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Impact of Race on Intraoperative Parathyroid Hormone Kinetics

An Analysis of 910 Patients Undergoing Parathyroidectomy for Primary Hyperparathyroidism

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Hypothesis: African American patients exhibit different intraoperative parathyroid hormone (IOPTH) profiles than non–African American patients.

Design: Retrospective review.

Setting: University medical center.

Patients: Nine hundred ten patients who underwent parathyroidectomy for primary hyperparathyroidism between July 2005 and August 2010.

Interventions: All patients underwent preoperative imaging with ultrasonography and sestamibi; operative exploration; and IOPTH measurement at 2 points preexcision and 5 and 10 minutes postexcision.

Main Outcome Measures: Preexcision and postexcision IOPTH measurements.

Results: Of the 910 patients, 734 self-reported their race as white (81%); 91, Latino/other (10%); 56, Asian (6%); and 28, African American (3%). African American patients had significantly higher initial preexcision IOPTH levels compared with white patients (348 vs 202 pg/mL; $P=.048$) and significantly higher 5-minute postexcision IOPTH levels (151 vs 80 pg/mL; $P=.01$). The 10-minute postexcision IOPTH levels were similar between the 2 groups (52 vs 50 pg/mL). A similar percentage of white and African American patients had a 50% drop in IOPTH level at 10 minutes postexcision. No differences in IOPTH kinetics were observed in the other racial groups examined.

Conclusions: African American patients with primary hyperparathyroidism exhibit significantly higher preincision and 5-minute postexcision IOPTH values when compared with white patients. The 10-minute postexcision IOPTH values did not differ between races. The altered IOPTH kinetics identified in African American patients may reflect the severity of biochemical disease but may also be related to genetically predetermined differences in parathyroid hormone metabolism.

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PRIMARY HYPERPARATHYROIDism (pHPT) is a common disease affecting approximately 1 in every 500 women and 1 in every 2000 men older than 40 years.[1] Several prior studies have investigated the impact of ethnicity and geography on the clinical presentation of pHPT.[2-5] In 2000, Bilezikian et al[3] investigated the presentation of pHPT among women in China. They found that Chinese women presented at a younger age than their American counterparts and manifested more severe biochemical and clinical disease, including more advanced bone disease. In 2001, Mishra et al[4] published similar findings regarding the presentation of young patients with pHPT in India. Few studies, however, have investigated pHPT in African American patients, and to our knowledge, there are no existing data regarding the impact of African American race on intraoperative parathyroid hormone (IOPTH) kinetics. The studies that do exist suggest that African American patients present with more advanced disease with regard to laboratory and pathologic findings.[2,4] The investigators cite race-related disparities in health care[6,7] and intrinsic biochemical differences[8] as potential causative factors. However, available data are limited, and, to our knowledge, there are no population-based studies to describe clinical presentation, outcomes, or even incidence of pHPT among African American individuals.

See Invited Critique at end of article

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A separate and more comprehensive body of literature describes metabolic and endocrine differences between African American and non–African American individuals with regard to calcium metabolism and bone turnover.[8-11] These studies focus on differences in renal calcium absorption, bone density, and skeletal sensitivity to parathyroid hormone (PTH).[12] They do not typically include patients with pHPT. Based on our awareness of these data, we hypothesized that race would impact IOPTH kinetics and might affect the optimal interpretation of IOPTH values.

METHODS

CREATION OF DATABASE

A retrospective database was created with approval of the University of California, San Francisco institutional review board, including all patients who underwent parathyroidectomy for pHPT by 1 of 4 endocrine surgeons between July 2005 and August 2010. Diagnosis of pHPT was based on an inappropriately elevated PTH level in a patient with hypercalcemia and a normal serum creatinine level.

Patient characteristics collected included age, sex, race, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), family history of pHPT, and history of nephrolithiasis or osteoporosis. Classification of race was based on the patient's self-identification at the time of initial clinic visit. Laboratory data included serum calcium level, ionized calcium level, 24-hour urine calcium excretion, intact PTH level, 25-hydroxyvitamin D level, alkaline phosphatase level, and creatinine level. Details of the preoperative evaluation were collected, including results of ultrasonography and sestamibi scan and concordance (or lack thereof) of preoperative study results. Intraoperative and postoperative variables examined included IOPTH level, focused vs bilateral exploration, findings of single or double adenoma vs four-gland hyperplasia, postoperative calcium level, and presence of persistent or recurrent disease.

