

# Obesity Is Associated with Secondary Hyperparathyroidism in Men with Moderate and Severe Chronic Kidney Disease

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**Background and Objectives:** Obesity is associated with secondary hyperparathyroidism in the general population. The objective of this study is to explore whether the same association is present in patients with chronic kidney disease.

**Design, Setting, Participants & Measurements:** Linear regression models were used to examine the association between intact parathyroid hormone level and body mass index in 496 male US veterans (age  $69.4 \pm 10.2$  yr, 22.8% black) who had chronic kidney disease stages 2 to 5 and were not yet on dialysis (estimated GFR  $31.8 \pm 11.2$  ml/min per  $1.73$  m<sup>2</sup>).

**Results:** Higher intact parathyroid hormone was associated with higher body mass index after adjustment for age, race, diabetes, and serum calcium and phosphorus levels. This association was independent of age, race, diabetes status, and serum calcium and phosphorus but was limited to patient groups with lower albumin ( $P = 0.005$  for the interaction term) or higher white blood cell count ( $P = 0.026$  for the interaction term).

**Conclusions:** Higher body mass index is associated with secondary hyperparathyroidism in patients who have chronic kidney disease and are not yet on dialysis, especially in patients with evidence of malnutrition and inflammation. Confirmation of these findings in other patient groups with chronic kidney disease and better characterization of the underlying mechanisms of action will be necessary before advocating weight loss as a means to treat secondary hyperparathyroidism in chronic kidney disease.

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Secondary hyperparathyroidism (SHPT) is a common abnormality in patients with chronic kidney disease (CKD) and is associated with a variety of complications, including bone disease (1,2), uremic pruritus (3), refractory anemia (4), cognitive and sexual dysfunction (5), and higher cardiovascular morbidity (6–8) and mortality (9,10). Elevated parathyroid hormone (PTH) levels develop early in the course of CKD and worsen with advancing stages of this disease (6,11–16). Studies exploring SHPT in patients with CKD have characterized the physiologic factors governing the relationship between PTH level and other components of bone and mineral metabolism, such as calcium, phosphorus, and vitamin D, mostly in the context of alterations in these factors occurring as a function of the level of severity of CKD (11–16). There is indication from populations without CKD that PTH levels are also influenced by various demographic (17,18), anthropometric (19), and comorbidity characteristics (20). Knowledge of such associations

in patients with CKD is important, because effect modification by clinical characteristics of SHPT in CKD may have therapeutic and prognostic implications. Obesity has been associated with hyperparathyroidism in non-CKD populations (19), but it is unknown whether a similar association exists in patients with CKD. We examined the association between intact PTH (iPTH) levels and body mass index (BMI) in 496 male US veterans who had CKD stages 2 to 5 and were not yet on dialysis.

## Materials and Methods

### Study Population and Data Collection

Data were collected from 1012 patients who were enrolled for evaluation and treatment for CKD (excluding those who required dialysis) at Salem VA Medical Center (VAMC) between January 1, 1990, and June 30, 2005, and followed until September 20, 2006. Eleven (1.1%) female patients and 5 (0.5%) patients whose race was other than white or black were excluded from analyses. Of the remaining 996 patients, 543 (54.5%) had at least one iPTH level measured. Twenty-two (4%) of these patients had their first PTH evaluation performed after August 10, 2005, when the assay for iPTH measurement was changed at Salem VAMC. Given the significant intermethod variability between different PTH assays (21), these patients were excluded from the analyses. Of the remaining 521 patients, 25 (4.8%) had no BMI measured at the time when PTH was evaluated, and they were also excluded from analyses. The final study population consisted of 496 patients.

