

# Race Is a Major Determinant of Secondary Hyperparathyroidism in Uremic Patients

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**Abstract.** In the general population, blacks have higher parathyroid gland mass and circulating parathyroid hormone (PTH) levels than whites. This may predispose black patients to more severe parathyroid disease when renal failure develops. Therefore, racial differences in the severity of uremic hyperparathyroidism were examined in a population of patients with end-stage renal disease (ESRD). Among ESRD patients receiving hemodialysis or peritoneal dialysis, two or more values of intact PTH (immunoradiometric assay, pg/ml) obtained at least 90 d apart were available in 1270 prevalent cases (61.1% blacks, 51% males, and 31.1% diabetic), including 466 incident cases with onset of ESRD after 1993. Maximum PTH levels were analyzed as a function of race, gender, age, diabetic status, and levels of serum calcium, phosphorus, alkaline phosphatase, and aluminum. Using a stepwise multiple regression

model, the determinants of maximum PTH in the order of their importance were black race, serum phosphorus, absence of diabetes, younger age, serum calcium, and female gender. The maximum PTH levels averaged 641.7 in blacks and 346.0 in whites after adjusting for age, gender, diabetic status, serum calcium, and phosphorus ( $P < 0.0001$ ). In blacks compared with whites, the odds ratio (95% confidence interval) for adynamic bone disease (maximum PTH  $< 150$  pg/ml) was 0.26 (0.17 to 0.41), whereas the odds ratio for hyperparathyroid bone disease (mean PTH  $> 500$  pg/ml) was 4.4 (2.10 to 9.25). Race is a major independent determinant of uremic secondary hyperparathyroidism. Among ESRD patients, blacks may be at an increased risk for hyperparathyroid bone disease and whites for adynamic bone disease.

Racial differences exist in the regulation of vitamin D–parathyroid hormone axis. Compared with whites, blacks have a lower urinary calcium (1,2) and increased circulating 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) despite lower levels of 25(OH)D (3). Parathyroid hormone (PTH) levels are higher in blacks, and the secondary hyperparathyroidism may be responsible for the increased synthesis of 1,25(OH)<sub>2</sub>D<sub>3</sub> (3). Furthermore, autopsy studies have shown that parathyroid mass is increased in blacks compared with whites (3–6).

Racial differences in the regulation of vitamin D–PTH axis and baseline parathyroid mass may influence the development of secondary hyperparathyroidism as renal function declines and perturbations in calcium, phosphate, and vitamin D set in. We have examined this hypothesis in a population of end-stage renal disease (ESRD) patients undergoing maintenance dialysis.

## Materials and Methods

We reviewed demographic, laboratory, and treatment information collected from an existing computerized registry of patients with ESRD receiving maintenance hemodialysis or peritoneal dialysis in the Greenfield Health Services-Henry Ford Health System. Data obtained after parathyroidectomy or successful renal transplantation were excluded from analysis. In patients with a previous history of renal transplantation, data during the period with a functional transplant, and for the 6 mo after failure of transplant and resumption of dialysis, were excluded from analysis. This registry includes PTH measurements performed every 4 to 6 mo, and other laboratory data measured every month.

In January 1993, the PTH assay was changed to an immunoradiometric assay for the intact molecule. ESRD patients who had two or more measurements of intact PTH at least 90 d apart after January 1993 were considered for inclusion in our analysis. A total of 1367 patients met the above criteria, of which 97 (7%) classified as Asian, Hispanic, or unspecified race were excluded. The remaining 1270 patients classified as black or white were retained for analysis. All serum PTH measurements since the onset of ESRD were available only for patients who started dialysis after January 1993, and additional analyses were performed on this incident population subgroup.

The following sets of variables were analyzed: demographic data including race, gender, age, and presence or absence of diabetic nephropathy as the cause of the renal failure; intact parathyroid hormone levels since the onset of ESRD and the date on which the maximum PTH level was obtained; laboratory data including serum calcium, phosphorus, alkaline phosphatase, albumin, and aluminum; and interdialytic weight gain as an indicator of patient's compliance with prescribed treatment. The values of laboratory and dialysis data

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recorded either at the same time or within 1 mo of the date of the maximum PTH were used for analysis. Therefore, for every patient a cross-sectional analysis was performed at the time of maximum recorded PTH level. The diabetic and nondiabetic groups were analyzed separately for any racial differences, since uremic hyperparathyroidism is a milder disease in diabetic patients (7).

### Statistical Analyses

The racial groups were compared by *t* test and by analysis of covariance models, which were used to compute and test adjusted means for the groups of interest. Multiple regression models were used for the analysis of covariance. Indicator variables (0, 1) were included for black race, male gender, and diabetic status.