PROTOCOL FOR MEASUREMENT OF IOPTH

During parathyroidectomy, PTH level was measured at 4 points. The first time was following induction of anesthesia but before incision. The second was preexcision, typically on identification of an abnormal-appearing gland. Times 3 and 4 were at 5 and 10 minutes postexcision. The Siemens ADVIA Centaur immunoassay was used, with the assay performed outside of the operating room within 10 minutes of the blood draw. The Miami criteria, which stipulate that the IOPTH level must fall by 50% from the highest preexcision value at 10 minutes postexcision, were used to assess adequacy of resection.[13]

REFERENCE VALUES

Reference ranges for key values at our institution include serum calcium, 8.8 to 10.3 mg/dL (to convert to millimoles per liter, multiply by 0.25); 24-hour urine calcium, 50 to 300 mg/24 h; intact PTH, 12 to 65 pg/mL (to convert to nanograms per liter, multiply by 1); alkaline phosphatase, 42 to 141 U/L (to convert to microkatals per liter, multiply by 0.0167); creatinine, 0.5 to 1.3 mg/dL (to convert to micromoles per liter, multiply by 88.4); and 25-hydroxyvitamin D, 30 to 100 ng/mL (to convert to nanomoles per liter, multiply by 2.496).

STATISTICAL ANALYSES

Comparison of binary variables was by χ^2 test. Comparison of continuous variables was by *t* test. Descriptive statistics were calculated for all variables. Simple linear regression was used to evaluate correlation between 2 continuous variables. A multivariate analysis including IOPTH level as a dependent variable and age, sex, race, and BMI as independent variables was performed using JMP 9 software (SAS Institute Inc).

RESULTS

Of the 910 patients who underwent surgery for pHPT between July 2005 and August 2010, 734 self-reported their race as white (81%), 91 reported Latino/other (10%), 56 reported Asian (6%), and 28 reported African American (3%). When compared with white patients, African American patients presented with a significantly higher mean serum calcium level (11.4 vs 10.9 mg/dL; $P<.001$) but lower mean 24-hour urine calcium level (192 vs 336 mg/24 h; $P=.007$). African American and white patients did not differ significantly in mean level of 25-hydroxyvitamin D (24.8 vs 30.5 pg/mL; $P=.28$); however, the percentage of African American patients presenting with vitamin D deficiency (defined as 25-hydroxyvitamin D level <20 ng/mL) was significantly higher (56% vs 26%; $P=.02$). African American patients also showed a trend toward higher BMI (30.6 vs 27.6; $P=.06$).

Fewer African American patients than white patients carried a diagnosis of osteoporosis (4% vs 19%; $P=.03$); however, fewer African American patients had undergone formal preoperative bone density testing. Seven percent of African American and 18% of white patients ($P=.20$) had a history of nephrolithiasis. There was no significant difference between the 2 groups in age, sex, serum alkaline phosphatase level, or serum creatinine level. Comparison of preoperative patient characteristics is summarized in **Table 1**. Although there was no significant difference between rate of either abnormal sestamibi scan or ultrasonography between races, African American patients were significantly more likely to have concordant preoperative study results (**Table 2**).

During surgery, African American patients had higher initial IOPTH measurements than white patients (348 vs 202 pg/mL; $P=.048$). Measurements at 5 minutes postexcision were also higher (151 vs 80 pg/mL; $P=.01$); however, IOPTH level at 10 minutes postexcision was nearly identical between the 2 groups (52 vs 50 pg/mL; $P=.85$). No significant differences in IOPTH kinetics were observed among the other races examined (**Table 3**). Rates of multigland disease were similar between African American and white patients (11% vs 13%; $P=.97$). A similar percentage of white and African American patients had a 50% drop in IOPTH level during surgery. However, 11% of African American patients vs 4% of white patients went on to have persistent disease despite a 50% drop in IOPTH level (not significant). In contrast, when criteria were expanded to also require a drop of IOPTH level into the normal range, none of the African American patients had persistent disease. Comparison of intraoperative and postoperative variables by race is summarized in Table 3.

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Table 1. Preoperative Characteristics of African American and White Patients With Primary Hyperparathyroidism

Variable	African American	White	*P* Value
Sample size	28	733	
Age, y, mean (SD)	61.5	61.0	.84
Female, %	86	73	.21
BMI, mean (SD)	30.6	27.6	.06
BMI >30, %	43	30	.11
Initial serum calcium level, mg/dL, mean (SD)	11.4	10.9	<.001[a]
24-urine calcium excretion, mg/24 h, mean (SD)	192	336	.007[a]
History of kidney stones, %	7	18	.20
PTH level (outpatient), pg/mL, mean (SD)	157	124	.08
25-Hydroxyvitamin D level, ng/mL, mean (SD)	24.8	30.5	.28
Vitamin D deficiency (<20 ng/mL), %	56	26	.02[a]
Alkaline phosphatase level, U/L, mean (SD)	87.8	92.6	.80
History of osteoporosis, %	4	19	.03[a]
Creatinine level, mg/dL, mean (SD)	1.02	0.97	.70

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PTH, parathyroid hormone.

