective—To compare levels of 25-hydroxyvitamin D (25[OH]D) associated with a plateauing of intact parathyroid (iPTH) across latitudes among adults with African ancestry.

Methods—This study included approximately 500 adults of African ancestry ages 25–45 years living in four sites: Chicago, IL (: 41° N), Jamaica (17° N), Ghana (6° N), and South Africa (34° S). Multivariate linear regression models, a non-linear logistic growth curve model and piecewise linear models with a single knot were fitted to estimate the 25[OH]D level associated with a plateauing of iPTH with adjustment for covariates. Goodness of fit was compared using computer intensive permutation tests.

Results—Mean age was 34.7 (SD 6.2) years and 46.5% were male. Within each site, the percentage of participants with iPTH level ≥ 65 pg/ml was higher among women vs. men and was most frequent among South African women (17.1%) and lowest among Jamaican men (0.6%). Goodness of fit tests supported linear regression as the preferred model for the association

between iPTH and 25[OH]D in the four sites with no 25[OH]D level associated with iPTH plateauing in any site. The slope of the association between 25[OH]D and iPTH differed by latitude and was strongest in U.S.. ($\beta = -0.81$; 95% CI = $-1.03, -0.59$), and weakest in Jamaica, ($\beta = -0.45$; 95% CI $-0.71, -0.18$) with covariate adjustment but differences in slopes were small.

Conclusion—The association between 25[OH]D and iPTH appears linear among adults with African ancestry regardless of latitude within a range of 25[OH]D levels between 10–60 ng/ml.

Keywords

Vitamin D; parathyroid hormone; African-Americans; race; latitude; environment; African ancestry

Introduction

Total 25-hydroxyvitamin D (25[OH]D) levels that define vitamin D deficiency are historically based on 25[OH]D levels associated with rickets in children. However, the level of 25[OH]D that defines optimal or sufficient vitamin D status remains controversial(1–3) and clinicians frequently rely on measures of intact parathyroid hormone (iPTH) along with serum calcium before recommending vitamin D supplementation. The controversy surrounding the definition of optimal 25[OH]D levels are especially relevant for African Americans because the majority of these individuals have 25[OH]D levels < 30 ng/ml (4, 5), with 25[OH]D levels ≥ 30 ng/ml considered optimal.(3) In addition, over 7 out of 10 African Americans have a 25[OH]D level less than 20 ng/ml.(5) While darker skin pigmentation is associated with a leftward shift in the distribution of 25[OH]D levels,(6) African Americans demonstrate lower 25[OH]D levels for a given level of iPTH compared to whites.(7, 8) The association between 25[OH]D levels and bone mineral density and response to 25[OH]D supplementation with regards to bone mineral density also differs by race/ethnicity.(7, 9–12)

We have previously demonstrated a leftward shift in the distribution of 25[OH]D levels among adults with African ancestry with increasing latitude.(4) Thus, higher sun exposure for adults with African ancestry is associated with higher levels of 25[OH]D and the low levels of 25[OH]D noted among African Americans is not the ancestral normal. This study extends those previous findings by examining the association between total 25[OH]D and iPTH across four study populations of young adults with African ancestry across a wide range of latitudes. We hypothesized that the level of 25[OH]D associated with a plateauing of iPTH differs by latitude.

Methods

Study population

The source population for this cross-sectional ecologic study was participants of the Vitamin D Ancillary (VIDA) study. VIDA was conceived as an extension of the Modeling of the Epidemiologic Transition Study (METS); the design and recruitment procedures for this study have been described in detail elsewhere (9). In brief, twenty-five hundred adults, ages 25–45, were enrolled between January, 2010 and December, 2011. Approximately 500 healthy adults between the ages of 18–40 were enrolled in each of five study sites: viz.,

