# Racial Differences in Parathyroid Hormone Dynamics*

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**ABSTRACT**

Elevations in PTH levels have been reported in black subjects. Such observations have not been consistent, however, and seem paradoxical in view of the known bone-resorptive action of this hormone and the fact that black subjects have a higher bone mineral density and fewer fractures than their white counterparts. In this study, we used dynamic stimulation of the calcium-PTH axis to fully characterize potential racial differences in PTH dynamics. We, therefore, defined the inverse sigmoidal curve that describes the relationship between serum ionized calcium concentration and intact PTH levels in six normal white and six normal black volunteers and determined the four parameters that characterize this relationship. An elevation in any one of these parameters can result in hyperparathyroidism. Black subjects had higher maximal and minimal PTH responses to hypo- and hypercalcemia (mean intact PTH levels of 9.2 ± 13 and 0.7 ± 0.1 pmol/L respectively) than white subjects (6.9 ± 0.6 and 0.3 ± 0.1 pmol/L, respectively). There were no differences in the set-points or slopes of the curves. Despite the higher baseline and stimulated endogenous PTH levels in black subjects, their baseline and stimulated osteocalcin levels were lower. Our dynamic studies, therefore, document mild hyperparathyroidism in black subjects and suggest mild skeletal resistance to PTH. (*J Clin Endocrinol Metab* **79**: 1642–1647, 1994)

**A**T ANY POINT during their lifetime, black subjects have bone mineral densities (BMD) approximately 10% higher than those of white subjects (1–5) and suffer only one third to one half the number of fractures (6, 7). Because of the significant impact of the PTH-vitamin D endocrine system on bone remodeling and calcium handling, several investigators have evaluated these hormones in black subjects in an attempt to elucidate the basis for their elevated bone mass and reduced risk of fractures.

Elevations in serum PTH or 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] levels, or both, have been noted in black subjects by several investigators (8–13). Although the high serum 1,25-$(OH)_2$D levels are consistent in many studies, the elevation in serum PTH levels is less well established. Studies that evaluated biological markers for PTH action, namely urinary cAMP and TmP/GFR (threshold for tubular reabsorption of phosphorus), have failed to resolve this issue (8, 14). Whereas Bell *et al.* (8) demonstrated high urinary cAMP excretion in the presence of elevated serum C-terminal PTH levels in black subjects, Meier *et al.* (14), in a large study of premenopausal women that controlled for dietary factors, demonstrated no differences in either serum PTH levels or TmP/GFR between the two races. Finally, an autopsy study showed that parathyroid glands of black subjects weighed more than those of white controls (15). The lack of a consen-

sus regarding the status of parathyroid function in previous studies may be explained by the fact that some used older assays, which detect inactive PTH fragments in addition to the biologically active hormone, and by inadequate control of dietary factors (calcium and vitamin D). Therefore, it is unclear at this point whether the previously observed differences in PTH levels between the two races are due to true racial differences in parathyroid physiology or are reflective of differences in environmental and/or dietary variables (14).

Serum ionized calcium (Ca$_i$) is the main regulator of PTH release. The relationship between serum Ca$_i$ and PTH is best described by a steep inverse sigmoidal curve that ensures maintenance of this essential ion within a narrow range. This curve can be defined *in vivo* by the sequential administration of calcium (to raise Ca$_i$) and citrate (to lower Ca$_i$) and can be described by four parameters: 1) maximal responsiveness to hypocalcemic stimuli, 2) maximal suppressibility of PTH in response to hypercalcemia, 3) set-point (the level of Ca$_i$ at which PTH release achieves half of its maximal suppression), and 4) slope of the curve at the set-point (16). Our group has demonstrated that an increase in any one or a combination of these parameters can produce hypersecretion of PTH (16). Therefore, we have employed dynamic modulation of the PTH-Ca$_i$ axis to amplify differences between the two racial groups that may not always be apparent under baseline conditions.

It has been suggested that the preservation of a high bone mass in black subjects, despite their relative hyperparathyroidism, is due to skeletal resistance to PTH action. Our group has also previously demonstrated that serum osteocalcin (OC), an index of bone formation and, therefore, turnover, increases in parallel with the increments in PTH levels during citrate infusion and correlates inversely with the decrements in serum Ca$_i$ (17). We, therefore, measured

serum OC levels concomitantly with serum PTH levels in both black and white subjects in response to citrate infusion to assess the responses of their skeleton to endogenous elevations in PTH levels.

