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REFERENCE RANGE FOR SERUM PARATHYROID HORMONE

John F. Aloia, MD, **Martin Feuerman, MS**, and **James K. Yeh, PhD**
From the Bone Mineral Research Center, Winthrop University Hospital, Mineola, New York.

Abstract

Objective—To determine whether the reference range for parathyroid hormone (PTH) should be lowered (from 65 pg/mL to a proposed value of 46 pg/mL) with use of the Allegro radioimmunometric assay.

Methods—We examined the reference range for PTH, adjusted for serum 25-hydroxyvitamin D (25-OHD), in 503 healthy African American and white women, who were 20 to 80 years old. We also analyzed other factors that are thought to influence PTH levels.

Results—Univariate predictors of PTH were identified, and a multivariate model was developed with use of the variables and PTH. Serum PTH was significantly higher in black study subjects than in white study subjects ($P<0.02$). Increasing PTH was also significantly correlated with increasing body mass index, age, and serum creatinine and with decreasing dietary calcium intake and serum 25-OHD levels. A stepwise multiple linear regression analysis yielded the following predictors of PTH: body mass index ($R^2 = 9.4\%$), age ($R^2 = 1.0\%$), and serum 25-OHD ($R^2 = 0.8\%$). In our study population, many PTH values were above the proposed new upper limit of 46 pg/mL.

Conclusion—The upper limit of the reference range for serum PTH should not be changed. Factors to be considered in analysis of serum PTH values in the upper reference range in patients with normocalcemia include obesity, race, 25-OHD levels, advanced age, serum creatinine, and dietary calcium intake.

Abbreviations

BMD = bone mineral density; **BMI** = body mass index; **CV** = coefficient of variation; **25-OHD** = 25-hydroxy-vitamin D; **PTH** = parathyroid hormone

INTRODUCTION AND BACKGROUND

The earliest radioimmunoassay for parathyroid hormone (PTH) used polyclonal antisera directed against intact PTH(1-84) (1). Most early assays were directed against the middle or C-terminus of the PTH peptide (2). Investigators soon found that several fragments of PTH in serum were derived from the parathyroid glands and from peripheral metabolism of PTH(1-84) (3–11). The later development of a 2-site radioimmunometric assay allowed measurement of primarily intact PTH(1-84) (12–19). This assay uses 2 antibodies directed toward different regions of the peptide. The antibody directed toward the C-terminus is bound to a solid support. The nonbinding PTH fragments are washed away, and a second antibody, directed at the N-terminus, is used. This 2-site radioimmunometric assay improved detection of intact PTH and decreased detection of PTH peptides that did not have both N- and C-terminus antigenic regions. The assay had a low detection limit, facilitating the diagnosis of hypoparathyroidism, and separated hyperparathyroidism from hypercalcemia of malignancy. It did not detect even

Address correspondence and reprint requests to Dr. John F. Aloia, Winthrop University Hospital, 222 Station Plaza North, Suite 510, Mineola, NY 11501..

a high concentration of inactive C-terminus fragments. The assay technique was accepted throughout the world (20).

During the past decade, however, studies showed that vitamin D insufficiency severe enough to increase serum PTH levels was present in many people (21–24). Because vitamin D is in large part derived from sunlight, low levels of serum 25-hydroxyvitamin D (25-OHD) are found particularly in dark-skinned persons, in the winter, in those living in northern latitudes, or in those with decreased exposure to sunlight because of clothing coverage or use of sunblock preparations. The high prevalence of hypovitaminosis D suggested that the "normal" populations used to determine the reference range for PTH could have included a large number of subjects with vitamin D insufficiency and secondary hyperparathyroidism, resulting in an elevated PTH reference range.