Chicago, IL (41° N), Kingston, Jamaica (17° N), Kumasi, Ghana (6° N), Cape Town, South Africa (34 S°) and Victoria Seychelles (4° S). All participants had predominantly African ancestry. The sites were chosen to cover a wide range of economic development and industrialization. The protocol was approved by the Institutional Review Board of Loyola University Chicago, IL, USA; the Committee on Human Research Publication and Ethics of Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; the Research Ethics Committee of the University of Cape Town, South Africa; the Board for Ethics and Clinical Research of the University of Lausanne, Switzerland and the Ethics Committee of the University of the West Indies, Kingston, Jamaica. Written informed consent was obtained from all participants. We did not include data from the Seychelles site in this analysis because iPTH values were missing or below the limit of quantification in over one-third of the sample. Thus, this study focuses on iPTH and 25[OH]D levels measured from adults living in the U.S., South Africa, Jamaica and Ghana. Figure 1 shows the total number of participants recruited from each site. We excluded individuals with iPTH values more than 4 standard deviations outside the overall average iPTH or with levels below the limit of quantification, 25[OH]D values below the limit of quantification and individuals with missing data on age, sex, serum creatinine to estimate glomerular filtration rate (eGFR), or body mass index (BMI). This left a total of 1,854 adults in the study sample (478 in U.S., 490 in South Africa, 396 in Jamaica and 490 in Ghana) with complete information (Figure 1).

25-hydroxyvitamin D (25[OH]D) and intact parathyroid hormone (iPTH)

Standardized protocols were used for blood sampling. Specimens were immediately processed to separate plasma, frozen and shipped to the Coordinating Center in Chicago. When all samples were available, they were aliquotted and then sent to the Department of Laboratory Medicine at the University of Washington for measurement of 25[OH]D and to the Fairview Laboratory in Minneapolis, MN for measurement of iPTH and serum creatinine. The liquid chromatography-tandem mass spectrometric assay was used to assay 25[OH]D levels.(13, 14) The calibration of the assay was verified using the NIST standard reference material SRM 972. Inter-assay variability was 6.0% at 11.5 ng/mL and 5.6% at 12.3 ng/mL for 25[OH]D₂ and 25[OH]D₃, respectively. Intact PTH was measured by Fairview Diagnostic Laboratories, Minneapolis, MN using the chemiluminescent immunology with 20.8% CV in the 7–18 pg/mL, 4.1% in the 19–117 pg/ml and 7.25% in the 118–158 pg/mL range.

Covariates

At the baseline clinic visit, height, weight, waist circumferences, and blood pressure were measured. Weight was measured without shoes to the nearest 0.1 kg using a standard balance (Health-o-meter, Bridgeview, IL). Height was measured using a stadiometer without shoes and head held in the Frankfort plane to the nearest 0.1 cm. Waist circumference was measured to the nearest 0.1 cm with a tape measure placed at the umbilicus and around the iliac crest. Each participant completed at least two 24-hour dietary recalls using the multiple pass method. The Nutrient Data System for Research (NDSR; U. Minnesota, Minneapolis, MN) was modified to accommodate foods and recipes unique to each site using the currently available site-specific nutrient databases and previously collected 24-hour recall data. Basic

health history information was collected using standardized questionnaires. Serum creatinine was measured at the St. Gallen Switzerland lab using nephelometry. Glomerular filtration rate was estimated using the CKD-EPI creatinine based equation.(15)

Statistical Methods

All analyses were carried out using STATA 14.0 (Stata Corp., College Station, TX). Characteristics of the four study populations are examined with continuous variables shown as means (standard deviation), categorical variables shown as frequency (%) and variables with a non-parametric distribution shown as medians (interquartile range). Descriptive statistics were calculated for all variables and comparisons across countries were performed via Analysis of Variance for continuous variables and χ^2 statistics for categorical variables. When applicable, tests were adjusted for multiple comparisons using the Bonferroni approach. The distribution of 25[OH]D and iPTH levels were estimated via kernel density estimators with the Epanechnikov kernel function.(16) Based on clinical cut-points that define increased iPTH, 3 categories of iPTH were created: < 45 pg/ml, 45–64.9 and 65 pg/ml.(17, 18) Four categories of 25[OH]D were examined: < 12 ng/ml, 12–20 ng/ml, 20–30 ng/ml and 30 ng/ml.(1, 3) The distribution of 25[OH]D categories by iPTH categories (< 45, 45–64.9 and 65 pg/ml) were determined by site for both men and women.

