The Severity of Secondary Hyperparathyroidism in Chronic Renal Insufficiency is GFR-Dependent, Race-Dependent, and Associated with Cardiovascular Disease

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Abstract. Secondary hyperparathyroidism (SHPT) is an important complication of end-stage renal disease. However, SHPT begins during earlier stages of chronic renal insufficiency (CRI), and little is known about risk factors for SHPT in this population. This study evaluated 218 patients in an ethnically diverse ambulatory nephrology practice at the University of California San Francisco during calendar years 1999 and 2000. Demographic data, comorbid diseases, medications, and laboratory parameters were collected, and independent correlates of intact parathyroid hormone (PTH) were identified by using multiple linear regression. The mean estimated GFR was 34 ml/min per 1.73 m² (10%–90% range, 13 to 61 ml/min per 1.73 m²); PTH was inversely related to GFR \( (P < 0.0001) \). The adjusted mean PTH was higher among African Americans and lower among Asian/Pacific Islanders compared with white patients \( (233 \text{ versus } 95 \text{ versus } 139 \text{ pg/ml}; P < 0.0001) \). Moreover, among the 196 patients with GFR <60 ml/min per 1.73 m², the slope of GFR versus PTH was significantly steeper among African Americans than among white patients \( (10.6 \text{ versus } 3.9 \text{ pg/ml per ml per min per } 1.73 \text{ m}^2; P = 0.01) \). After adjusting for age and diabetes, PTH was associated with a history of myocardial infarction \( (\text{OR, } 1.6; 95\% \text{ CI, } 1.1 \text{ to } 2.3 \text{ per unit natural log PTH}) \) and congestive heart failure \( (\text{OR, } 2.0; 95\% \text{ CI, } 1.3 \text{ to } 2.9 \text{ per unit natural log PTH}) \) and not associated with other co-morbid conditions. These factors should be considered when screening and managing SHPT in CRI.

Secondary hyperparathyroidism (SHPT) is a common, important, and treatable complication of chronic renal insufficiency (CRI) and end-stage renal disease (ESRD). Although its exact pathogenesis is unknown, hyperphosphatemia, \( (1,2) \), hypocalcemia \( (3) \), deficiency of 1,25-dihydroxyvitamin D₃ \( (4) \), decreased expression of calcium and vitamin D receptors \( (5,6) \), and parathyroid hormone (PTH) resistance \( (7) \) may each play a part. Longstanding SHPT results in osteitis fibrosa cystica (a high turnover bone lesion) and increases the risks for bone pain and fracture. Osteitis fibrosa cystica (OFC) may be present in 30 to 50% of CRI patients before the initiation of dialysis \( (8–12) \).

The prevalence and severity of SHPT have been shown to increase with declining renal function in CRI \( (13–17) \). Drug therapy with 1,25-dihydroxyvitamin D₃ and calcium salts have been reported to retard the progression of SHPT \( (18,19) \), improve BMD \( (20) \), and reverse abnormal bone histology \( (19,21,22) \).

In the dialysis population, the degree of SHPT varies widely, although higher PTH has been associated with African American race, female gender, younger age, and lack of diabetes mellitus \( (23,24) \), along with higher serum phosphorus and lower serum calcium concentrations. We hypothesized that, in CRI, the degree of SHPT would be correlated inversely with GFR and the serum concentrations of calcium and bicarbonate and directly with the use of loop diuretics.

Materials and Methods

Study Subjects

We included patients evaluated in the ambulatory nephrology faculty practices at the University of California, San Francisco (UCSF). These practices are staffed by faculty and fellows in the Division of Nephrology at UCSF and serve an ethnically and economically diverse population, mostly comprised of individuals living in and around San Francisco and other communities in Northern California. All persons seen between January 1, 1999, and December 31, 2000, were screened for eligibility, and those with at least one PTH value collected were included in this study. Patients were excluded if they had undergone maintenance dialysis or kidney transplantation before their first qualifying PTH value or if they had evidence of primary hyperparathyroidism.