Souberbielle et al (25), using a common immunoradiometric assay (Allegro intact PTH, Nichols Institute, San Juan Capistrano, CA), found that exclusion of subjects with low 25-OHD levels had a significant effect on the upper limits of the PTH reference range. They found that when 25-OHD levels were considered, the upper limits of "normal" of PTH declined from 65 pg/mL to 46 pg/mL in subjects with 25-OHD levels above 30 nmol/L, a change that would have clinical ramifications. Subsequently, these investigators validated their proposal of 46 pg/mL as the upper limit of the reference range of PTH by a review of medical records in patients with osteopenia (26). In an editorial accompanying their publication, however, their conclusions were questioned (27). It was pointed out that their patients had either osteopenia or osteoporosis, rather than being "normal." In addition, the authors used an in-house assay for 25-OHD that yields values 40% lower than those from commercial assays. The editorial called for rigorous establishment of the normal range for PTH in subjects who are both vitamin D sufficient and without metabolic bone disease. Because PTH levels increase with advancing age, it was also suggested that normal values should be determined in subjects of all ages rather than simply the age-group with a mean of 59 ± 13 years included in the study by Souberbielle et al (25).

In a previously published study of skeletal physiology in healthy black and white women who were 20 to 80 years of age, we measured serum 25-OHD levels and PTH levels (28). In this report, we analyze those data to answer the following questions: (*1*) What are the factors, including serum 25-OHD, that influence serum PTH levels? and (*2*) Should the reference range of serum PTH be lowered?

MATERIAL AND METHODS

Study Participants

Participants were recruited from advertising in the local media and through a direct mail campaign. Exclusion characteristics consisted of any chronic illness, including hypertension, diabetes, or morbid obesity, any past history of illness or use of medication known to affect bone metabolism, any use of oral contraceptives or hormone replacement therapy, or a history of hysterectomy. After telephone screening, women were further excluded from the study because of abnormal results of blood chemistry studies (multichannel chemistries, complete blood cell count, urinalysis, free thyroxine, thyroid-stimulating hormone) or abnormal physical findings. The study was approved by the Institutional Review Board of Winthrop University Hospital, and written informed consent was obtained from each participant. A detailed history and physical questionnaire for risk factors was completed by each study participant, with the assistance of a nurse clinical research coordinator and physician. A 3-day diet history was obtained and was reviewed with the study dietitian, who used food models to estimate portion sizes.

The most common causes for exclusion from the study were undiagnosed diabetes, thyroid disease, and anemia. The study group consisted of 148 black and 129 white premenopausal participants and 87 black and 139 white postmenopausal subjects.

Laboratory Studies

Initial screening of the study participants demonstrated normal findings on physical examination and routine laboratory studies, including serum calcium, phosphorus, and alkaline phosphatase. Serum PTH was measured by the Allegro intact PTH immunoassay, purchased from Nichols Institute. The intra-assay coefficient of variation (CV) was 5.2%, and the interassay CV was 9.0%. Serum 25-OHD was measured by a radioreceptor assay purchased from Incstar. The intra-assay CV was 4.1%, and the interassay CV was 7.0%. This assay is now manufactured by DiaSorin (Stillwater, MN).

Bone Mineral Density

For each participant, we obtained individual scans of the proximal femur, radius, and lumbar spine (L2 through L4), using a Lunar Radiation densitometer (Lunar Radiation, Madison, WI, model DPX-L, software program 1.3Y). The scan was run at medium speed. In addition, the bone mineral density (BMD) of the radius was measured on a Hologic densitometer (Hologic, Waltham, MA). The CV of each site measured was 1% to 1.5%.

Statistical Analysis

Values for continuous variables are reported as means ± SD. Because of skewness (that is, the lognormal nature) of PTH and other serum values, we assessed the correlation of continuous predictors of PTH with the nonparametric (Spearman) correlation. Differences between ethnic groups for PTH were analyzed by the nonparametric rank sum test. Stepwise multiple linear regression was used to determine the best independent predictors of PTH; $P<0.05$ was the cutoff value. Because PTH was not normally distributed, we used a nonparametric approach for reference intervals (that is, selecting 2.5 and 97.5 percentiles), instead of the mean ± 2 SD. All calculations were performed with use of SAS (Version 8.2) for Windows. Results were considered statistically significant when P values were <0.05.

Metabolic bone disease was considered present if the Z-score was below −2.0 for either the lumbar spine or the femoral neck. Z-scores for each patient were calculated by computing the number of standard deviations below an age-matched BMD. Formulas for age-matched BMD were provided by GE Medical Systems (Lunar, Madison, WI).