Descriptive analyses were performed to assess the baseline charac-

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Table 1. Baseline characteristics of individuals stratified by quartiles of BMI<sup>a</sup>

Characteristic	BMI (kg/m <sup>2</sup> )				P
	<25.0 (n = 124)	25.0 to 28.0 (n = 124)	28.1 to 33.0 (n = 124)	>33.0 (n = 124)	
Age (yr; mean ± SD)	72.1 ± 10.1	70.4 ± 10.5	69.7 ± 9.5	65.5 ± 9.4	<0.0001
Black race (n [%])	26 (21)	25 (20)	29 (23)	33 (27)	0.6
Diabetes (n [%])	48 (39)	67 (54)	74 (60)	93 (75)	<0.001
eGFR (ml/min per 1.73 m <sup>2</sup> ; mean ± SD)	29.0 ± 10.3	31.3 ± 11.1	32.9 ± 11.9	34.1 ± 11.1	0.002
CKD stage 2/3/4/5 (%)	0/43/48/9	2/52/39/7	2/53/40/5	1/64/30/5	0.055
Calcium (mg/dl; mean ± SD)	9.5 ± 0.6	9.4 ± 0.5	9.5 ± 0.5	9.6 ± 0.5	0.03
Phosphorus (mg/dl; mean ± SD)	4.1 ± 0.7	4.1 ± 0.8	3.9 ± 0.7	4.0 ± 0.7	0.1
Albumin (g/dl; mean ± SD)	3.5 ± 0.5	3.6 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	0.15
WBC count (1000/mm <sup>3</sup> ; mean ± SD)	7.6 ± 3.1	7.5 ± 2.1	7.1 ± 2.0	7.3 ± 1.8	0.4
PTH (pg/ml; geometric mean [95% CI])	103 (90 to 119)	105 (92 to 121)	108 (96 to 122)	101 (88 to 117)	0.9

<sup>a</sup>Comparisons are made by ANOVA or  $\chi^2$  test. BMI, body mass index; CI, confidence interval; eGFR, estimated GFR; PTH, parathyroid hormone; WBC, white blood cell.

teristics of the study population at the time of the first iPTH measurement, as recorded in the course of their routine clinical care. BMI was calculated as the weight in kilograms divided by the square of the height in meters and was divided into quartiles for statistical analyses. Diabetes was defined as the presence of an abnormal fasting glucose level or antidiabetic therapy. GFR was estimated using the abbreviated equation developed for the Modification of Diet in Renal Disease Study (22) and categorized according to the staging system advocated by the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification (23). Serum calcium concentration was corrected for serum albumin concentration using the following formula: Corrected calcium = measured calcium + 0.8 × (4 – serum albumin level in g/dl) (24). All of the PTH levels included in the study were measured by the same method in a single clinical laboratory at Salem VAMC using the Allegro-intact PTH assay (Nichols Institute, San Clemente, CA), with a normal range of 10 to 65 pg/ml and a coefficient of variation of <3.4%.

Statistical Analyses

Baseline characteristics of the patient cohort were expressed as means ± SD, number (% of total), or geometric means (95% confidence interval [CI]). iPTH levels showed a skewed distribution and were natural log-transformed for analyses. The association between PTH level and BMI was assessed in linear regression models, with *a priori* adjustments for covariates that are believed to be important determinants of PTH level (age, race, diabetes, estimated GFR [eGFR], serum calcium, and phosphorus). The multivariable-adjusted geometric means (95% CI) of PTH by BMI quartiles were estimated from the multivariable regression models by using Stata postestimation commands (ADJUST). Subgroup analyses were performed in categories divided along the mean values of age, eGFR, calcium, and phosphorus and by race and diabetes status. Additional subgroup analyses were performed after dividing patients along the mean values of serum albumin and white blood cell (WBC) count, both surrogate markers of malnutrition and inflammation, and interactions were formally tested by the inclusion of interaction terms. *P* < 0.05 was considered significant. Statistical analyses were performed using Stata statistical software version 8 (Stata Corp., College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

Results

The mean age of the study population was 69.4 ± 10.2 yr, and mean eGFR was 31.8 ± 11.2 ml/min per 1.73 m<sup>2</sup>. A total of 113 (22.8%) of the patients were black. Compared with the 470 patients with no iPTH measurement, those 543 with available measurements were older, had higher phosphorus levels, and had lower eGFR and serum albumin (data not shown). iPTH had an overall geometric mean value (95% CI) of 105 pg/ml (98 to 112), and the mean BMI was 29.1 kg/m<sup>2</sup> (range 17.3 to 55.0). Table 1 shows the baseline characteristics of the study population, categorized by BMI quartiles. Patients with higher BMI were younger, were more likely to have diabetes, and had higher levels of eGFR and calcium.