Data Collection

Data were collected from the UCSF electronic medical record known as the Summary Time Oriented Record (STOR). Over 625,000 patient records are currently in the STOR database. The STOR includes clinical and administrative data on all patients who receive inpatient, outpatient, and emergency department care at UCSF Med-
clinical Center sites. It provides an online display of demographic information and detailed clinical data, including ambulatory diagnoses, vital signs, discharge summaries, allergies, medical history, clinic visit information, provider progress notes, medical and surgical therapies, laboratory tests, electrocardiography results, radiology reports, and pathology and operative reports.

Laboratory data drawn on the same day or, if not available, within 30 d of the date of PTH collection were classified as concurrent. Fewer than 5% of laboratory values were missing, except for albumin (missing in 23%) and hemoglobin (missing in 12%). The intact PTH assay (Nichols, San Juan Capistrano, CA) was used during the study period. GFR was estimated using the abbreviated MDRD formula, incorporating the serum creatinine, age, gender, and race (25).

Data were abstracted by two independent researchers, with reciprocal checks to verify accuracy. Limited paper chart review was performed in the few cases in which sufficient data were not available in STOR. A 10% random sample (by random number generator) of records was reviewed to validate the electronic medical record. Age, gender, and diagnosis of hypertension matched exactly in 24 of 24 records. Diabetes was coded correctly in 22 (92%) of 24 records. Loop diuretic (22 of 24 records) and calcium (21 of 24 records) prescriptions were slightly under-ascertained by STOR. The study protocol was approved by the UCSF Committee on Human Research.

Statistical Analyses

Continuous data were expressed as mean ± SD or median with 10%–90% range, and compared using ANOVA, the Wilcoxon rank sum test, or the Kruskal-Wallis test, where appropriate. Correlation among PTH and other variables was described with the Spearman rank-based coefficient. Highly skewed variables were log transformed before inference testing in regression models. Categorical variables were expressed as proportions and compared using χ² analysis. We used multiple linear regression to determine correlates of PTH, incorporating backward elimination variable selection, with acceptance criteria set at P < 0.05. We performed additional analyses to examine whether the relations described deviated from linearity. We incorporated multiplicative interaction terms to evaluate the effect of race on the GFR-PTH relation. In model building, we elected not to include candidate laboratory variables that might be affected by PTH (e.g., serum phosphorus and calcium) in the primary analyses. We later fit companion models in which calcium and phosphorus were included as candidate variables. Serial PTH analyses were conducted using the random effects (MIXED) model (26). In these analyses, we applied an unstructured variance-covariance matrix to obviate assumptions regarding data structure and to ensure that P-values were conservatively estimated (27). Model fitness was assessed using the Akaike information criteria (27). Two-tailed P-values < 0.05 were considered statistically significant. All analyses were conducted using SAS 8.0 (SAS Institute, Cary, NC). Graphs were created using Sigma Plot (SPSS, Inc., Chicago, IL).

Results

Seven hundred and eighty-four individual patients were evaluated in the UCSF nephrology faculty practices over the 2-yr period. PTH values were obtained on 251 (32%) during the same time frame. Of these, 32 were excluded for having had a history of requiring dialysis or transplantation, and one for primary hyperparathyroidism; 218 patients comprised the analytic sample.

PTH levels were usually obtained among individuals with evidence of CRI, although some with other problems (e.g., nephrolithiasis) were also included. The mean serum creatinine was 2.7 mg/dl (10%–90% range, 1.1 to 4.0 mg/dl; range, 0.5 to 26.6 mg/dl). The estimated GFR was 34 ml/min per 1.73 m² (10%–90% range, 13 to 61 ml/min per 1.73 m²), corresponding roughly to chronic kidney disease (CKD) classification stages 3 and 4 (25).