Statistical methods have been developed for formal consideration of whether reference ranges should be partitioned (29). A stringent approach is to calculate the difference between the 2 subgroup means and divide it by the length of the reference range of the combined single group (30). If the ratio exceeds 25%, partitioning should be considered. A “middle-of-the-road” approach uses about 10% rather than 25% as the threshold ratio (31,32). This is the approach recommended by the National Committee for Clinical Laboratory Standards, now called the Clinical and Laboratory Standards Institutes. We analyzed our data with use of both methods for race, menopausal status, race-menopausal status, body mass index (BMI), and 25-OHD dichotomized by using various cutoff values from >30 nmol/L versus ≤30 nmol/L to >80 nmol/L versus ≤80 nmol/L, in increments of 10 nmol/L.

RESULTS

Predictors of PTH—Univariate and Multivariate Analysis

In Table 1, we provide descriptive statistics of all continuous variables and the univariate correlations with PTH. Mean PTH was significantly higher in black study subjects (38.9 ± 14.0

pg/mL) than in white study subjects (35.8 ± 12.6 pg/mL) ($P<0.02$). Increasing PTH was also significantly correlated with increasing BMI (Fig. 1), increasing age (Fig. 2), decreasing dietary calcium, increasing serum creatinine, and decreasing 25-OHD (Fig. 3). The largest correlation was between PTH and BMI ($r = 0.29$; $P<0.0001$).

All significant correlations and race were used as candidates for a stepwise multiple linear regression analysis, as well as interaction terms with race. Predictors of PTH in order of decreasing importance were BMI ($R^2 = 9.4\%$; $P<0.0001$), age ($R^2 = 1.0\%$; $P<0.01$), and serum 25-OHD ($R^2 = 0.8\%$; $P<0.04$). The total R^2 for this model was 11.2% ($P<0.001$). Analysis of our unadjusted data showed that 22.3% of our overall study population had serum PTH levels above 46 pg/mL (27.8% of black study subjects and 17.5% of white study subjects) (Fig. 3).

Reference Ranges for PTH for Various 25-OHD Cutoff Values

We computed reference ranges for PTH for various cutoff values of serum 25-OHD and reported these data separately for black subjects and white subjects as well as for both study groups combined (Table 2). Reference ranges were computed for 25-OHD cutoff values of >30 nmol/L and, in 10-unit increments, up to and including >80 nmol/L.

In addition to the unadjusted 2.5 and 97.5 percentiles, the corresponding PTH reference ranges adjusted for age were compiled (Table 2). The adjusted PTH percentiles were obtained by adjusting each patient's PTH values by age with use of the following method. By regression of PTH values against age for each race, we obtained regression coefficients (slopes) of 0.29 pg/mL per year for black study subjects and 0.09 pg/mL per year for white study subjects. A race-specific PTH adjustment was made for each patient, which either increased or decreased the PTH value for each year of patient age that was above or below the respective mean age of the race. In other words, the formula we used for PTH adjustment for age was PTH (adjusted) = PTH (unadjusted) + slope X (mean age – patient age). As shown in Table 2, adjustment for age did not significantly change the reference ranges. With relatively large sample sizes for the various 25-OHD cutoff values, only a very slight decline in the 97.5 percentile of PTH for increasing cutoff values was noted (Table 2). This finding is consistent with the small negative correlation of PTH versus 25-OHD (Fig. 3); however, the finding by Souberbielle et al (25) of 46 pg/mL as a proposed revised upper limit of the reference range for PTH does not appear to have been replicated with our data.

PTH Values Adjusted for *Z*-Scores and 25-OHD Level: Reference Ranges for Age Decades

In Table 3, the study participants with serum 25-OHD levels above 50 nmol/L are considered (214 participants). When we also excluded patients with *Z*-scores below −2.0 for the lumbar spine or the femoral neck, the number declined by 5% of participants. Thus, the data in Table 3 are based on 205 study participants (40 black and 165 white women). This 5% decline appears reasonable on the basis of our *Z*-score criterion of −2.0. A scatterplot of the PTH values generating the reference ranges for each age decade is shown in Figure 2. Examination of the 97.5 percentiles (where sample sizes are largest) does not suggest lowering of the upper limit of normal PTH from 65 pg/mL to 46 pg/mL. For both groups combined in Figure 2, many plotted points exist between these 2 PTH limits for most of the age decades. In contrast, relatively few data points are above 65 pg/mL. These graphical observations seem to indicate the adequacy of the current upper limit of normal PTH of 65 pg/mL.