Figure 1 shows the adjusted geometric mean (95% CI) levels of PTH by quartiles of BMI. Patients in the higher BMI quartiles had significantly higher PTH levels (geometric mean [95% CI] in patients with BMI <22, 22 to 28, 28.1 to 33, and >33 kg/m<sup>2</sup> 84 [73 to 97], 92 [80 to 106], 102 [89 to 116], and 105 [92 to 120]; *P* = 0.008 for linear trend) after adjustment to an age of 69 yr,

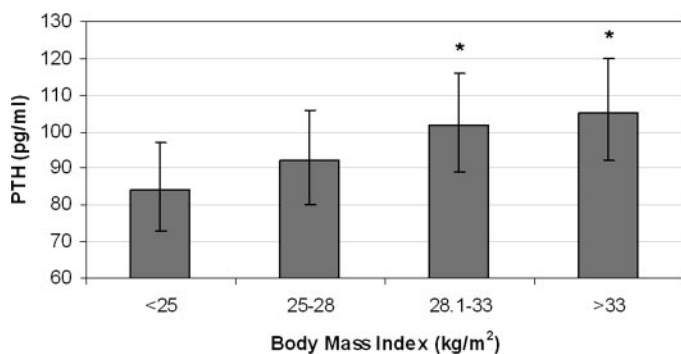


Figure 1. Adjusted intact parathyroid hormone (iPTH) levels (95% confidence intervals [CI]) in patients with different levels of body mass index (BMI). iPTH levels were adjusted to an age of 69 yr, estimated GFR (eGFR) of 32 ml/min per 1.73 m<sup>2</sup>, corrected calcium of 9.5 mg/dl, phosphorus of 4 mg/dl, white race, and diabetes status. \**P* < 0.05.

eGFR of 32 ml/min per 1.73 m<sup>2</sup>, corrected calcium of 9.5 mg/dl, phosphorus of 4 mg/dl, white race, and diabetes state. Black race, lower levels of serum calcium and eGFR, and nondiabetic status were also associated with a significantly higher PTH level in the multivariable regression model (data not shown).

Figure 2 shows adjusted PTH levels by quartiles of BMI, in subgroups divided by the mean value of serum albumin. PTH levels showed linearly increasing values with higher BMI quartiles in patients with serum albumin ≤3.6 g/dl (geometric mean [95% CI] in patients with BMI <22, 22 to 28, 28.1 to 33, and >33 kg/m<sup>2</sup> 84 [69 to 101], 96 [80 to 115], 116 [98 to 138], and 123 [105 to 145]; *P* < 0.001 for linear trend) but not in patients with serum albumin >3.6 g/dl (geometric mean [95% CI] in patients with BMI <22, 22 to 28, 28.1 to 33, and >33 kg/m<sup>2</sup> 79 [63 to 99], 85 [70 to 104], 78 [63 to 97], and 79 [64 to 99]; *P* = 0.8 for linear trend), with a statistically significant interaction be-