## Materials and Methods

### Subjects

Twelve healthy men, six black and six white, were studied. Subjects were defined as blacks if both parents were of the black race. None was taking medications or had any diseases that could affect calciotropic hormones and/or bone metabolism. Before enrollment in the study, each subject underwent a physical examination and had a laboratory evaluation, which included a multichannel chemistry analysis and complete blood count with differential. Four of the six white subjects have had their data presented in a previous publication and are included to generate the white group control data (18). These subjects were chosen as the ones studied closest in time to the present study and according to the same protocol. There were no differences in the time of year during which the two racial groups were studied. To avoid any confounding effect of obesity on the PTH axis in white subjects (19), all subjects were within ±10% of expected weight for height (midweight for average frame by 1983 Metropolitan Life Insurance tables). The mean calcium intake of black subjects was evaluated with a calcium questionnaire generated by the General Clinical Research Center dietician and averaged 700 ± 100 mg/day. The study was reviewed and approved by the Committee for the Protection of Human Subjects of Brigham and Women's Hospital. Informed written consent was obtained from each subject before participation.

### Study design

The design of the protocol has been described in detail in a previous publication examining PTH dynamics in healthy white volunteers (18). The protocol required two visits to the Ambulatory Clinical Center, usually on two consecutive mornings, the first for a citrate and the second for a calcium infusion. For each visit, the subject arrived at 0800 h, after having fasted for at least 8 h. An iv catheter was placed in a vein of each antecubital fossa and kept open with 5% dextrose in water (D5W). One iv line was used for blood sampling, and the other for infusion of calcium or citrate.

*Day 1.* Citrate [anticoagulant-citrate-dextrose USP Formula A (ACD-A) containing per 100 mL: 2.45 g dextrose, 2.2 g sodium citrate, and 0.7 g citric acid; Fenway Laboratories, Deerfield, IL] mixed in D5W was administered via an iv infusion pump (Travenol, Deerfield, IL). Throughout the course of the infusion, blood pressure was monitored by an automated blood pressure recorder (adult/pediatric vital sign monitor, Critikon, Tampa, FL), and an electrocardiogram was obtained from a cardiac monitor (Physio Control Lifepak 7, Rowayton, CT) at each step before the infusion rate was increased. The study consisted of four 30-min pulse-step intervals of citrate infusions. Briefly, a rapid 5-min infusion of citrate was followed by a slower infusion for 25 min. Progressively increasing rates of both the fast and slow infusions were used for three additional 30-min periods. The citrate dose was 42 mg citrate/kg·h, followed by 20 mg citrate/kg·h for the first 30-min interval; dosages for subsequent intervals were 70/33, 96/44, and 130/60 mg citrate/kg·h, respectively. Blood samples were collected anaerobically for determination of serum $Ca_i$, OC, and intact PTH levels at 0, 5, 10, 20, and 30 min for each step of the infusion. Serum magnesium (Mg) and 1,25-$(OH)_2D$ levels and chemistries, including phosphorus ($PO_4$), blood urea nitrogen, and creatinine (Cr), were determined at the beginning and completion of each infusion in the black subjects.

*Day 2.* Calcium gluconate (Astra, Westboro, MA) was infused over three 30-min pulse-step intervals via an iv infusion pump similarly to citrate. The doses for calcium for the fast/slow infusions were 2.4 mg/kg·h followed by 0.75 mg/kg·h in step 1; 3.4 mg/kg·h followed by 0.25 mg/kg·h in step 2, and 4.4 mg/kg·h followed by 1.75 mg/kg·h in step 3. $Ca_i$, PTH, and osteocalcin levels were determined at baseline and every 10 min throughout the infusion.

The following indices of parathyroid function were used to evaluate the relationship of PTH to $Ca_i$: the maximal PTH response to hypocalcemia from the citrate infusion, the minimal PTH level after induced hypercalcemia from the calcium infusion data, and the set-point for PTH and the slope of the curve (calculated from data obtained during both infusions). The set-point is defined as the serum $Ca_i$ concentration at which the PTH level is half-maximal (16). We used GraphPad InPlot software (version 4.0, GraphPad Software, San Diego, CA) to fit sigmoidal curves to our data. This computer program generates the four variables mentioned above. In addition, the peak PTH response, which usually occurs between 5–10 min of each 30-min stepwise decrement in $Ca_i$ from the citrate infusion, was used to assess PTH responsiveness to rapid changes in $Ca_i$. Lastly, 1,25-$(OH)_2D$ levels were determined before and after the citrate and calcium infusions.

### Laboratory tests

Serum levels of Ca, $PO_4$, and Mg were determined by the clinical chemistry laboratory using a calorimetric method with an Olympus AU-5061 analyzer (Olympus Corp., Lake Success, NY). Values are reported as the mean ± SEM. The intra- and interassay coefficients of variation (CV) for Ca, $PO_4$, and Cr are 1.09%/1.36%, 2.95%/3.64%, and 1.24%/4.63%, respectively. Blood for $Ca_i$ assessment was collected anaerobically and measured with a Nova 7 calcium analyzer (Nova Biomedical, Waltham, MA), which has a precision of 0.59% (normal range, 1.12–1.37 mmol).