Differences in the linear association between iPTH and 25[OH]D in the US and all other sites were tested via the application of multivariate linear regression models including 25[OH]D by site interactions in addition to covariates sex, age, BMI, eGFR, and dietary intake of calcium, phosphate, vitamin D and the season of blood collection for each site.. Age, BMI, eGFR, and dietary intake of calcium, phosphate and vitamin D were all fitted in the model as continuous variables. Given the potential non-linear association between iPTH and 25[OH]D, a locally weighted regression smooth scatterplot (LOESS) line was fitted to characterize the association between iPTH and 25[OH]D. A scatter plot diagram was constructed and a locally weighted smooth scatter (LOWESS) curve was superimposed to graphically describe the association between iPTH and total 25[OH]D.(19, 20) In addition to the multivariate linear regression model, two parametric models were fitted: a non-linear logistic growth curve model and a piecewise linear model with a single knot.

Precisely,

$$\text{Logistic Growth: } PTH = A + B \exp(C \times 25[OH]D) + \Omega \times Z + \varepsilon$$

$$\text{Piecewise Linear: } PTH = \beta_0 + \beta_1 (25[OH]D - \tau)_- + \beta_2 (25[OH]D - \tau)_+ + \Omega \times Z + \varepsilon$$

In these models Z denotes the vector of confounders (site, age, sex, BMI, and eGFR), τ is a knot of the piecewise linear model, and X_- takes on the value X if $X < 0$ and zero otherwise. Similarly, X_+ takes on the value X if $X > 0$ and zero otherwise. These models are used to capture the non-linear association between iPTH and 25[OH]D and to estimate the 25[OH]D level associated with a plateauing of iPTH. Under the piecewise linear model the 25[OH]D level associated with a plateauing of iPTH is estimated by τ . A grid search approach was implemented for estimating the change point parameter.(21) The non-linearity of the

association between iPTH and 25[OH]D was assessed by comparing the goodness of fit of a piecewise model and a linear model, using a computer intensive permutation test.(22) All models adjusted for covariates sex, age, BMI, eGFR, and dietary intake of calcium, phosphate and vitamin D and the season of blood collection for each site.

Results

Table 2 shows the characteristics of the study sample by site and by sex. Mean age and BMI ranged as high as 35.6 (6.2) years and 33.7 (5.6) kg/m², respectively, among U.S. men to an age as low as 33.7 (5.6) years among men in South Africa and a BMI as low as 22.2 (2.7) among men in Ghana. Among women, mean age ranged as high as 35.0 (6.3) years among U.S. women to as low as 33.1 (6.0) years among women in South African while mean BMI ranged from 34.1 (8.9) kg/m² among U.S. women to 25.4 kg/m² among women in Ghana. Estimated glomerular filtration rate (eGFR) was > 80 ml/min/1.73 m² among all participants for all sites. The distribution of total 25[OH]D levels across sites has been previously reported.(4) Mean total 25[OH]D levels were lowest in the U.S. and highest in Ghana for both men and women. Overall, iPTH values were higher among women vs. men for all study sites but mean iPTH values were fairly similar across the site for men and women. Calcium intake for both men and women was highest in the U.S. and lowest in South Africa.

Figure 2 shows the distribution of iPTH levels in the four sites. The overall distribution of iPTH for each site showed substantial overlap and all sites showed a rightward skewness. Table 2 shows the distribution of vitamin D categories by iPTH groups < 45, 45–64.9 and 65 pg/ml by site for both men and women. Within each site, the percentage of participants with iPTH level 65 pg/ml was higher among women vs. men and was most frequent among women in South Africa (17.1%) and lowest among men in Jamaica (0.6%). Jamaica showed the lowest percentage of participants with iPTH 65 pg/ml (0.6%) and no participant in Jamaica or Ghana had a total 25[OH]D level 12 ng/ml.. Among participants with total 25[OH]D values 30 ng/ml., prevalence of iPTH levels < 45 pg/ml ranged from as high as 84.4% in Jamaica to as low as 67.2% in Ghana. Across all sites, less than 10% of participants with a low calcium intake (< 405 mg/day) had an iPTH value 65 pg/ml.