Trichotomized BMI as a Predictor of PTH

To investigate high BMI further as a predictor of PTH, we trichotomized BMI. If we redo the regression by taking logs of PTH and consider normal BMI as the reference group, we are able to estimate the percentage increase of PTH attributable to being overweight or obese, in comparison with normal BMI, adjusted for age and 25-OHD. The unadjusted percentage

increases of PTH from normal to overweight and from normal to obese are 16.3% and 27.7%, respectively. Clearly, being overweight or obese is associated with a much higher percentage increase of PTH in comparison with increasing age as much as 10 years or decreasing 25-OHD by 10 nmol/L. Adjusted percentage increases for high BMI are just slightly less than the unadjusted increases.

Ethnic Group as a Predictor of PTH

Univariate analysis showed that black study subjects had significantly higher PTH values than did white study subjects ($P<0.02$). Nonetheless, in the multivariate analysis, with use of $P<0.05$ as a cutoff, ethnic group failed to enter into the multivariate analysis. It is of interest to determine why this result eventuates—that is, how differences in PTH by race are explained by other variables and to what extent. An analysis of mean age, BMI, and 25-OHD, stratified by race, is presented in Table 4. Black subjects in our study population had significantly higher BMI, younger age, and lower levels of serum 25-OHD than did white subjects. These 3 continuous variables, however, were univariate and multivariate predictors of PTH; once entered into the equation in a stepwise manner, race became insignificant ($P = 0.80$). We adjusted mean PTH by race for various combinations of variables in a regression model. When we adjusted only for age and 25-OHD, differences in PTH by race could not be completely explained, inasmuch as race was still significant ($P = 0.05$). With the additional adjustment for BMI, ethnic mean differences of PTH became very small (0.4 pg/mL) and insignificant ($P = 0.80$).

Partitioning of Subgroups in the PTH Reference Range

The more stringent approach, proposed by Sinton et al (30), indicated no need for consideration of partitioning of any of the subgroups, including the variables of BMI and serum 25-OHD. The less stringent analysis, recommended by the National Committee for Clinical Laboratory Standards, would support the conclusion that partitioning would not be considered for 25-OHD (and other variables) but could be considered for normal weight versus overweight and obese subjects. The PTH reference range for normal weight subjects was 16.0 to 59.6 pg/mL in comparison with 18.4 to 72.7 pg/mL for those who were overweight or obese. Thus, if one chose to partition PTH values, it would be done on the basis of adiposity rather than serum 25-OHD levels.

DISCUSSION

The current study confirms the manufacturer's reference range for serum PTH with use of the Allegro radioimmunometric assay and establishes that its upper limit should not be lowered from 65 pg/mL. Our study participants were healthy volunteers recruited through a direct mail campaign. Volunteers with chronic illness, morbid obesity, hypertension, diabetes, thyroid disease, or osteoporosis were excluded from the study. They were further found to be healthy by a thorough history and physical examination and routine laboratory studies. Adjustment of the data by excluding subjects with a *Z*-score below −2.0 had no influence on the reference range. Unlike most previous studies, our study included subjects from 20 to 79 years of age. The size of our study population was sufficient to develop a reference range. Formal analysis to determine whether any subgroup should be partitioned suggested only that consideration could be given to partitioning for BMI. We believe it is practical that consideration be given to BMI, age, renal function, vitamin D status, and calcium intake when PTH levels are evaluated.