Serum intact PTH was measured by the Allegro immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). The detection limit of the assay is 0.1 pmol/L (normal range, 1–6.9 pmol/L), and the intra- and interassay CVs are 2% and 10%, respectively (20).

Serum 25-hydroxyvitamin D (25OHD) was measured by a competitive protein binding assay (normal range, 25–137 nmol/L). A RRA kit (Nichols Institute Diagnostics) with the 1,25-$(OH)_2D$ receptor from calf thymus was used for the 1,25-$(OH)_2D$ assay (normal range, 36–156 pmol/L). The reported intra- and interassay CVs averaged 10% and 14% or less, respectively, for both assays.

Serum OC levels were determined with a RIA (21). The detection limit is 0.5 µg/L, and intra- and interassay CVs are 2.3% and 8.3%, respectively. OC concentrations range from 2–12 µg/L in normal men.

Serum samples were stored at −70 F; all samples from each patient (except $Ca_i$) were run in duplicate and in the same assay.

### Statistical methods

Data from the infusion studies included multiple measures (*i.e.* $Ca_i$, PTH, and OC) sampled repeatedly over time and were analyzed with use of repeated measure analysis of variance. Summary measures for each racial group, including functions of the maximal responsiveness, minimal responsiveness, set-point, and slope derived from the sigmoidal curve, were compared by *t* test. In addition, $\Delta PTH/\Delta Ca_i$ [defined as PTH(max − min)/$Ca_i$(max − min)] were examined. The results are expressed as the mean ± SEM. Significance is indicated for $P < 0.05$.

## Results

### Baseline characteristics

As shown in Table 1, there were no significant study group differences in mean age or body weight. Mean baseline serum $Ca_i$ levels were lower ($P = 0.016$) and serum PTH levels were higher in the black subjects, but the latter only approached significance ($P = 0.088$). 25OHD levels were lower in the black subjects, with a mean of 27 ± 3 nmol/L, which is at the lower limit of normal (normal, 25–137 nmol/L). There were no significant differences in mean baseline serum Ca, $PO_4$, alkaline phosphatase, Mg, OC, or 1,25-$(OH)_2D$ levels between the two racial groups.

**TABLE 1.** Baseline characteristics of six healthy white and six healthy black men in a study of racial differences in PTH dynamics

| Characteristic | Baseline value | | $P$ value |
|---|---|---|---|
| | White | Black | |
| Age (yr) | 33 ± 3 | 28 ± 3 | NS |
| Wt (kg) | 74 ± 3 | 80 ± 7 | NS |
| Ca (mmol/L) | 2.32 ± 0.05 | 2.29 ± 0.03 | NS |
| $Ca_i$ (mmol/L) | 1.23 ± 0.02 | 1.14 ± 0.02 | 0.017 |
| $PO_4$ (mmol/L) | 1.06 ± 0.1 | 1.08 ± 0.15 | NS |
| Alkaline phosphatase (μkat/L) | 0.9 ± 0.1 | 1.2 ± 0.2 | NS |
| PTH (pmol/L) | 2.5 ± 0.3 | 3.8 ± 0.5 | 0.08 |
| 25OHD (nmol/L) | 46 ± 9 (n = 2) | 27 ± 3 | 0.024 |
| 1,25-$(OH)_2$D (pmol/L) | 97 ± 4 | 105 ± 8 | NS |
| Osteocalcin (μg/L) | 6.8 ± 1.5 | 4.6 ± 1.5 | NS |