Figure 3 shows the scatter plot of iPTH values by 25[OH]D levels and corresponding LOWESS curve in each of the four sites. A linear association could be appreciated between iPTH levels and 25[OH]D levels for each of the sites and all sites combined. Figure 4 represents the comparison of the three statistical models, exponential, linear, and piecewise linear, for each of the four sites, whereas Figure 5 demonstrates the relationship between iPTH and 25[OH]D in all sites combined, as captured by the three statistical models. The permutation test comparing the linear and piecewise models resulted in a non-statistical goodness-of-fit improvement in each of the sites, US (p=0.92), South Africa (p=0.92), Ghana (p=0.75), Jamaica (p=0.99), and all sites combined (p=0.213). Thus, a linear regression model was the preferred model for studying the association between iPTH and 25[OH]D and no level of 25[OH]D was associated with a plateauing of iPTH in any of the four sites or in the four sites combined. Differences in the strength of the linear relationship between iPTH and 25[OH]D, or slope, as assessed by multivariate linear regression with adjustment for covariates by site, yielded statistically significant results (p-value for

interaction = 0.024). The corresponding slopes for each of the four sites were: US, -0.81 (95% CI = 1.03, -0.59, South Africa, -0.39 (95% CI -0.60, -0.18), Ghana, -0.72 (95% CI -0.97, -0.47), and Jamaica, -0.45 (95% CI -0.71, -0.18).

Discussion

This study utilized data from four different populations with African ancestry with a wide range of mean 25[OH]D values. Despite the large differences in the distribution of 25[OH]D values, the distribution of iPTH values was fairly similar across sites for both men and women. The association between 25[OH]D and iPTH was linear with no 25[OH]D threshold associated with a plateauing of iPTH levels in all four sites. The strength of the linear relationship between iPTH and 25[OH]D, or slope, differed by site with the strongest association noted in the Chicago, IL site but overall differences were small. Thus, while increasing sun exposure is associated with higher 25[OH]D levels, the overall association between 25[OH]D and iPTH does not differ markedly by latitude among adults with African ancestry. Deficient levels of 25[OH]D (< 12 ng/ml) were limited to the U.S. and South African study groups and over half of the participants with deficient 25[OH]D levels had an iPTH level < 45 pg/ml and approximately 20% had an iPTH level > 65 pg/ml. These findings are consistent with another study which examined 25[OH]D and iPTH levels among women referred to a bone clinic.(23) Most previous studies that examined the association between iPTH and 25[OH]D have focused on adults living in the U.S. or Europe and have not been able to compare the association between 25[OH]D and iPTH across a wide range of latitudes that will influence sun exposure. We found that the association between 25[OH]D and iPTH was linear in each of the four sites and in the four sites combined. Thus, no level of 25[OH]D level could be linked with an iPTH plateau. While the healthy adult populations we studied in Jamaica, Ghana and South Africa had substantially higher levels of 25[OH]D compared to African Americans, the percentage of iPTH values > 65 pg/ml were fairly similar across the study sites. Therefore it may be premature to assert a population optimal value for 25[OH]D, especially for adults with African ancestry.

Optimal 25[OH]D levels are defined as levels > 30 ng/ml by the Endocrine Society's Clinical Guideline for the Evaluation, Treatment and Prevention of Vitamin D Deficiency, which also defines 25[OH]D deficiency as 25[OH]D levels < 20 ng/ml and 25[OH]D insufficiency as 25[OH]D levels 20–29 ng/ml.(3) The justification for the 25[OH]D level defining sufficient 25[OH]D (> 30 ng/ml) is based on studies showing a plateau of iPTH (24–26) and optimal calcium absorption with 25[OH]D levels above a range of 30–32 ng/ml. (27). However, defining vitamin D sufficiency as 25[OH]D levels associated with a plateauing of iPTH has been criticized because not all studies have demonstrated a threshold effect with many studies showing a linear association between 25[OH]D and iPTH across the entire spectrum of 25[OH]D levels.(2) Sai et al summarized data from a total of 70 studies which examined levels of serum 25[OH]D by serum iPTH levels in a variety of populations and settings.(28) In 59 studies, no consistent 25[OH]D cut-point was associated with a plateau in iPTH. Valcour and colleagues utilized data from over 300,000 adults with paired measurement of both iPTH and 25[OH]D levels and found no threshold of 25[OH]D above which higher 25[OH]D levels were associated with a plateauing of iPTH levels in the total study population and within groups stratified by age.(29) The IOM Committee to