Baseline characteristics of the 218 patients with PTH values are presented in Table 1, stratified by race-ethnicity. Diabetes was more common among persons of African American and Asian/Pacific Islander background. Height and weight were significantly lower among persons of Asian/Pacific Islander background. Serum creatinine and diastolic BP were higher and estimated GFR lower among African Americans compared with other race-ethnicity groups. The prevalence of comorbid conditions, including preexisting cardiovascular disease, was generally similar across the population, as was the use of selected medications.

Cross-Sectional Correlates of PTH

The mean PTH was 146 ± 139 pg/ml (median, 101 pg/ml; 10%–90% range, 29 to 328 pg/ml). The PTH was directly correlated with age (r = 0.17; P = 0.01), black race (median, 171.5 pg/ml; P < 0.0001), loop diuretic use (median PTH, 116 pg/ml; P = 0.009), and serum phosphorus (r = 0.25, 0.004), and it was inversely correlated with Asian/Pacific Islander race (median PTH, 74 pg/ml; P = 0.003), estimated GFR (r = −0.48; P < 0.0001), hemoglobin (r = −0.19; P = 0.01), serum calcium (r = −0.35; P < 0.0001), and serum bicarbonate (r = −0.37, P < 0.0001). Gender (P = 0.83) and diabetes (P = 0.96) were not significantly related to PTH on univariate analysis, nor were other factors listed in Table 1.

In constructing the multivariable models, we felt that, although known to be associated with PTH, serum calcium and phosphorus should not be included in the primary model, because PTH may directly affect serum calcium and phosphorus concentrations. In other words, the effects among PTH, calcium, and phosphorus are likely to be bi-directional. In addition to those variables significant on univariate screening, we also included gender and diabetes as potential confounding variables on the basis of published experience in patients with end-stage renal disease. Tables 2 and 3 shows the multivariable linear regression results. The primary analysis shows the significant associations of race, bicarbonate, and GFR with PTH. When added to this model, calcium was independently associated with PTH, although phosphorus was not. When calcium was added to the multivariable model, bicarbonate was no longer statistically significant (P = 0.11). As expected, the inclusion of serum calcium in the model increased the extent of variation explained (R² = 0.43, rather than 0.35).

PTH, GFR, and Race

On the basis of clinical experience and existing literature describing race-specific differences in PTH dynamics in non-uremic individuals (28,29), we considered whether race influenced the GFR-PTH relation. Figure 1 shows the curvilinear relation between PTH and GFR across the 218-patient cohort (confirmed by models including linear and quadratic GFR terms). As has been previously described (8,9,14–17), the inflection point of the PTH-
GFR curve appears to be in the range of 60 ml/min per 1.73 m². We then calculated the estimated linear effect of GFR on PTH among the 196 patients with estimated GFR 60 ml/min per 1.73 m² or below. Overall, there was a 4.4 pg/ml increase in PTH per ml/min per 1.73 m² decrease in GFR ($P < 0.0001$), although these trends differed significantly by race. Among African Americans, there was a 10.6 pg/ml increase in PTH per ml/min per 1.73 m², compared with a 3.9 pg/ml increase in white patients (race × GFR interaction, $P = 0.01$). The trend in PTH by GFR was nonsignificant among Asian Americans ($P = 0.38$). Table 4shows the unadjusted mean PTH values stratified by race, as well as the fraction of patients with PTH 1, 2, and 3 times the upper limit of normal.

**PTH and Cardiovascular Disease**

After adjusting for the significant (and expected) effects of age and diabetes, higher levels of PTH were significantly associated with congestive heart failure (OR, 2.0; 95% CI, 1.3 to 2.9 per unit increase in natural log PTH) and myocardial infarction (OR, 1.6; 95% CI, 1.1 to 2.3 per unit increase in natural log PTH). PTH was not significantly associated with other comorbid conditions.

**Longitudinal Data**

Serial PTH values (two to seven in number) were available for 90 patients (41%). Using the random effects (MIXED) model, we observed a significant reduction in PTH after the index office visit ($P = 0.03$), probably reflecting the effects of a variety of interventions (e.g., dietary modification, provision of vitamin D and calcium). As in the cross-sectional analysis, GFR varied inversely with serial PTH values over time ($P = 0.003$).