*PTH responsiveness to hypocalcemic stimuli (data from the citrate infusion)*

We previously demonstrated that serum PTH levels measured at 5 min of each step of the pulse-step infusion reflect the effect of the rate of change in $Ca_i$ on PTH release, whereas the 30-min points, when serum $Ca_i$ is more stable, reflect the effect of $Ca_i$ concentration *per se* on PTH dynamics (18). The serum PTH responses to hypocalcemia were higher in the black subjects, with values at 0, 30, 60, and 90 min of 3.9 ± 0.6, 7.1 ± 1.3, 8.2 ± 1.1, and 8.8 ± 1.1 pmol/L in the blacks and 2.6 ± 1.1, 4.4 ± 0.3, 5.7 ± 0.6, and 5.9 ± 0.5 pmol/L in the white subjects (Fig. 1A; $P$ = 0.044). When all data points from the citrate infusion up to 90 min (n = 13 observations) were taken into consideration (Fig. 1A), both groups displayed a sharp serum PTH rise that peaked within the first 10 min of each step. The peak PTH levels were 9.5 ± 1, 12.4 ± 2.5, 12.3 ± 1.5, and 10.2 ± 1.2 pmol/L in the black subjects and 6.8 ± 1.8, 8.8 ± 0.6, 8.6 ± 0.8, and 8.9 ± 0.2 pmol/L in the whites in steps 1, 2, 3, and 4, respectively. The differences between the racial groups using all 13 data points approached significance ($P$ = 0.053). Moreover, serum $PTH/Ca_i$ ratios at the end of each of the three steps (at 30, 60, and 90 min) differed between the two racial groups, with values of 6, 7.5, and 9 in blacks and 3.7, 5, and 5.5 in whites, respectively ($P$ = 0.04). Finally, when we compared the serum $\Delta PTH/\Delta Ca_i$ for each step, a formula allowing us to correct for differences in $Ca_i$ and PTH levels between the two groups at the start of the infusion, the exuberance of the PTH response in our black subjects was even more striking; the ratios were 120, 95, and 202 for black subjects and 98, 98, and 70 for white subjects for steps 1, 2, and 3, respectively. These differences did not reach significance due to the increased variability in PTH levels at step 3 in the black subjects. Finally, despite the fact that black subjects achieved higher serum PTH levels at the end of the citrate infusion, their serum $Ca_i$ level was 1 ± 0.01 mmol/L, which was lower than that in the white subjects (1.05 ± 0.02 mmol/L; Fig. 1B). Serum 1,25-$(OH)_2$D levels were unchanged in the black subjects at the end of the citrate infusion and before and at the end of the calcium infusion (91 ± 6, 103 ± 5, and 107 ± 7 pmol/L, respectively).

*PTH suppressibility (data from the calcium infusion)*

On day 2, the black subjects again initially had higher baseline serum PTH levels than the white controls (4 ± 0.7 *vs.* 2.7 ± 0.1 pmol/L, respectively). In black subjects, hypercalcemia failed to suppress PTH as effectively as in white subjects; the minimal serum PTH level was 0.3 ± 0.1 pmol/L in whites and 0.7 ± 0.1 pmol/L in black subjects ($P$ = 0.04). Moreover, when we applied analysis of variance to the 0, 30, 60, and 90 min data points or all data points from the calcium infusion, the racial groups differed ($P < 0.001$ in both analyses). Finally, the serum $PTH/Ca_i$ ratio at 0, 30, 60, and 90 min of the calcium infusion also differed between the two racial groups ($P < 0.04$).
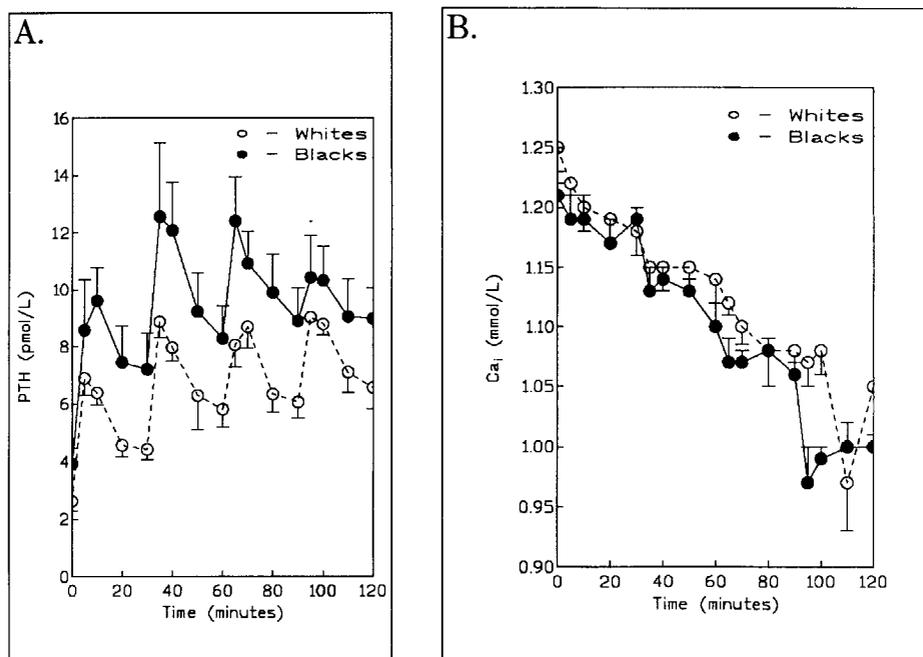


FIG. 1. Levels of PTH (A) and $Ca_i$ (B) during the induction of hypocalcemia with the pulse citrate infusion in black (●) and white (○) healthy male subjects.