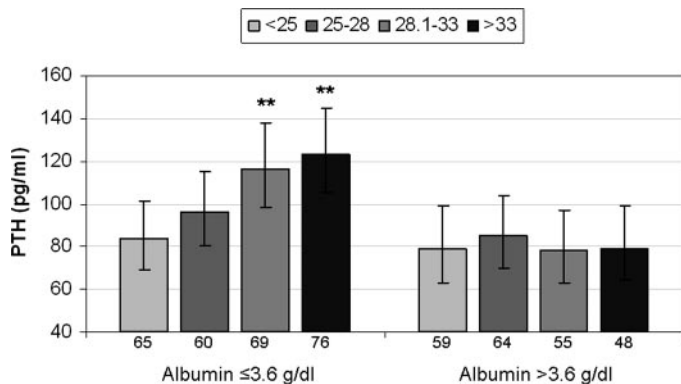


Figure 2. Adjusted iPTH levels (95% CI) in patients with different levels of BMI, in subgroups with serum albumin level of ≤3.6 and >3.6 g/dl. iPTH levels were adjusted to an age of 69 yr, eGFR of 32 ml/min per 1.73 m<sup>2</sup>, corrected calcium of 9.5 mg/dl, phosphorus of 4 mg/dl, white race, and diabetes status. The numbers below the columns represent the number of patients in each category. \*\**P* < 0.01.

tween BMI and serum albumin (*P* = 0.005 for the interaction term).

Figure 3 shows adjusted PTH levels by quartiles of BMI, in subgroups divided by the mean value of WBC count. PTH levels were increasing with higher BMI quartiles in patients with WBC count >7200/ml (geometric mean [95% CI] in patients with BMI <22, 22 to 28, 28.1 to 33, and >33 kg/m<sup>2</sup> 80 [66 to 98], 99 [82 to 119], 98 [81 to 119], and 119 [100 to 141]; *P* = 0.002 for linear trend) but not in patients with WBC count ≤7200/ml (geometric mean [95% CI] in patients with BMI <22, 22 to 28, 28.1 to 33, and >33 kg/m<sup>2</sup> 85 [69 to 106], 86 [70 to 106], 102 [84 to 123], and 87 [71 to 106]; *P* = 0.48 for linear trend), with a statistically significant interaction between BMI and WBC count (*P* = 0.026 for the interaction term).

Figure 4 shows adjusted PTH levels in 16 subgroups of patients divided by their serum albumin, WBC count, and BMI levels. Patients with a serum albumin of ≤3.6 g/dl and a WBC count >7200/ml showed the most consistently increasing trend in PTH levels with higher BMI quartiles, with a weaker but similarly increasing tendency noted in the subgroups with serum albumin of ≤3.6 g/dl and WBC count ≤7200/ml and with serum albumin of >3.6 g/dl and WBC count >7200/ml. The subgroup with serum albumin >3.6 g/dl and WBC count ≤7200/ml showed a weak decreasing tendency in PTH levels with higher BMI quartiles. The association between PTH and BMI did not vary significantly in the subgroups divided along the mean values of age, eGFR, calcium, and phosphorus and by race and diabetes status.

### Discussion

SHPT is an almost universal feature of CKD. This abnormality develops as a result of a combination of events, namely deficiency of 1,25-dihydroxycholecalciferol [1,25(OH)<sub>2</sub>D] (16,25), decreased expression of the vitamin D receptor (26) and the calcium-sensing receptor (27), hyperphosphatemia (28), hypocalcemia (29), and PTH resistance (30). In addition to these

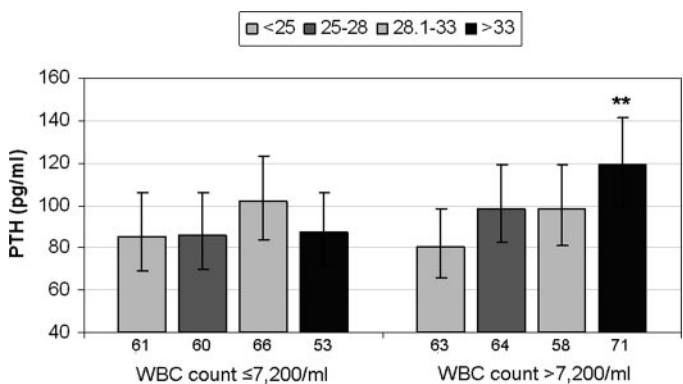


Figure 3. Adjusted iPTH levels (95% CI) in patients with different levels of BMI, in subgroups with white blood cell (WBC) counts of ≤7200 and >7200/ml. iPTH levels were adjusted to an age of 69 yr, eGFR of 32 ml/min per 1.73 m<sup>2</sup>, corrected calcium of 9.5 mg/dl, phosphorus of 4 mg/dl, white race, and diabetes status. The numbers below the columns represent the number of patients in each category. \*\**P* < 0.01.