The problem with standardization and operator variability in 25-OHD assays should be emphasized (33). A variety of methods are available, and different extraction procedures are used. The International Vitamin D External Quality Assessment Scheme is an effort to

harmonize 25-OHD assays among different laboratories (33). Our laboratory is a member of this effort at standardization. Our serum 25-OHD level was based on a radioimmunoassay developed by Incstar, which became the current widely used assay manufactured by DiaSorin. The current DiaSorin assay differs from the original Incstar assay by only +2.75 nmol/L (DiaSorin technical report, 1999).

In addition, comment should be made about the Allegro radioimmunoassay used in the study by Souberbielle et al (25) and our study. Improvements have been made in this assay for intact PTH, resulting in the Immulite and Nichols intact assays (15,34,35). The correlations between these assays and the Allegro assay have been reported to be greater than 0.9 (15,34,35). Moreover, the reference ranges for these assays are essentially the same as that reported for the Allegro assay (36–38). Our findings should apply to these intact PTH assays as well. Because we did not study the newer Scantibodies assay in this population, we cannot comment on the reference range for that assay (39).

Levels of PTH in the highest quartile of the reference range may not always be deleterious. In our comparative study of African American and white women, we found that, despite having lower levels of serum 25-OHD and higher levels of serum PTH, black women have lower bone turnover and higher bone density (28). The higher PTH values found in African American subjects (which some investigators have hypothesized may even be beneficial) seem to be due to lower serum 25-OHD levels and a higher BMI in black women because race did not enter our multivariate model. Moreover, in a recent clinical trial examining vitamin D supplementation in African American women in midlife, we found no effect of vitamin D supplements on bone density (40).

Obesity is associated with low 25-OHD and high PTH levels (41–43). Wortsman et al (44) investigated the mechanism for low serum 25-OHD in the setting of obesity. They compared obese and nonobese subjects after ultraviolet exposure and oral administration of vitamin D_2. Serum concentrations of vitamin D_3 (ultraviolet irradiation) and vitamin D_2 (oral intake) were inversely correlated with BMI. These authors concluded that there is decreased bioavailability of vitamin D because of its deposition in body fat.

Of note, in our current study group, only 12.5% of participants were obese; nevertheless, BMI emerged as the strongest predictor of PTH levels. Our trichotomized analysis of BMI demonstrated that the reference range for PTH is considerably influenced by the presence of obesity. The importance of obesity as a determinant of PTH levels is underscored by the observation that our study population was less obese than the general population in the United States (45).

Age also entered our model for determinants of serum PTH levels. Secondary hyperparathyroidism has been thought to be common in the elderly population because of declining renal function. Vieth et al (46) showed that, for similar 25-OHD concentrations, PTH levels were higher in elderly subjects than in younger persons. This observation is consistent with our findings. They proposed that older adults need more vitamin D to prevent secondary hyperparathyroidism because they require higher 25-OHD concentrations to suppress the elevated PTH levels that accompany declining renal function.

CONCLUSION

The data in this healthy female population suggest that the upper limit of the reference range for PTH with use of the intact Allegro radioimmunometric assay should not be lowered. Instead, in patients with normal serum calcium levels and PTH in the upper reference range, clinicians should consider whether they have higher PTH values because of increased body weight, advanced age, reduced renal function, low dietary calcium intake, or low serum 25-

OHD levels. When these variables are not present, it is appropriate to consider the entity of normocalcemic hyperparathyroidism (25,35–37). Because they are heavier and have lower 25-OHD levels as a group, African American women have higher PTH values than do white women.

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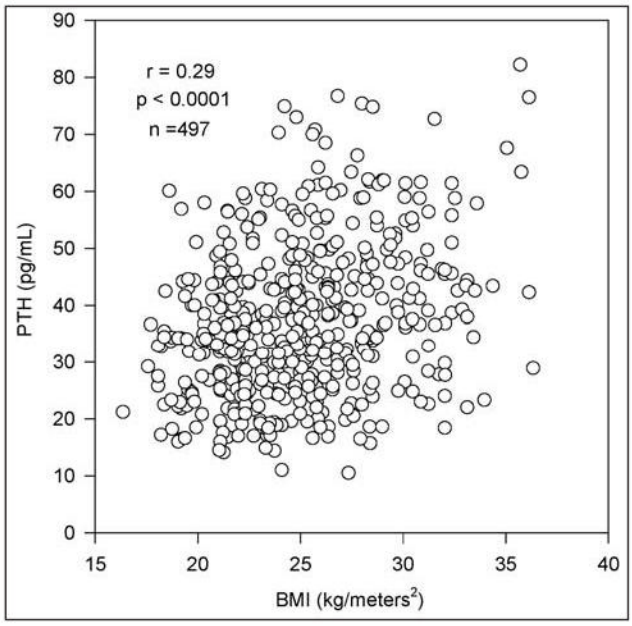