*Comparison of data points from both infusions*

To evaluate differences in PTH release due to changes in $Ca_i$ concentration *per se*, we derived $Ca_i$/PTH curves in each individual by using the 0, 30, 60, and 90 min points from the citrate and calcium infusions (Fig. 2). Comparison of all 30 min points (when $Ca_i$ was changing very little) during both the citrate and calcium infusions revealed significant differences between the two races ($P = 0.0001$). Similar significant differences were obtained by comparing the PTH/$Ca_i$ ratios for the same time points on both days ($P = 0.001$).

*Set-points*

The set-point is defined as the calcium concentration at which there is half-maximal inhibition of PTH secretion. We have previously demonstrated that rapid changes in serum $Ca_i$ can shift the sigmoidal curve relating $Ca_i$ to PTH levels to the right, thereby elevating the observed set-point (18). Using the 30 min points from both the citrate and calcium infusions to plot the sigmoidal curve, we can evaluate the effect of changing calcium concentration *per se* rather than the effect of the rate of change in $Ca_i$ on PTH levels. The set-point for each race was defined by two different methods. The first involved the fitting of a sigmoidal curve for each individual to derive individual set-points, which were then averaged to calculate a mean set-point for each racial group. The average of the individual set-points was 1.2 ± 0.02 mmol/L for black subjects and 1.2 ± 0.02 mmol/L for white subjects ($P = NS$). In the second method, the set-point was derived from the sigmoidal curve determined for each racial group; we averaged the 30 min points for both the citrate and calcium infusions for each racial group, thus generating two separate sigmoidal curves, which are shown in Fig. 2. The set-points derived from these two curves were again similar (1.2 mmol/L in both racial groups). The set-points derived from the sigmoidal curves generated with the 5 min data points, when $Ca_i$ is changing rapidly, were also similar, with values of 1.2 ± 0.1 mmol/L in the blacks and 1.2 ± 0.02 mmol/L in the white subjects ($P = NS$).

*Slopes of the curves*

The slope at the set-point for each subject and a mean slope for each racial group were determined. Although the exuberance of the PTH response in black subjects suggested a steeper slope, the values in blacks and whites were not significantly different; the slopes of the curves were −3.65 and −2.3, respectively ($P = 0.07$).

*OC response*

As shown in Fig. 3, the serum OC response to a pulse infusion of citrate was, in general, parallel to changes in serum PTH levels and inversely correlated with decrements in serum $Ca_i$. The baseline serum OC levels were slightly lower in the black subjects than in the white group (4.6 ± 1.5 vs. 6.82 ± 1.5 µg/L; $P = NS$). Comparison of serum OC responses suggested greater patient to patient variability in the black group; as a whole, the black subjects achieved lower serum OC levels, but the increments in serum OC above baseline absolute values were comparable to those in the white subjects. To assess whether the increments in serum OC were due to changes in serum PTH and/or serum $Ca_i$ in response to citrate, we administered PTH-(1–34) (200 IU) over 1 h to one subject. There were no changes in serum $Ca_i$, OC, or intact PTH levels.

*Response to a D5W infusion*

Artifactual changes in serum PTH and $Ca_i$ due to periodic sampling of blood are unlikely, because the levels determined
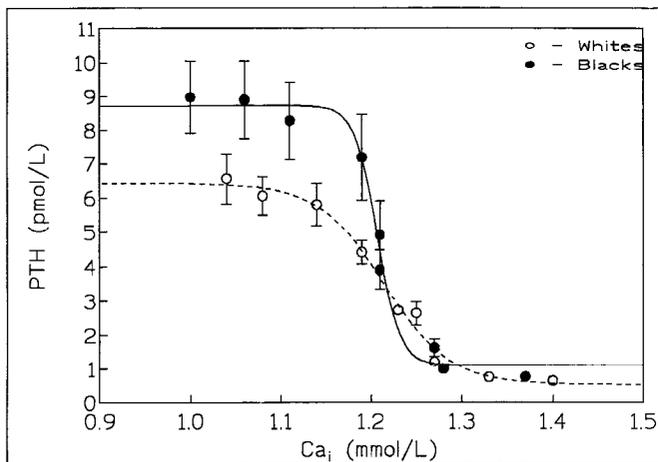