### Results

The patient characteristics of this population are shown in Table 1. The prevalence study population (*n* = 1270) comprised 776 blacks (61.1%), 494 whites (38.9%), 648 males (51%), and 395 diabetic patients (31.1%). The subpopulation of incident cases (*n* = 466) was similar to the overall study population in patient characteristics, comprised of 264 blacks (57%), 202 whites (43%), 240 males (52%), and 179 diabetic patients (38%).

There were small but statistically significant racial differences in some clinical and laboratory parameters including serum calcium and phosphorus (Table 2). The subpopulation of incidence cases was similar to the prevalence study population in clinical and laboratory parameters (data not shown).

The number of PTH values available per patient (mean  $\pm$

SD) was  $7.4 \pm 4$  in the entire study population and  $5.4 \pm 3$  among the incident cases. The distribution of maximum PTH levels among the 776 black and 494 white ESRD patients in the prevalence study population is shown in Figure 1. Maximum PTH values were significantly higher in blacks, regardless of diabetic status (Table 3). The average maximum PTH level for blacks was  $>200$  pg/ml higher ( $P < 0.001$ ) when the analysis was restricted to patients with serum phosphorus  $<6$  mg/dl or restricted to patients with serum phosphorus  $<6$  mg/dl and corrected calcium  $>9.5$  mg/dl (data not shown). PTH levels for the study population were adjusted for age, gender, interdialytic weight gain, diabetic status, and serum levels of phosphorus, calcium, aluminum, and albumin, using multiple regression analysis. After adjustment, PTH levels remained higher in blacks than in whites ( $641.7$  versus  $346.0$ ,  $P < 0.0001$ ). Using a stepwise multiple regression model, coefficients for maximum PTH were determined (Table 4). Race was found to be the most important independent determinant of maximum PTH followed by serum phosphorus, diabetes, age, serum calcium, and gender. Presence of diabetes, male gender, lower serum phosphorus, and older age were independently associated with a lower lifetime maximum PTH value. Each 1-yr increase in age was associated with a decrease of  $4.11 \pm 1.1$  pg/ml in maximum PTH levels (mean  $\pm$  SEM). Maximum PTH levels were approximately  $69.6 \pm 32.9$  pg/ml lower in males than females (mean  $\pm$  SEM). The positive correlation between serum calcium and maximum PTH suggests that PTH may be driving calcium. However, the positive adjusted correlation between PTH and corrected calcium is restricted to patients with PTH  $>250$  pg/ml. If the multiple regression model is restricted to patients with PTH  $<250$  pg/ml, the adjusted correlation is negative, suggesting that PTH is being driven by calcium at lower levels of PTH. Serum albumin, a marker of nutritional status, was not found to be a determinant of maximum PTH. Higher PTH levels were associated with increased serum alkaline phosphatase and use of vitamin D (data not shown), as would be expected.

Severity of uremic hyperparathyroidism in ESRD is an important determinant of the type of renal bone disease present. Severe hyperparathyroidism (mean 1–84 PTH,  $>500$  pg/ml) predisposes patients to develop hyperparathyroid bone disease and relative hypoparathyroidism (maximum 1–84, PTH  $<150$

Table 1. Demographics of the dialysis population<sup>a</sup>

Characteristic	Nondiabetic ( <i>n</i> = 875)	Diabetic ( <i>n</i> = 395)
Age	54.4 (17.0)	58.2 (12.7)
Race		
black	531 (60.7%)	245 (62.0%)
white	344 (39.3%)	150 (38.0%)
Gender		
male	466 (53.3%)	182 (46.1%)
female	409 (46.7%)	213 (53.9%)

<sup>a</sup> Results are given as mean (SD).

Table 2. Clinical and laboratory parameters of the dialysis population in the prevalence study<sup>a</sup>

Parameter	Nondiabetic		Diabetic	
	Black ( <i>n</i> = 531)	White ( <i>n</i> = 344)	Black ( <i>n</i> = 245)	White ( <i>n</i> = 150)
Interdialytic weight gain (kg)	2.3 (1.5) <sup>b</sup>	2.0 (1.2)	2.4 (1.3)	2.5 (1.2)
Albumin (g/dl)	3.8 (0.5)	3.8 (0.4)	3.7 (0.5)	3.7 (0.4)
Calcium (mg/dl)	9.4 (1.0) <sup>b</sup>	9.7 (0.8)	9.3 (0.9)	9.6 (0.8)
Phosphorus (mg/dl)	6.4 (2.1)	6.4 (2.1)	6.1 (1.7)	6.5 (1.9)
Alkaline phosphatase (IU/L)	147 (117.5) <sup>b</sup>	119 (83.1)	129 (92.5)	116 (76.3)

<sup>a</sup> Results are given as mean (SD).

