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Obesity is associated with increased parathyroid hormone levels independent of glomerular filtration rate in chronic kidney disease

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Abstract

The objective of the study was to examine the relationship of obesity and parathyroid hormone (PTH) levels among persons with chronic kidney disease (CKD). This was a cross-sectional analysis of 4551 participants in the National Kidney Foundation–Kidney Early Evaluation Program found to have CKD (estimated glomerular filtration rate <60 mL/[min 1.73 m^2]) examining the relationship of body mass index (BMI) and PTH levels. In unadjusted analysis, PTH levels increased with increasing BMI quartiles. After adjustment for age, race, sex, diabetes, calcium, phosphorus, estimated glomerular filtration rate, and presence of microalbuminuria, PTH levels were 7.3% (P = .008), 11.9% (P < .0001), and 18.1% (P < .0001) higher in the second, third, and fourth BMI quartiles, respectively, as compared with the first quartile. In a companion analysis, higher BMI was associated with increased odds of having an elevated PTH measurement (>70 pg/mL). Compared with the first quartile, odds ratios for elevated PTH were 1.26 (95% confidence interval, 1.06-1.50; P = .01), 1.38 (1.15-1.65, P = .0005), and 1.66 (1.37-2.00, P < .0001) for the second, third, and fourth quartiles, respectively. We found no effect modification by race, diabetes, or presence of microalbuminuria. Therefore, in a large community-dwelling population with CKD, the presence of obesity and of increasing BMI is associated with higher PTH levels independent of measured confounders and may be an additional target in the management of secondary hyperparathyroidism in CKD.
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1. Introduction

Secondary hyperparathyroidism (2HPT) is common in chronic kidney disease (CKD). The prevalence of 2HPT and elevations of the parathyroid hormone (PTH) occur in the early stages of CKD and progressively increase as renal function declines [1-3]. Obesity as it relates to diabetes contributes significantly to the morbidity associated with CKD. Indeed, obesity and increased body weight have been associated with hyperparathyroidism in non-CKD populations [4,5]; and recently, this association has been extended to men with CKD [6]. Furthermore, this association appeared stronger among CKD patients with lower serum albumin levels and higher white blood cell counts, possibly suggesting a modification by inflammation and malnutrion [6].

Given that obesity and increases in body weight may be a modifiable risk factor for CKD and 2HPT, identifying whether these factors are independent contributors might suggest an additional therapeutic role for weight loss in the

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management of 2HPT. Thereby, we sought to determine if obesity and increasing body mass index (BMI) contribute to increases in intact PTH levels in a large, representative CKD population.

The Kidney Early Evaluation Program (KEEP 2.0), conducted by the National Kidney Foundation, is the first national health screening program that targets adult populations at high risk for CKD. It is a free, community-based screening program with sites in 48 states in the United States and represents a large, diverse population enriched in CKD with measures of calcium, phosphorus, PTH, and estimated glomerular filtration rate (eGFR) [7,8]. Because of the large sample size and availability of such measures, KEEP was an ideal database for examining this association. We hypothesized that increasing BMI would be associated with 2HPT in CKD patients.

2. Methods

2.1. Study participants

The KEEP recruitment methods and screening protocols have been described previously [7,8]. Eligibility criteria included age of at least 18 years; a personal history or diabetes or hypertension; or a first-degree relative with kidney disease, diabetes, or hypertension. The KEEP database from November 1, 2005, to December 31, 2007, was examined. Participants found to have an eGFR less than 60 mL/(min 1.73 m^2) (see below) had additional testing for calcium, phosphorus, and intact PTH (see below) and were selected for inclusion. Those missing data on BMI, diabetes, and microalbuminuria were excluded, for a final sample size of 4551.

2.2. Study variables

2.2.1. Body mass index

Body mass index was calculated as the weight in kilograms divided by the square of the height in meters using standard measures.

2.2.2. Parathyroid hormone

The intact PTH assay was performed using Immulite 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA), a 2-site chemiluminescent enzyme-labeled immunometric assay. The intraassay coefficient of variation was 4.2% to 5.7%, and the interassay coefficient of variation ranged from 6.3% to 8.8%. Intact PTH level was defined as *elevated* if it was greater than 70 pg/mL.