FIG. 2. Ca-PTH sigmoidal curves. Data obtained from the end of each 30-min step from each of the citrate and calcium infusions describe the inverse sigmoidal relationship between serum ionized calcium ($Ca_i$) and PTH levels in black (●) and white (O) subjects.
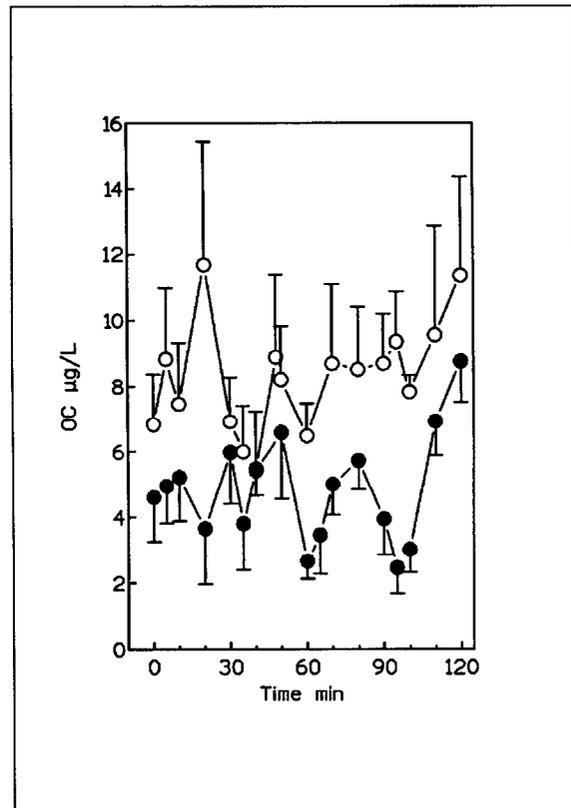


FIG. 3. Osteocalcin responses to the citrate infusion; serum osteocalcin levels during the induction of hypocalcemia in black (●) and white (O) subjects.

for these two parameters changed in opposite directions. To further rule out this possibility, in three of our volunteers who had the pulse citrate infusion, we duplicated the original protocol using D5W instead of citrate. There was no effect of such an infusion on serum PTH or $Ca_i$ levels. At time zero, the mean serum PTH and $Ca_i$ levels were 4.7 pmol/L and 1.31 mmol/L; at the termination of the dextrose infusion, they were 4.6 pmol/L and 1.32 mmol/L, respectively.

## Discussion

In this study we were able to demonstrate small, but nonsignificant, differences in PTH levels between black and white subjects at baseline, which are consistent with the results of several other investigators (8, 9, 11). However, only one of these three studies showing higher serum PTH levels in blacks used the intact PTH assay (11). Such findings have not been consistently confirmed (12, 14); moreover, the only other study evaluating racial differences in the calciotropic hormones using this specific assay did not demonstrate any difference between the two races (12). Thus, rather than simply comparing baseline measurements in serum PTH levels, we used dynamic modulation of the $Ca_i$-PTH axis to determine whether there were any significant differences in serum PTH dynamics between the two racial groups. Two of the four parameters that define the relationship between serum $Ca_i$ and serum PTH were elevated. Indeed, black subjects demonstrated a more exuberant response than whites to a hypocalcemic stimulus and did not suppress PTH levels in response to hypercalcemia to the same extent. The exuberance of the response in blacks was also suggested by the steeper slope of their sigmoidal curves and is consistent with mild secondary hyperparathyroidism, which has been documented in an autopsy study showing parathyroid hyperplasia in blacks (15).

The major factors that stimulate PTH secretion and PTH gland hyperplasia are hypocalcemia and reduced vitamin D levels. The former can be caused by malabsorption, vitamin D deficiency, or renal hypercalciuria. It is possible that black subjects have mild secondary hyperparathyroidism due to malabsorption of calcium. Indeed, Dawson-Hughes *et al.* (12) demonstrated that black subjects had fractional calcium absorption similar to that of whites in the presence of higher $1,25-(OH)_2D$ levels, thereby suggesting gut resistance to vitamin D action. This observation was not confirmed in a group of black adolescent subjects (13). The changes in PTH dynamics observed in our study, namely changes in maximal and minimal PTH, were similar to those observed by Cloutier *et al.* (22) in an animal model of chronic $Ca_i$ deficiency. Our subjects had good calcium intake, however, and denied any symptoms of malabsorption, yet their 25OHD and $Ca_i$ levels were lower than those in white subjects. Nevertheless, the aim of our studies was to evaluate racial differences in PTH dynamics when black subjects are exposed to their usual environmental conditions.

Alternatively, renal hypercalciuria could result in secondary hyperparathyroidism. Even though we did not perform formal 24-h urine analyses for our subjects, the most consistent finding in the literature examining racial differences in calcium metabolism has been the presence of reduced 24-h urinary calcium excretion in black subjects (8, 9, 13, 14).