<sup>b</sup>  $P < 0.05$  black versus white.

pg/ml) to adynamic bone disease. Racial differences in uremic parathyroid disease prompted us to compare the odds for development of these two types of bone lesions between white and black patients in the incidence subpopulation (Table 5). Blacks were 4.4 times more likely to have severe hyperparathyroidism than whites. Whites were 3.8 times more likely to have relative hypoparathyroidism than blacks. Similar odds ratios were obtained when the analysis was restricted to 169 incident patients that were not receiving intravenous calcitriol therapy around the time of maximum PTH. We did not collect data on treatment with oral calcitriol. However, <10% of our hemodialysis patient population is treated with oral vitamin D analogs due to reimbursement issues.

## Discussion

This study confirmed the recognized role of phosphate control, diabetic status, and age in regulating the activity of parathyroid gland in uremic patients. However, these factors, either singly or in combination, are often insufficient to explain the patient-to-patient variance in the severity of secondary hyperparathyroidism. This study has identified race and gender as two other important regulators of parathyroid activity, of which race appears to be more important.

The effect of gender on parathyroid activity may be regulated by sex steroids, since estrogen receptors are present in parathyroid cells and estrogens increase PTH mRNA levels (8). Even though estradiol levels are normal in the majority of women on dialysis (9,10), amenorrhea or anovulatory periods

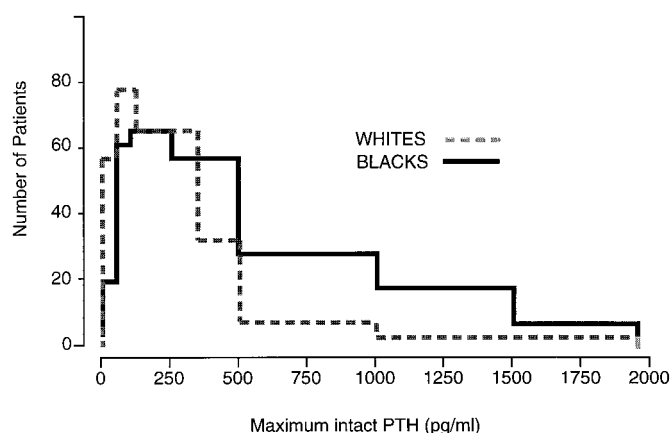
are common, and long periods of unopposed estrogen exposure may lead to stimulation of the parathyroid gland. In a recent study, hyperparathyroid bone disease was more frequently seen in uremic women than men (68.5% versus 51%,  $P = 0.04$ ) (11). However, in the general population, men and women have similar PTH levels (3).

The factors responsible for the racial differences in uremic hyperparathyroidism are unknown. The biologic significance of small but statistically significant racial differences in serum calcium and phosphorus values is doubtful, considering the inconsistency between the diabetic and nondiabetic patient subgroups. Serum vitamin D levels are not routinely monitored in our dialysis population, and this factor could not be addressed in the present study. It has been speculated that the skin pigmentation in blacks is responsible for the decreased synthesis of 25(OH)D in response to sun exposure (2,3), leading to secondary hyperparathyroidism and increased parathyroid gland mass in the general population (2,4,5). The decline in

**Table 4.** Multiple linear regression model coefficients for maximum PTH<sup>a</sup>

Independent Variables	Coefficient (SEM)	P Value
<b>Demographic parameters</b>		
black race	295.7 (32.9)	<0.001
age (yr)	−4.11 (1.1)	0.002
male	−69.6 (32.7)	0.033
<b>Laboratory parameters</b>		
phosphorus (mg/dl)	53.8 (8.1)	<0.001
calcium (mg/dl)	55.8 (19.7)	0.005
albumin	50.6 (39.0)	0.196
aluminum	0.12 (1.01)	0.905
<b>Other parameters</b>		
interdialytic weight gain	8.4 (12.0)	0.485
diabetes mellitus	−158.9 (34.1)	<0.001

<sup>a</sup> The regression coefficients show the estimated change in maximum PTH (pg/ml) per unit change in each predictor, after accounting for other variables. Therefore, on average the maximum PTH level is 295.7 pg/ml higher in blacks than whites, 158.9 pg/ml lower in diabetic than nondiabetic patients, and 69.6 pg/ml lower in males than females. Furthermore, the maximum PTH level decreased by 4.1 pg/ml for each additional year of age, and increased by 53.8 pg/ml for every 1 mg/dl increase in serum phosphorus.