**Discussion**

SHPT is a well-known complication of ESRD. Among several forms of renal osteodystrophy, the predominant effect of
SHPT on bone is termed osteitis fibrosa cystica (OFC), a condition associated with high bone turnover, pain, and an increased risk of fractures. SHPT has also been implicated in the pathogenesis of visceral and vascular calcification (30), cardiomyopathy (30), uremic calcific arteriolopathy (calciphylaxis) (31), uremic pruritus (32), hypertension (33), erythropoietin hyporesponsiveness (34), protein catabolism (35), increased energy expenditure (36), and cognitive (37) and sexual dysfunction (38).

Much less is known about SHPT in persons with mild to moderate CRI. Published studies have demonstrated elevations in PTH with CrCl or GFR below approximately 60 ml/min per 1.73 m² (8,9,14–17). Indeed, relatively few patients with CRI undergo testing for SHPT, and most have serum phosphorus and calcium concentrations within the normal laboratory ranges (39). In a description of CRI practice patterns in the Northeast United States (an academic medical center and several affiliates), Kausz et al. (40) showed that only 15% of 602 patients with CRI (defined as serum creatinine ≥1.5 mg/dl in women and ≥2.0 mg/dl in men) ever had PTH tested over a 4-yr observation period. We therefore undertook this study to characterize in more detail the prevalence, severity, and correlates of SHPT in a diverse CRI population.

We confirmed the cross-sectional association between PTH and GFR. In addition, we demonstrated that PTH values differed significantly by race or ethnicity, as did the slope of the GFR-PTH relation. These findings were confirmed in a longitudinal analysis of patients who had repeat PTH testing (2 to 7 times) over the 2-yr study period.

In hemodialysis patients, Gupta et al. (23) reported that mean PTH was nearly 300 pg/ml higher in African Americans than in white patients, with regression adjustment for age, gender, diabetes, and serum calcium and phosphorus. The extension of race-specific PTH values to patients with CRI is noteworthy, particularly in view of the relative increase in bone density (41) and decrease in fracture rates observed among African Americans with (42) and without (43) ESRD. We were struck by the fact that published bone biopsy studies in ESRD have failed to report results stratified by race (9–12,44–46, among others). Other studies have suggested a relative resistance to PTH and lower vitamin D levels in African Americans (42) and Asian/Pacific Islander; v, Black; v, Hispanic.

Table 2. Multivariable linear regression model—calcium not included (n = 218)\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>p(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>329.1</td>
<td></td>
</tr>
<tr>
<td>Age (per yr age)</td>
<td>0.6123</td>
<td>0.14</td>
</tr>
<tr>
<td>Female</td>
<td>9.279</td>
<td>0.60</td>
</tr>
<tr>
<td>African American</td>
<td>98.23</td>
<td>0.0003</td>
</tr>
<tr>
<td>Asian Pacific Island</td>
<td>−38.58</td>
<td>0.06</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.552</td>
<td>0.53</td>
</tr>
<tr>
<td>GFR (per ml/min per 1.73 m²)</td>
<td>−6.220</td>
<td>0.0002</td>
</tr>
<tr>
<td>GFR squared</td>
<td>3.598 × 10(^{-2})</td>
<td>0.02</td>
</tr>
<tr>
<td>Bicarbonate (per mEq/L)</td>
<td>−3.877</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

\(^a\) GFR squared terms not significant when samples restricted to GFR ≤ 60 ml/min per 1.73 m². Parameter estimates of age, gender, and race/ethnicity represent residual effect estimates after accounting for the contribution of these factors within the GFR estimate.

\(^b\) P-value from model using log transformed intact PTH as dependent variable; R\(^2\) = 0.35.