Vitamin D is the other modulator of PTH secretion. The active metabolite calcitriol reduces not only PTH secretion (23), but also PTH messenger ribonucleic acid levels (24). Thus, low levels of calcitriol could result in mild hyperparathyroidism similar to that observed in renal failure. Mild and severe renal failures are characterized by increased maximal PTH release and decreased suppressibility (25). The calcitriol levels were normal in our black subjects and similar to those measured in their white counterparts. Mild kidney failure (serum Cr >2 mg/dL or Cr clearance <60 mL/min) without any changes in vitamin D could result in an elevation of serum levels of intact PTH (26, 27). Our black subjects had normal kidney function, as assessed by serum Cr levels.

Finally, skeletal resistance to the bone-resorbing effect of PTH could result in mild hyperparathyroidism. Indeed, the normal calcium homeostatic response to hypocalcemia involves raising PTH and possibly $1,25-(OH)_2D$ levels in order to restore normocalcemia. The minute to minute normalization of $Ca_i$ relies partially on mobilization of calcium from bone through the bone-resorptive actions of PTH. However, despite the higher baseline PTH levels in the black subjects, their OC levels were lower, an observation consistent with data gathered by Bell *et al.* (8) and with data obtained from a large population of normal white and black male subjects (Gundberg, C., data unpublished). They are also consistent with the histomorphometric study of Weinstein and Bell (28) demonstrating lower bone formation in blacks. In addition, the black subjects achieved OC increments similar to those of whites in response to larger increments in endogenous PTH levels. Both observations are consistent with a relative skeletal resistance to PTH action in blacks. Formal PTH infusion studies evaluating OC responses in blacks and whites are needed to evaluate this possibility further.

Calcitriol stimulates OC and suppresses PTH synthesis and secretion through the vitamin D receptor. The lower OC levels in blacks are not due to differences in $1,25-(OH)_2D$ levels. However, recently, polymorphisms for this receptor have been described in Caucasians with differences in bone turnover, as assessed through biochemical markers and bone density (29, 30). It is, therefore, possible that our findings of high PTH and low OC levels reflect differences in the biological activity of the vitamin D receptor at the level of several organs, such as the parathyroid gland, the intestine, or bone. The administration of PTH to humans results in a decline in serum OC (31–33). However, our group has shown that endogenous acute elevations in PTH levels are accompanied by parallel increments in OC levels, which inversely correlate with decrements in $Ca_i$. The mechanisms for such changes include the possibility that rapidly falling $Ca_i$ concentrations may cause a change in OC $\alpha$-helical configuration and, therefore, its affinity for hydroxyapatite. Therefore, the cyclic OC response may be related to the balance between decreasing serum $Ca_i$ and increasing PTH levels (17). The OC changes are, however, unlikely to result from altered clearance of this protein, in view of its estimated half-life of 20 min (34). Indeed, a rapidly changing clearance would have to be implicated to account for the observed OC response.

Our study establishes the presence of relative hyperpara-

thyroidism in black subjects. Despite the relatively small number of subjects, the increased sensitivity of growth curve modeling of dynamic studies allows the determination of significant differences in the parameters that characterize the Ca-PTH relationship. The use of dynamic testing allowed the definition of specific parameters that are altered in the black subgroup. Further dynamic studies are needed to evaluate the mechanisms for such alterations and their implications at the level of bone.

## Acknowledgments

## References

1. Bell NH, Shary J, Stevens J, et al. 1991 Demonstration that bone mass is greater in black than in white children. J Bone Miner Res. 6:719–723.

2. Gilsanz V, Roe TF, Mora S, et al. 1991 Changes in vertebral bone density in black girls and white girls during childhood and puberty. N Engl J Med. 235:1597–600.

3. Li J-Y., Specker BL, Ho ML, et al. 1989 Bone mineral content in black and white children 1 to 6 years of age. Am J Dis Child. 143:1346–1349.

4. Cohn SH, Abesamis C, Yasumura S, et al. 1977 Comparative skeletal mass and radial bone mineral content in black and white women. Metabolism. 26:171–178.

5. Luckey JJ, Meier DE, Mandeli JP, et al. 1989 Radial and vertebral bone density in white and black women: evidence for racial differences in premenopausal bone homeostasis. J Clin Endocrinol Metab. 6:762–770.

6. Liel, Y., Edwards J, Shary J, et al. 1988 The effects of race and body habitus on bone mineral density of the radius, hip, and spine in premenopausal women. J Clin Endocrinol Metab. 66:1247–1250.

7. Farmer ME, White LR, Brody JA. 1984 Race and sex differences in hip fracture incidence. Am J Public Health. 44:1374–80.

8. Bell NH, Greene A, Epstein S, et al. 1985 Evidence for alteration of the vitamin D-endocrine system in blacks. J Clin Invest. 76:470–473.