**Figure 1.** Distribution of maximum parathyroid hormone (PTH) levels among the 776 black and 494 white end-stage renal disease patients.

**Table 3.** Unadjusted maximum 1-84 PTH (pg/ml)<sup>a</sup>

Group	All Cases <sup>b</sup>		Incident Cases Subpopulation <sup>b</sup>	
	Black (n = 776)	White (n = 494)	Black (n = 264)	White (n = 202)
Diabetic	500.3 (448)	247.8 (230)	469.0 (344)	248.6 (177)
Nondiabetic	700.4 (608)	447.6 (562)	618.3 (578)	347.2 (393)

<sup>a</sup> Results are given as mean (SD). PTH, parathyroid hormone.

<sup>b</sup>  $P < 0.0001$  black versus white.

Table 5. Risk of severe secondary hyperparathyroidism or relative hypoparathyroidism in the incidence subpopulation<sup>a</sup>

Severity of Uremic Parathyroid Disease	Black (n = 264)	White (n = 202)	Odds Ratio for Black:White
Relative hypoparathyroidism (maximum PTH <150 pg/ml)	34	73	0.26 (0.17 to 0.41):1
Severe secondary hyperparathyroidism (mean PTH >500 pg/ml)	45	9	4.4 (2.10 to 9.25):1

<sup>a</sup> 95% confidence interval is given in parentheses.

1,25(OH)<sub>2</sub>D<sub>3</sub> production as renal failure develops may have a permissive effect on this baseline secondary hyperparathyroidism. On the other hand, serum levels of calcitriol are uniformly low in patients with ESRD, regardless of their race. However, there is indirect evidence to suggest that race may influence the end-organ response to serum calcitriol. First, recent studies suggest that common allelic polymorphisms in the vitamin D receptor (VDR) gene may affect the parathyroid response in patients with ESRD (12,13). In these studies, *BsmI* and *ApaI* restriction analysis of the VDR gene in ESRD patients revealed that [B] and [A] alleles are associated with milder parathyroid disease. Consistent with these findings, in patients with primary hyperparathyroidism, the [B] allele of VDR gene is associated with milder disease (14). Second, a comparison of the VDR allele frequencies between American blacks and whites in the general population reveals that [B] and [b] alleles are present in a ratio of 0.5:0.5 among whites and 0.3:0.7 among blacks (12,15). This raises the tantalizing possibility that the more frequent occurrence of the [b] allele in blacks is causally related to more severe uremic hyperparathyroidism.

PTH is a surrogate marker of bone turnover, and the severity of secondary hyperparathyroidism is an important determinant of the histologic type of bone disease (16). Adynamic bone disease is present in about 30% of hemodialysis and 50% of peritoneal dialysis patients (17–19). In uremia, bone is resistant to PTH action and patients with relative hypoparathyroidism (1–84 PTH <150 pg/ml) are predisposed to adynamic bone disease (20). On the other hand, severe secondary hyperparathyroidism (1–84 PTH >500 pg/ml) is associated with osteitis fibrosa cystica (21). However, the correlations between PTH levels and bone turnover have been largely described in Caucasian dialysis populations, and whether these data apply to blacks is not known.

More severe uremic hyperparathyroidism in blacks may not necessarily lead to more severe hyperparathyroid bone disease, since black patients may have a relative resistance to PTH action as suggested by decreased serum Gla protein and bone turnover despite an increase in serum PTH in black subjects without renal disease (3,22). Therefore, more severe uremic hyperparathyroidism in blacks may be a physiologic adaptive response to maintain bone turnover. Based on studies conducted predominantly in white subjects, an intact PTH level of 120 to 240 pg/ml (2 to 4 times normal) is considered optimal in ESRD (21). If parathyroid disease in black patients is treated based on these guidelines, there is a risk of inappropriately aggressive treatment, oversuppression of parathyroid gland, and development of adynamic bone disease. Therefore, it is

important to define the spectrum of renal osteodystrophy in black dialysis patients as a function of the severity of parathyroid disease. Renal osteodystrophy is indeed an important problem in blacks, since the relative risk of hip fractures is increased three- to fourfold in the U.S. Medicare dialysis population compared with the general population, regardless of race (23).

In conclusion, there are significant racial differences in the severity of uremic hyperparathyroidism. Additional studies are needed to elucidate the molecular mechanisms for these differences, and to define the histologic spectrum of renal osteodystrophy and optimal levels of parathyroid hormone in black patients with uremia.

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