Fig. 1.
Direct correlation of parathyroid hormone (*PTH*) and body mass index (*BMI*) in 497 study subjects.

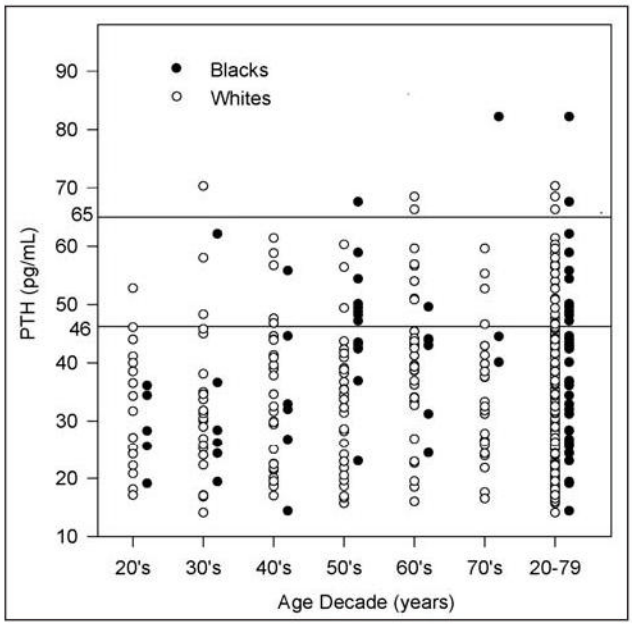

Fig. 2.

Parathyroid hormone (*PTH*) levels for each decade of life from the 20s through the 70s and for the inclusive ages 20 through 79 years. The current upper limit of the reference range for PTH (65 pg/mL) has an expected number of outliers. Use of 46 pg/mL as the upper limit of the reference range would result in a large number of subjects with hyperparathyroidism.

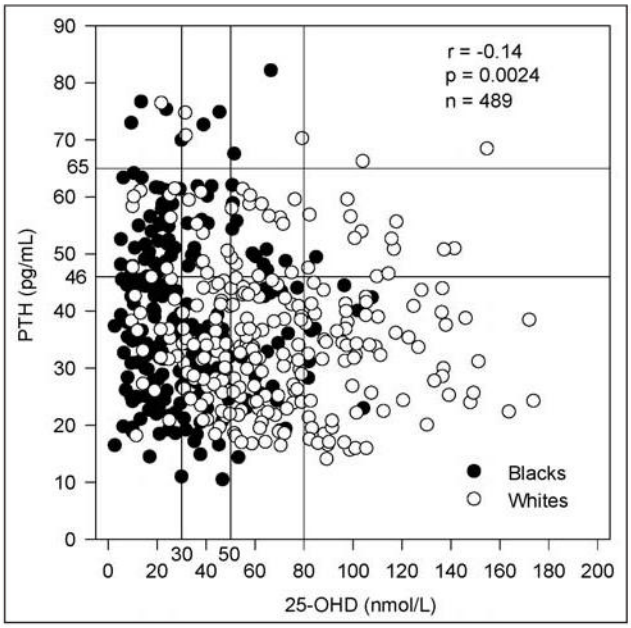

Fig. 3.
Inverse relationship between parathyroid hormone (*PTH*) and serum 25-hydroxyvitamin D (*25-OHD*).