Table 3. Multivariable linear regression model—calcium included (n = 218)\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>p(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>613.2</td>
<td></td>
</tr>
<tr>
<td>Age (per yr age)</td>
<td>0.7405</td>
<td>0.06</td>
</tr>
<tr>
<td>Female</td>
<td>23.93</td>
<td>0.58</td>
</tr>
<tr>
<td>African American</td>
<td>93.52</td>
<td>0.0009</td>
</tr>
<tr>
<td>Asian Pacific Island</td>
<td>−40.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.126</td>
<td>0.33</td>
</tr>
<tr>
<td>GFR (per ml/min per 1.73 m²)</td>
<td>−6.120</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GFR squared</td>
<td>3.496 × 10(^{-2})</td>
<td>0.02</td>
</tr>
<tr>
<td>Calcium (per 0.1 mg/dL)</td>
<td>−4.354</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\) GFR squared terms not significant when samples restricted to GFR ≤ 60 ml/min per 1.73 m². Parameter estimates of age, gender, and race/ethnicity represent residual effect estimates after accounting for the contribution of these factors within the GFR estimate.

\(^b\) P-value from model using log transformed intact PTH as dependent variable; R\(^2\) = 0.43; bicarbonate not independently associated with PTH when calcium included in model.

Figure 1. Log PTH by GFR by race. ◆, White; ○, Asian/Pacific Islander; ▽, Black; ▽, Hispanic.
Table 4. PTH results by race

<table>
<thead>
<tr>
<th></th>
<th>All (n = 218)</th>
<th>White (n = 95)</th>
<th>African American (n = 48)</th>
<th>Asian or Pacific Islander (n = 58)</th>
<th>Hispanic (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PTH (pg/ml)</td>
<td>146</td>
<td>130</td>
<td>249</td>
<td>93</td>
<td>130</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted mean PTH (pg/ml)†</td>
<td>NA</td>
<td>139</td>
<td>233</td>
<td>95</td>
<td>131</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% above 65 pg/ml</td>
<td>69%</td>
<td>65%</td>
<td>90%</td>
<td>60%</td>
<td>59%</td>
<td>0.005</td>
</tr>
<tr>
<td>% above 130 pg/ml</td>
<td>38%</td>
<td>33%</td>
<td>67%</td>
<td>21%</td>
<td>33%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% above 195 pg/ml</td>
<td>24%</td>
<td>20%</td>
<td>48%</td>
<td>9%</td>
<td>29%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, estimated GFR, and serum bicarbonate concentration.

patients had severe OFC (9%) or adynamic bone disease (24%).

Acidosis was associated with SHPT in this population. Previous studies in ESRD have shown that correction of acidosis with either oral bicarbonate supplementation or increases in dialysate bicarbonate led to relative reductions in PTH and improvements in bone histology (50,51). The mechanism of the bicarbonate-PTH association is unknown, though direct effects on PTH secretion (52), increased sensitivity of the parathyroid gland to calcium (53), and an indirect effect due to acidosis-related hypercalcemia (54) have been proposed. Fewer studies have examined the association between acidosis and SHPT in CRI. St. John et al. (14) examined correlates of PTH in 39 patients with mild to moderate CRI (GFR 20 to 90 ml/min per 1.73 m²) and showed GFR, bicarbonate, and serum 25-hydroxy vitamin D₃ to be independently associated with PTH. Coen et al. (54) showed a trend toward higher PTH in CRI patients with metabolic acidosis, accompanied by more severe mineralization defects on histomorphometry. In our study, collinearity between calcium and bicarbonate (r = 0.37, P < 0.0001) probably explains the lack of statistical significance in the calcium-adjusted model, rather than the absence of a true bicarbonate-PTH association.

Race and bicarbonate may be proxies for dietary protein and phosphorus intake. Mean serum phosphorus did not differ among races; however, transient elevations in serum phosphorus may have led to increased PTH secretion, augmenting phosphaturia, and maintaining phosphorus homeostasis. Forcing BUN (a rough proxy for dietary protein intake once GFR is accounted for) into the PTH regression model did not extinguish the significance of the race terms (data not shown).