9. M'Buyamba-Kabangu JR, Fagard R, Lijnen P, et al. 1987 Calcium, vitamin D-endocrine system, and parathyroid hormone in black and white males. Calcif Tissue Int. 41:70–74.

10. Wilson P, Parikh N, Hill J, et al. 1993 Skeletal biochemistry in older healthy black and white women: reference data [Abstract]. J Bone Miner Res. 8(Suppl 1):533.

11. Brickman AS, Nyby MD, Griffiths RF et al. 1993 Racial differences in platelet cytosolic calcium and calcitropic hormones in normotensive subjects. Am J Hypertens. 6:46–51.

12. Dawson-Hughes B, Harris S, Kramich C, et al. 1993 Calcium retention and hormone levels in black and white women on high- and low-calcium diets. J Bone Miner Res. 8:779–787.

13. Bell NH, Yergey AL, Vieira NE, et al. 1993 Demonstration of a difference in urinary calcium, not calcium absorption, in black and white adolescents. J Bone Miner Res. 8:1111–1115.

14. Meier DE, Luckey MM, Wallenstein S, et al. 1991 Calcium,

15. Ghandur-Mnaymneh L, Cassady J, Hajanpour MA, et al. 1986 The parathyroid gland in health and disease. Am J Pathol. 125:292–299.

16. Brown EM. 1983 Four-parameter model of the sigmoidal relationship between parathyroid hormone release, extracellular calcium concentration in normal and abnormal parathyroid tissue. J Clin Endocrinol Metab. 56:572–581.

17. Gundberg CM, Grant FD, Conlin PR, et al. 1991 Acute changes in serum osteocalcin during induced hypocalcemia in humans. J Clin Endocrinol Metab. 72:438–443.

18. Grant FD, Conlin PR, Brown EM. 1990 Complete rate and concentration dependence of parathyroid hormone dynamics during stepwise changes in serum ionized calcium in normal humans. J Clin Endocrinol Metab. 71:370–378.

19. Bell NH, Epstein S, Greene A, et al. 1985 Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest. 76:370–373.

20. Nussbaum SR, Zahradnik RJ, Lavigne JR et al. 1987 Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. Clin Chem. 33:1364–1367.

21. Gundberg CM, Hauschka PV, Lian JB, et al. 1984 Osteocalcin: isolation, characterization, and detection. Methods Enzymol. 107:516–544.

22. Cloutier M, Gascon-Barre M, D'Amour P. 1992 Chronic adaptation of dog parathyroid function to a low-calcium-high-sodium-vitamin-D deficient diet. J Bone Miner Res. 7:1021–1028.

23. Chan YL, McKay C, Dye E, et al. 1986 The effect of 1,25 dihydroxycholecalciferol on parathyroid hormone secretion by monolayer cultures of bovine parathyroid cells. Calcif Tissue Int. 38:27–32.

24. Silver J, Russell T, Sherwood IM. 1985 Regulation of vitamin D metabolites of messenger ribonucleic acid for parathyroid hormone in isolated bovine parathyroid cells. Proc Natl Acad Sci USA. 82:42–70.

25. Felsenfeld AJ, Llach F. 1993 Parathyroid gland function in chronic renal failure. Kidney Int. 43:771–789.

26. Fajtova VT, Sayegh M, Hickey N, et al. Intact parathyroid hormone levels in renal insufficiency. J Bone Miner Res. 6 [Suppl. 1]:423.

27. John A, Thomas MB, Davies CP, et al. 1992 Determinants of intact parathyroid hormone and free 1,25-dihydroxyvitamin D levels in mild and moderate renal failure. Nephron. 61:422–427.

28. Weinstein RS, Bell NH. 1988 Diminished rate of bone formation in normal black adults. N Engl J Med. 319:1698–1701.

29. Morrison NA, Yeoman R, Kelly PS, et al. 1992 Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Natl Acad Sci USA. 89:6665–6669.

30. Morrison NA, Qi JC, Toketa A, et al. 1994 Prediction of bone density from vitamin D receptor alleles. Nature. 367:284–287.

31. Calvo MS, Freyer MJ, Laakso KJ, et al. 1985 Structural requirements for parathyroid hormone action in mature bone. J Clin Invest. 26:2348–2354.

32. Cole DEC, Gundberg CM. 1985 Changes in serum osteocalcin associated with parathyroid infusion in X-linked hypophosphatemic rickets. Clin Chim Acta. 151:1–7.

33. Riggs BL, Tsai KS, Mann KG. 1986 Effect of acute increases in bone matrix degradation on circulating levels of bone-gla protein. J Bone Miner Res. 1:539–542.

34. Melick RA, Farrugia W, Quelch KJ. 1985 Plasma osteocalcin in man. Aust NZ J Med. 15:410–416.