2.2.3. Other laboratory measurements and patient characteristics

Age, sex, and race were defined by self-report. Diabetes was defined as self-reported taking medication or *increased blood glucose*, defined as glucose level of 126 mg/dL or greater (≥7.0 mmol/L) if fasting or greater than 200 mg/dL (≥11.1 mmol/L) if nonfasting. Calcium and phosphorus levels were determined by using the Architect c8000 (Abbott Laboratories, Abbott Park, IL), with Arsenazo-III (Stanbio Laboratory, Boerne, TX) dye for calcium and ammonium molybdate for phosphorus. Calcium levels were not corrected because albumin levels were not available in KEEP. Estimated glomerular filtration rate was calculated by using the isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease Study equation (175 × [serum creatinine {in milligrams per deciliter}$^{-1.154}$] × [age {in years}$^{-0.203}$]) × [0.742 for women] × [1.21 for African Americans]), as previously described. [9] *Microalbuminuria* was defined as a spot urine albumin to creatinine ratio of at least 30 mg/g (to also include those with ratios >300 mg/g).

2.3. Statistical methods

Univariate associations of clinical and demographic variables were compared across quartiles of BMI using analysis of variance for continuous variables and χ^2 test for categorical variables. Subsequently, multivariate linear regression was used to evaluate the association of BMI (modeled both continuously as 5-kg/m^2 increase and categorically across BMI quartiles) and intact PTH. Intact PTH levels were found to be skewed and were natural log transformed to approximate a normal distribution. Data are presented after back transformation. An initial model was unadjusted. A second model was adjusted for age, sex, and race. The final model was adjusted for age, race, sex, diabetes, calcium, phosphorus, microalbuminuria, and eGFR. In companion analysis, we evaluated the association of serum BMI and elevated PTH as a dichotomous outcome using logistic regression. The model was adjusted for identical covariates as in the linear regression analysis described above. Multiplicative interaction terms were included to assess for effect modification for race [1], diabetic status [10], and microalbuminuria for both the linear and logistic models. Microalbuminuria was used as a surrogate marker for inflammation [11], as the KEEP database lacked other measures of inflammation. A P value < .05 was considered statistically significant.

3. Results

Baseline characteristics by BMI quartiles are depicted in Table 1. As compared with the first quartile, participants in the fourth quartile were younger and more frequently female, black, and diabetic. Importantly, there was no difference across BMI quartiles in measured serum calcium and phosphorus, eGFR, or presence of microalbuminuria.

To explore intact PTH levels across BMI quartiles, there was a strong graded relationship between increasing BMI quartiles and an elevated PTH (Fig. 1). This association persisted in adjusted models. In the fully adjusted model, as compared with the first quartile, PTH levels were 7.3% (P = .008), 11.9% (P < .0001), and 18.1% (P < .0001) higher in

Table 1
Baseline demographic, clinical, and laboratory data across BMI quartiles

BMI range	1st BMI quartile (≤25.7, n = 1147)	2nd BMI quartile (25.8-29.3, n = 1150)	3rd BMI quartile (29.4-33.7, n = 1115)	4th BMI quartile (>33.7, n = 1139)	*P* value
Demographics					
Age (y)[a]	71.3	70.3	67.7	63.9	<.0001
Male (%)	32.4	39.1	32.5	22.2	<.0001
Race					<.0001
White (%)	72.6	71.4	67.9	65.1	
Black (%)	15	17.6	22.2	25.2	
Other (%)	12.4	11	10	9.7	
Comorbidities					
Diabetes (%)	24.2	30.7	41	53.6	<.0001
Laboratory data					
Calcium (mg/dL)[a]	9.6	9.6	9.6	9.6	.57
Phosphorus (mg/dL)	3.8	3.7	3.8	3.8	.005
eGFR (mL/[min 1.73 m^2])[a]	48	48.3	48.2	48.2	.90
Microalbuminuria (%)	23.7	20.7	24.6	24.4	.10

[a] Analysis of variance for continuous variables.

the second, third, and fourth quartiles, respectively, when holding all other variables constant. When taken as a continuous predictor, each 5 kg/m^2 in BMI was associated with a 4.9% (95% confidence interval [CI], 3.4%-6.5%; $P <$ .0001) increase in intact PTH levels. The association was not modified by race, diabetic status, or presence of microalbuminuria (P for all interactions = not significant).

In companion analysis, the odds of elevated PTH measurement increased across BMI quartiles (Table 2). In the fully adjusted model, as compared with the first quartile, the odds of elevated PTH measurement was 26% (P = .01), 38% (P = .0005), and 66% ($P <$ .0001) higher in the second, third, and fourth quartiles, respectively. When taken as a continuous predictor, each 5-kg/m^2 increase in BMI was associated with 16% (95% CI, 10%-22%; $P <$ .0001) higher odds of elevated PTH levels. The association was not modified by race, diabetic status, or presence of the microalbuminuria (P for all interactions = not significant).