Review Dietary Reference Intakes for Vitamin D and Calcium did not delineate cut-points to define 25[OH]D deficiency or insufficiency but instead stated that 25[OH]D levels < 12 ng/ml and 12–20 ng/ml were states of being at risk for vitamin D deficiency and insufficiency, respectively, because low 25[OH]D levels may not be associated with rickets or osteomalacia in settings of adequate calcium intake.(1)

The strengths of this study include the use of a 25[OH]D assay that utilizes an NIST standard and standardized methods of collecting demographic and dietary data from four study populations across a wide range of latitudes. The limitations of the study include lack of information on serum calcium and urinary calcium excretion and additional measures of bone turnover. Study participants were overall healthy and young and hypocalcemia would be uncommon in each of the sites. Another limitation is use of dietary recalls to estimate calcium intake. Across all three sites, 24-hour dietary recalls have been shown to underestimate dietary energy intake.(33) This study was restricted to adults with African ancestry and findings may not be generalizable to populations without African ancestry. While the distribution of total 25[OH]D levels consistently differs by race/ethnicity,(4) the distribution of bioavailable 25[OH]D levels does not appear to differ by race/ethnicity.(30–32) Future studies should examine the association between bioavailable 25[OH]D and iPTH in study populations that differ by race/ethnicity and by environmental latitude.

Conclusion

Despite a wide range of 25[OH]D levels across latitudes, the distribution of iPTH levels across latitude is fairly similar among young adults with African ancestry. The linear relationship between 25[OH]D and iPTH among adults with African ancestry within 25[OH]D levels between 10–60 ng/ml does not support the use of 25[OH]D thresholds associated with iPTH plateaus in previous studies to define optimal vitamin D status.

Acknowledgments

Funding: This study was supported in part by funding from the National Institutes of Health 1R01DK90360-1A1 (RD), 5R01DK080763-04 (AL), and by Loyola University Chicago – Intramural Award LU#204006.

Abbreviations

25[OH]D	25-Hydroxyvitamin D
iPTH	Intact Parathyroid Hormone
UV	ultraviolet
METS	Modeling of the Epidemiologic Transition Study
VIDA	Vitamin D Ancillary

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Figure 1. Flowchart for selection of study participants included in the analyses

¹PTH levels below the limit of quantification (LOQ) were defined as missing;

²25(OH)D values below the limit of quantification (LOQ) were defined as missing

³Confounders included estimated glomerular filtration rate, body mass index, age, and sex

Figure 2. Distribution of intact Parathyroid Hormone Levels (pg/ml) for each of the four sites, United States (41° N), South Africa (34° S), Ghana (6° N), and Jamaica (17° N)

Figure 3. Scatter plot and Locally Weighted Scatterplot Smoothing (LOWESS) curve of intact Parathyroid Hormone by 25-Hydroxyvitamin D Levels by Study Site. The open circles represent women while the closed circles represent men

Figure 4.

Graph showing the association between 25[OH]D and iPTH using linear regression, piecewise linear regression and exponential models with adjustment for sex, age, body mass index, estimated glomerular filtration rate, calcium, phosphate and vitamin D intake and season of blood collection within each site

Figure 5.

Graph showing the association between 25[OH]D and iPTH for all sites combined using linear regression, piecewise linear regression and exponential models with adjustment for sex, age, body mass index, estimated glomerular filtration rate, calcium, phosphate and vitamin D intake and season of blood collection within each site.