SI conversion factors: To convert serum calcium to millimoles per liter, multiply by 0.25; PTH to nanograms per liter, multiply by 1; 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496; alkaline phosphatase to microkatals per liter, multiply by 0.0167; and creatinine to micromoles per liter, multiply by 88.4.

[a] Significant.

Table 2. Preoperative Imaging Studies of African American and White Patients Undergoing Parathyroidectomy for Primary Hyperparathyroidism

	%		
	Abnormal Ultrasonography	Abnormal Sestamibi Scan	Concordant Study Results
African American	89	96	86
White	79	91	62
P value	.24	.50	.01[a]

[a] Significant.

Simple linear regression was used to evaluate correlation between initial IOPTH measurement and individual continuous variables that might account for racial differences. Variables evaluated in this manner include age, BMI, serum creatinine level, and 25-hydroxyvitamin D level (data not shown). Of these variables, only BMI reached significance ($P=.005$). Graphs of IOPTH curves by race and BMI are shown in the **Figure**.

A multivariate analysis was then performed evaluating the association between age, sex, race, and BMI and initial IOPTH measurement. In this analysis, BMI remained a significant predictor ($P=.006$), while African American race did not quite reach significance ($P=.08$). This suggests that differences in BMI explain at least part of the racial difference seen in our initial comparison of means.

COMMENT

To our knowledge, only 2 previous studies have investigated differences between African American and non–African American patients undergoing parathyroidectomy for pHPT.[2,4] In 2004, Barker et al[2] conducted a case-control comparison of 36 African American and 36 white patients with pHPT. They reported that preoperative serum calcium level was equivalent for the 2 groups but that African American patients had a higher preoperative intact PTH level. African American and white patients had equivalent rates of "objective symptoms" including osteoporosis, nephrolithiasis, pancreatitis, and mental status changes, leading Barker et al to conclude that the PTH level differences might be clinically insignificant and attributable to biochemical racial differences such as decreased skeletal sensitivity to PTH.[2] Subsequently, in 2008, Kandil et al[4] evaluated the clinical presentation of 113 African American and 475 non–African American patients with pHPT. African American patients had significantly higher serum calcium and PTH levels at presentation, as well as higher adenoma weight on pathologic analysis. Kandil et al identified vitamin D deficiency and increased BMI as potential contributors. However, they concluded that African American patients presented with more severe disease and that late presentation due to disparities in access to health care should be considered a likely explanation. More recently, Jabiev et al[12] reported higher serum calcium and PTH levels at presentation among underinsured and uninsured patients with pHPT, although they did not evaluate the potential contribution of race to these trends.

Our data confirm higher serum calcium and higher initial IOPTH levels in African American patients. However, we, like Barker et al,[2] did not observe higher rates of either osteoporosis or nephrolithiasis, raising the issue of whether African American patients truly present with more severe disease. Current guidelines for patient selection for parathyroidectomy rely heavily on presence of clinical manifestations of the disease, so it is not clear that African American patients in this study had a delay in operative intervention.[14] However, our data are potentially biased by the lower index of suspicion for osteoporosis among clinicians evaluating African American patients, as these patients had lower rates of bone density testing. We can only truly conclude that African American patients have lower rates of hyperparathyroidism-related renal disease. Further investigation will be needed to clarify whether they have lower rates of hyperparathyroidism-related osteoporosis as well. Other important limitations of our data include the absence of information on insurance status or preoperative neuropsychological symptoms.

The finding of decreased 24-hour urine calcium excretion was unexpected and raised concern for familial hypocalciuric hypercalcemia. However, on review of the available data, this finding in African American individuals has previously been described.[15-17] Very recently, Taha et al[17] reported that a low urine calcium level is frequently seen in African American individuals with pHPT,

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Table 3. Intraoperative and Postoperative Measures, by Race, for Patients Undergoing Parathyroidectomy for Primary Hyperparathyroidism

Variable	White	African American	*P* Value[a]	Asian	*P* Value[a]	Latino	*P* Value[a]
IOPTH level, pg/mL, mean							
Incision	202	348	.048[b]	254	.28	272	.19
Preexcision	220	240	.87	226	.94	195	.76
5 min Postexcision	80	151	.01[b]	79	.96	85	.82
10 min Postexcision	50	52	.85	50	.99	45	.49
Multigland disease, %	13	11	.97	11	.83	13	.99
50% Drop in PTH level at 10 min, %	93	88	.33	96	.76	100	.16
50% Drop but persistent disease, %	4	11	.11	0	.24	2	.90
50% Drop in PTH level and into normal range at 10 min, %	79	71	.36	77	.68	78	.83
50% Drop and into normal range but persistent disease, %	2	0	.99	0	.99	2	.99

Abbreviations: IOPTH, intraoperative parathyroid hormone; PTH, parathyroid hormone.
SI conversion factor: To convert IOPTH to nanograms per liter, multiply by 1.
[a] *P* value reflects comparison with white patients.
[b] Significant.

even in the setting of significant hypercalcemia. Racial differences in renal calcium resorption provide one possible explanation. Race-associated polymorphisms in the calcium-sensing receptor may offer a clue to the underlying etiology.[10] Among the African American patients in our database, 6 (21%) had a urine calcium level less than 200 mg/24 h. However, all 6 patients had durable resolution of hypercalcemia with parathyroidectomy, in 5 cases after single-gland excision.