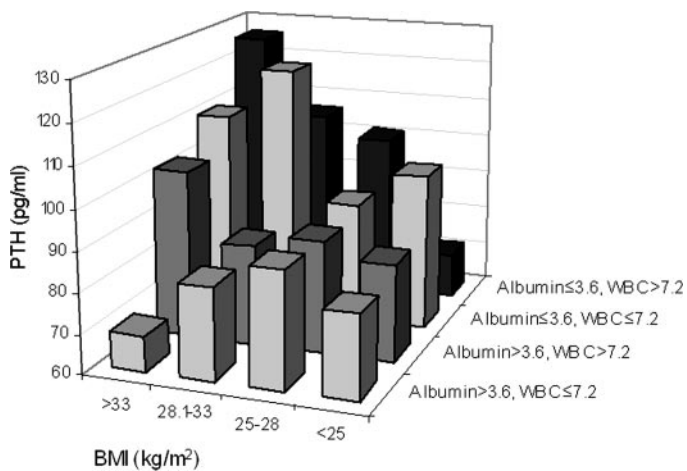


Figure 4. Adjusted iPTH levels in subgroups of patients divided by their BMI, serum albumin, and WBC count levels. iPTH levels were adjusted to an age of 69 yr, eGFR of 32 ml/min per 1.73 m<sup>2</sup>, corrected calcium of 9.5 mg/dl, phosphorus of 4 mg/dl, white race, and diabetes status.

CKD-specific mechanisms, SHPT has been associated with obesity in populations with normal kidney function (19). The relationship between PTH level and obesity has not been studied yet in patients with any stage of CKD. We explored the association between BMI and PTH level in patients who had CKD stages 2 to 5 and were not yet on dialysis. Unadjusted PTH levels were not significantly different in obese patients, largely because patients with higher BMI levels were also more likely to be younger and have diabetes and had higher eGFR and calcium levels, all determinants of lower PTH levels. Adjustment for these confounders revealed that higher BMI was in fact associated with significantly higher PTH levels. This association was independent of age, race, diabetes, serum calcium and phosphorus levels, and eGFR but was present only in the subgroups of patients with lower serum albumin and with higher WBC counts.

The mechanism of action behind the observed association between BMI and PTH is unclear. Several studies that were performed in patients with normal kidney function indicated that higher BMI was associated with elevated PTH and lower 25 hydroxycholecalciferol [25(OH)D] levels (19,31–34). Measurements of body composition by dual-energy x-ray absorptiometry showed that hyperparathyroidism was even better correlated with total body fat compared with BMI, suggesting that adiposity and not simply higher body weight was responsible for the detected associations (34). Possible explanations for these associations include less sun exposure in obese individuals (possibly as a result of clothing habits or lower mobility) and higher storage of vitamin D in adipose tissue (33,35) or a decreased skeletal response to the actions of PTH as a result of the greater strain on the skeleton imposed by the higher body weight (19). Weight loss by obese people has been shown to lower their PTH levels, supporting these proposed mechanisms of action (36). A similar mechanism of action was suggested as explanation for the higher PTH levels seen in black patients, in

whom an increased skeletal strain by the higher muscle mass could lead to a lower responsiveness to PTH (37). The higher bone mineral density (38) and the lower fracture rates (39,40) seen in black individuals despite their higher PTH levels support the idea that their skeletal response to PTH is diminished (37,41). It is unclear whether the different calcium/vitamin D/PTH status of black patients results in differences in their association between BMI and PTH compared with white patients, but we did not detect significant effect modification from race in our study.