Table 1

Variables and Their Spearman Correlation With Serum Parathyroid Hormone*

Variable	No. of patients†	Mean	Median	SD	Spearman*R*	*P*value‡
Parathyroid hormone (pg/mL)	497	37.3	35.5	13.4	..	..
Age (yr)	503	47.8	48.0	14.6	0.16	0.0005
Dietary calcium (mg/day)	464	659.0	598.0	307.8	−0.12	0.0135
Serum creatinine (mg/dL)	498	0.94	0.93	0.11	0.11	0.0128
Height (cm)	503	163.9	163.0	6.3	0.02	0.6972
Body mass index (kg/m^2)	503	25.0	24.7	3.9	0.29	<0.0001
25-OHD (nmol/L)	492	51.5	44.9	33.8	−0.14	0.0024

* 25-OHD = 25-hydroxyvitamin D.

† Number for whom data were compiled for each specific variable.

‡ Significance of the correlation.

Table 2

Parathyroid Hormone Reference Ranges for Various 25-Hydroxyvitamin D Cutoff Values, Shown for Black Study Subjects, White Study Subjects, and Both Collectively

Cutoff value (nmol/L)	Black study subjects		White study subjects		Black + white study subjects	
	No.	Reference range*	No.	Reference range*	No.	Reference range*
30 or less	127	18.5–70.0 (17.3–67.5)	27	18.2–76.5 (16.5–77.8)	154	18.2–73.0 (17.2–72.2)
>30	101	14.9–72.7 (14.8–67.2)	234	16.6–61.4 (16.0–62.2)	335	16.6–66.3 (16.0–66.0)
>40	65	14.4–74.9 (13.8–74.6)	206	16.6–59.6 (16.0–59.4)	271	16.5–62.1 (15.7–65.2)
>50	42	19.1–67.6 (19.1–66.0)	172	16.5–60.3 (15.8–59.6)	214	16.5–62.1 (15.8–63.8)
>60	30	19.1–82.2 (20.4–74.6)	131	16.0–59.6 (15.7–59.0)	161	16.5–59.6 (15.8–59.0)
>70	15	19.1–49.5 (20.4–47.1)	109	16.0–66.3 (14.8–65.2)	124	16.0–59.6 (15.7–58.8)
>80	9	23.0–49.5 (20.4–45.4)	82	16.0–59.6 (15.7–58.8)	91	16.0–59.6 (15.7–58.8)
No cutoff	228	16.5–72.7 (17.2–67.5)	261	16.8–61.5 (16.4–62.2)	489	16.6–67.6 (16.6–67.2)

* Reference ranges (pg/mL) refer to the 2.5 and 97.5 percentiles (values in parentheses are percentiles adjusted for age).

Table 3

Parathyroid Hormone Reference Ranges Shown by Age Decade for Black Study Subjects, White Study Subjects, and Both Collectively*

Age decade (yr)	Black study subjects		White study subjects		Black + white study subjects	
	No.	Reference range†	No.	Reference range†	No.	Reference range†
20–29	5	19.1–36.1	17	17.1–52.8	22	17.1–52.8
30–39	6	19.4–62.1	24	14.1–70.3	30	14.1–70.3
40–49	6	14.4–55.8	30	17.0–61.4	36	14.4–61.4
50–59	14	23.0–67.8	32	15.7–60.3	46	16.6–60.3
60–69	6	24.4–49.6	38	16.0–68.5	44	16.0–66.3
70–79	3	40.1–82.2	24	16.5–59.6	27	16.5–82.2
Overall (20–79)	40	16.7–74.9	165	16.5–60.3	205	16.5–62.1

* Patients with *Z*-scores less than −2.0 were excluded; all patients had 25-hydroxyvitamin D values >50 nmol/L.

† Reference ranges (pg/mL) refer to the 2.5 and 97.5 percentiles.

Table 4

Analysis of Age, Body Mass Index, and 25-Hydroxyvitamin D, Stratified by Race*

Variable	Black study subjects		White study subjects		*P*value†
	Mean	SD	Mean	SD	
Age (yr)	43.7	13.4	51.4	14.7	<0.0001
Body mass index (kg/m^2)	26.3	4.1	23.9	3.3	<0.0001
25-OHD (nmol/L)	32.7	21.1	67.8	34.3	<0.0001

* 25-OHD = 25-hydroxyvitamin D.

† By rank sum test.