PTH was significantly associated with cardiovascular disease (myocardial infarction and congestive heart failure) in this cohort, confirming previous reports that linked PTH to cardiovascular disease in experimental models (55) and case series (33). The mechanism of cardioxicity of PTH has been the subject of much investigation. Published reports have highlighted the role of intracellular calcium in myocytes and postulate a direct toxicity of PTH leading to cardiomyopathy (56) with left ventricular hypertrophy and fibrosis (57). In a short-term (15-wk) study, correction of SHPT with calcitriol was associated with a significant reduction in left ventricular mass and wall thickness (58). Several case reports highlight anecdotal improvements in left ventricular ejection fraction after subtotal parathyroidectomy in ESRD patients with severe SHPT (59), although other reports show no direct effect (60). We recently reported that PTH was directly related to the severity of aortic calcification by electron beam tomography (EBT) in 205 hemodialysis patients, although we failed to find a significant association between PTH and coronary artery calcification (61).

There are several important limitations to this study. It was performed within a single University-affiliated Nephrology Division, and the results may not be generalizable to community-based practices or practices elsewhere in the United States or overseas. A large number of patients did not have a PTH value available on STOR during the 1999 and 2000 calendar years. In some cases, patients may have been seen for reasons other than CRI (e.g., hypertension with normal renal function). Alternatively, many CRI patients underwent laboratory testing off campus. Therefore, we included fewer patients than those who actually had PTH assessment due to our lack of access to commercial laboratories and other hospital systems. Although the demographics of the populations who did and did not have UCSF-based laboratory testing likely differed, it is unlikely that these differences explain the associations described here. The population served was extremely diverse in terms of age, sex, race or ethnicity, and comorbid conditions, as well as socioeconomic and insurance status (the latter not reported). Dietary intake was not measured or estimated in this study. GFR was estimated. The use of iothalmate or inulin clearance might have improved the precision with which the degree of CRI was characterized. Although equations estimating GFR have been recently refined and more widely used, the abbreviated MDRD equation has not been specifically validated in Asian/Pacific Islander or Hispanic populations. In other words, the abbreviated MDRD equation considers persons of European, Asian/Pacific Islander, and Hispanic heritage as “non-African American.” If the equation underestimated GFR, then the lower PTH attributed to Asian/Pacific Islander race could be explained by the higher than estimated GFR. Use of a single PTH value likely led to some misclassification, probably biasing associations between PTH and laboratory and other clinical variables toward the null. Confounding by calcium and vitamin D therapy may have lessened the power to detect associations between PTH and other variables by directly influencing PTH. Inclusion of 25-hydroxy- and 1,25-dihydroxy vitamin D₃ levels might have informed the analyses. Bone biopsy would have
also been of interest, particularly in comparing the relative effects of SHPT on bone by race. Cardiovascular disease was determined clinically (based on provider problem lists) and may have been underascertained. Finally, as with all cross-sectional analyses, one cannot infer causality from the associations described here.

In summary, in a cohort of 218 patients from an ambulatory nephrology practice, SHPT was common and mild to moderate in degree. The severity of SHPT differed significantly by race, as did the GFR-PTH relation, with the steepest curve seen among African Americans. Given the frequency and severity of SHPT in CRI, especially among African Americans, additional observational data using objective measures of bone and vascular health (e.g., bone biopsy, EBT) are urgently needed. Moreover, these findings collectively raise the question of whether PTH targets in CRI or ESRD should be uniform or race- or ethnicity-specific and highlight the need for additional research, especially regarding the influence of race, diet, and other factors in the pathogenesis of SHPT in CRI. Ultimately, clinical trials comparing dietary modifications, phosphate binders, provision of physiologic doses of biologically active vitamin D, or other therapies will be required to guide management and potentially avoid complications of mild to moderate SHPT in CRI and more severe SHPT in ESRD.

Acknowledgments

This study was supported in part by an unrestricted grant from Amgen, Inc. Dr. Chertow is also supported by NIH NIDDK RO1 DK58411-01.

References


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