To our knowledge, this is the first report demonstrating a difference in IOPTH kinetics between African American and white patients with pHPT. We found that African American patients undergoing surgery for pHPT had elevated levels of initial IOPTH and IOPTH at 5 minutes postexcision but an equivalent level of IOPTH at 10 minutes postexcision. However, a similar percentage of African American and white patients had an adequate drop in IOPTH level by the Miami criteria. We did observe a trend toward a higher rate of persistent disease among African American patients when the Miami criteria alone were applied (11% vs 4%), although this did not reach significance. This effect was abrogated when IOPTH level was required to drop into the normal range. It seems plausible that given the higher starting IOPTH level among African American patients, a drop of more than 50% should be expected. However, additional studies with larger numbers of patients will be necessary to determine whether this is the case, and if so, what percentage drop should be required.

Although no previous studies have evaluated the impact of race on IOPTH level, several authors have investigated other patient characteristics that may impact presentation of pHPT and IOPTH kinetics. Untch et al[18] describe a characteristic trend of perioperative PTH levels in patients with vitamin D deficiency. Their vitamin D–deficient patients had an elevated initial IOPTH level but equivalent postexcision values, closely mirroring the pattern of IOPTH level in the African American patients in our study. Similar findings are reported by Adler et al,[19] who emphasize that IOPTH is as predictive of cure

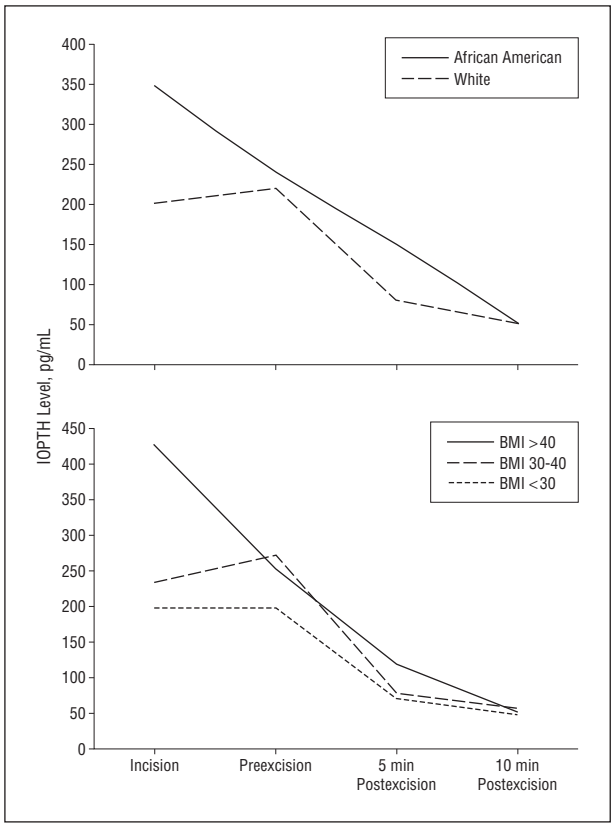

Figure. Intraoperative parathyroid hormone (IOPTH) curves by race and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) for patients undergoing parathyroidectomy for primary hyperparathyroidism. To convert IOPTH to nanograms per liter, multiply by 1.

in vitamin D-deficient patients as in nondeficient patients.[20] Although we found that African American patients had a higher rate of vitamin D deficiency, vitamin D level did not significantly correlate with initial IOPTH measurement in our linear regression analysis. The study by Adam et al,[20] describing a higher preoperative PTH level in obese patients with pHPT, prompted us to con-

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sider BMI as a possible contributor to the racial differences we noted. In fact, we found that BMI was not only correlated with higher initial IOPTH level in single-variable linear regression but remained the only significant predictor in multivariate analysis after controlling for age, sex, and race.

African American patients with pHPT show significant differences in preoperative laboratory values and IOPTH curves when compared with white patients. However, these findings do not appear to be associated with more severe clinical manifestations of pHPT. African American race may be associated with lower sensitivity of the Miami criteria in detection of multigland disease during parathyroidectomy. Further investigation is needed to clarify this. Additional investigation is also needed into the contribution of other variables such as vitamin D deficiency and BMI to the racial differences we observed.

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