Another intriguing possibility is an opposite direction for cause and effect between obesity and elevated PTH level, namely that higher PTH causes accumulation of fat mass and obesity. Increased PTH promotes calcium influx into adipocytes, enhancing lipogenesis (42,43). Clinical trials that separately examined calcium supplementation (44) and activated vitamin D administration (45) (both of which lower PTH levels) showed increased weight loss in the active treatment arms compared with placebo.

Although it is tempting to extrapolate these findings from the general population to patients with CKD, there are important differences between these two groups that need to be considered. The changes in 1,25(OH)<sub>2</sub>D and 25(OH)D seen in the general population in response to higher PTH levels may be markedly different in patients with CKD, in whom 25(OH)D levels are in general lower and 1,25(OH)<sub>2</sub>D levels show a progressively declining level with advancing stages of CKD (16). It is unclear how these differences might have an impact on the association between BMI and PTH in patients with CKD, but we speculate that the interactions that we observed with serum albumin and with WBC count may be explained by such CKD-specific characteristics. Lower albumin is a marker of malnutrition and inflammation in CKD (46), and higher WBC count is a marker of inflammation and it correlates with C-reactive protein levels (47). Lower albumin was associated with adynamic bone disease in patients who were on peritoneal dialysis (48), and malnutrition may be associated with lower 25(OH)D levels, which could potentially unmask a BMI-associated effect on PTH. Inflammation has been shown to suppress PTH production *in vitro* (49,50); this effect could have been exacerbated in patients with lower BMI (in itself a surrogate marker for malnutrition and inflammation). We found the association between higher BMI and higher PTH to be strongest in the subgroup with both low albumin and high WBC count and weaker (but still present) in the groups with the presence of only one of these characteristics (Figure 4), suggesting that both malnutrition and inflammation may be independent effect modifiers. Measurements involving more specific markers of nutritional status and inflammation [*e.g.*, 25(OH)D, C-reactive protein, or IL-6 levels] will be necessary to test these hypotheses.

Several limitations of our study need to be stressed. We examined exclusively male patients in a single institution; therefore, our findings may not apply to women or to patients from other geographic areas. The retrospective and observational design allows for detection of associations but does not prove causality. This design also does not allow for determination of the direction of a possible cause–effect relationship;

therefore, it remains unclear whether obesity induces higher PTH or *vice versa*. Our cohort included patients who were enrolled over a prolonged period of time; changing clinical practices (*e.g.*, a switch in the clinical assay for iPTH) could have influenced some of the associations. We addressed the issue of a different PTH assay by including only patients who were measured with the same method, but other secular trends may have been present and remained unaddressed. Use of a single PTH value could have led to misclassification, potentially biasing associations between PTH and other variables. Inaccuracies in estimating GFR in obese individuals could have led to erroneous assessments of kidney function. The lack of measured 1,25(OH)<sub>2</sub>D and 25(OH)D levels and of specific markers of inflammation makes it difficult to prove some of the portended mechanisms of action underlying our observations. The relatively smaller number of black patients in our sample did not allow us to assess the impact of malnutrition and inflammation separately by race.

## Conclusions

We characterized the association between iPTH and BMI in patients who had CKD and were not yet on dialysis and found that higher BMI was associated with SHPT, independent of the other known determinants of this condition. This association seemed to be limited to patients who displayed features of malnutrition and inflammation. Current therapeutic interventions that target abnormalities in PTH levels are aimed at the correction of abnormal levels of 1,25(OH)<sub>2</sub>D, 25(OH)D, calcium, and phosphorus. It is unclear whether modifications in BMI could have an impact on PTH levels or, conversely, whether treatment of SHPT by other means could lead to weight loss in CKD, even though this has been shown in the general population. Before advocating weight loss as a therapeutic means to treat SHPT or treatment of SHPT as a means of weight loss in CKD, our findings will have to be confirmed in other patient populations (including patients who are on dialysis), and the underlying mechanisms of action will have to be better characterized.

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## Disclosures

None.

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