Table 1

Characteristics of the Study Participants by Site and by sex

	Chicago, IL (41° N)	Cape Town, South Africa (34° S)	Kingston, Jamaica (17° N)	Kumasi, Ghana (6° N)	ANOVA p-values
Men					
Sample size [n]	237	227	157	203	
iPTH [pg/mL]	36.7 ± 20.8	34.2 ± 17.9	[†] 30.6 ± 12.7	36.4 ± 16.6	< 0.01
25[OH]D [ng/mL]	17.3 ± 7.7	[*] 24.4 ± 9.3	[*] 29.6 ± 7.3	[*] 31.8 ± 7.2	< 0.001
Age [y]	35.6 ± 6.2	[†] 33.7 ± 5.6	[†] 34.1 ± 6.0	34.7 ± 6.7	< 0.01
BMI [kg/m ²]	29.8 ± 7.6	[*] 22.4 ± 4.2	[*] 23.5 ± 4.5	[*] 22.2 ± 2.7	< 0.001
Calcium Intake [mg/d]	697.2 ± 390.8	[*] 308.3 ± 172.0	[*] 596.7 ± 332.3	[*] 366.0 ± 156.0	< 0.001
Phosphate Intake [mg/d]	1290.2 ± 540.5	[*] 621.5 ± 281.8	[*] 1070.7 ± 435.2	[*] 1019.7 ± 382.6	< 0.001
Vitamin D Intake [µg/d]	5.4 ± 8.1	[*] 2.0 ± 2.4	[†] 3.2 ± 4.2	4.1 ± 7.6	< 0.001
Women					
Sample size [n]	241	263	239	287	
iPTH [pg/mL]	43.9 ± 21.8	42.6 ± 23.4	40.3 ± 16.4	47.6 ± 23.8	< 0.01
25[OH]D [ng/mL]	17.0 ± 8.4	[*] 22.7 ± 6.9	[*] 28.2 ± 6.8	[*] 29.2 ± 6.2	< 0.001
Age [y]	35.0 ± 6.3	[*] 33.1 ± 6.0	34.7 ± 6.3	[†] 34.0 ± 6.7	< 0.01
BMI [kg/m ²]	34.1 ± 8.9	[*] 32.0 ± 8.2	[*] 29.3 ± 6.4	[*] 25.4 ± 5.0	< 0.001
Calcium Intake [mg/d]	611.9 ± 291.6	[*] 311.0 ± 147.2	[*] 496.2 ± 240.5	[*] 315.1 ± 139.4	< 0.001
Phosphate Intake [mg/d]	1058.3 ± 415.0	[*] 551.1 ± 205.4	[*] 870.2 ± 318.7	[*] 802.8 ± 280.8	< 0.001
Vitamin D Intake [µg/d]	3.6 ± 3.6	[*] 2.0 ± 2.3	[†] 2.7 ± 2.8	5.1 ± 15.5	< 0.001

* P < 0.001 compared to Chicago, IL site;

[†] P < 0.01 compared to Chicago, IL site

Table 2

Distribution of intact parathyroid hormone (pg/ml) categories by site and by 25-hydroxyvitamin D levels*

	Chicago, US (41° N)		Cape Town, South Africa (34° S)		Kingston, Jamaica (17° N)		Kumasi, Ghana (6° N)	
	iPTH (pg/ml)		iPTH (pg/ml)		iPTH (pg/ml)		iPTH (pg/ml)	
	< 45	65	< 45	65	< 45	65	< 45	65
Overall	64.4%	12.1%	70.0%	13.1%	72.5	4.6%	60.8	13.3%
By 25[OH]D (ng/ml)								
12	53.6%	20.0%	62.5%	18.8%	---	---	---	---
> 12 – 19.9	61.4%	13.2%	61.3%	19.7%	58.3%	5.6%	43.5%	17.4%
20	78.5%	3.4%	74.7%	9.5%	73.9%	4.4%	61.8%	13.1%
30	83.3%	2.8%	82.4	3.9%	84.4%	2.0%	67.2%	7.8%
Males	71.7%	11.0%	79.3%	8.4%	84.7%	0.6%	72.4%	4.9%
Females	57.3%	13.3%	62.0%	17.1%	64.4%	7.1%	52.6%	19.2%

* Note that data from individuals with iPTH 45–64 pg/ml are not shown