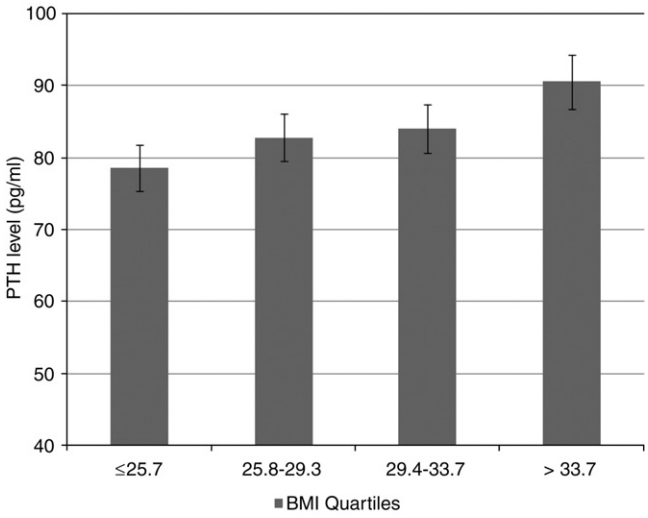

Fig. 1. Mean PTH levels across BMI quartiles.

4. Discussion

Our results suggest that obesity, identified by the presence of increasing BMI, is independently associated with elevations in serum PTH levels. To our knowledge, this is the largest study examining the relationship of body mass and 2HPT in CKD. Our finding that there are elevations in PTH levels in a representative CKD population is not novel, as 2HPT is common in CKD and occurs even at early stages [1-3]. Factors associated with higher intact PTH levels include the severity of renal dysfunction [1-3,10], black race [1,10], nondiabetic status [6,10], low calcium [1-2,6], high phosphorus [2], and low circulating vitamin D [12]. In addition, persons with CKD may have skeletal resistance to PTH [13], a finding that may also extend to the skeleton of

Table 2
The association of BMI and elevated PTH (>70 pg/mL)

		Odds ratio	95% CI	*P* value
Model 1	1st BMI quartile (ref)	1.00		
	2nd BMI quartile	1.21	1.02-1.42	.03
	3rd BMI quartile	1.23	1.04-1.45	.01
	4th BMI quartile	1.35	1.14-1.59	.0004
Model 2	1st BMI quartile (ref)	1.00		
	2nd BMI quartile	1.21	1.02-1.43	.03
	3rd BMI quartile	1.28	1.08-1.52	.004
	4th BMI quartile	1.53	1.29-1.82	<.0001
Model 3	1st BMI quartile (ref)	1.00		
	2nd BMI quartile	1.26	1.06-1.50	.01
	3rd BMI quartile	1.38	1.15-1.65	.0005
	4th BMI quartile	1.66	1.37-2.00	<.0001

Model 1 unadjusted. Model 2 adjusted for age, race, and sex. Model 3 adjusted for age, race, sex, calcium, phos, microalbuminuria, diabetes, and eGFR.

obese persons without CKD [4]. Here, the mechanical strain induced by heavier weight may lead to such resistance accompanied by a compensatory rise in PTH levels [4]. Alternatively, this effect may also be independent of weight-induced strain. In support of this, studies have suggested that increasing adiposity in nonobese populations is more strongly associated with PTH levels than total or lean body mass [14,15].

The relationship of adiposity with 2HPT may also be mediated through vitamin D. Studies have consistently shown obesity to be associated with lower circulating vitamin D levels in non-CKD populations [4,16,17]. Although there has been much speculation as to the cause of this relationship, it has been suggested that there is decreased bioavailability of vitamin D because of increased sequestration in adipose tissue [17]. Here, obese subjects exhibit a blunted rise in serum vitamin D after total body ultraviolet radiation or oral vitamin D load [17]. The higher PTH levels may therefore be explained by decreased feedback inhibition by 25-hydroxy-vitamin D [18]. However, PTH elevations have been described in obese populations with normal vitamin D [19]; and the association of total adiposity with PTH levels appears to be independent of vitamin D in nonobese populations [14]. Thus, other factors may be involved as intermediaries in this association.

Among CKD patients, previous reports have suggested that higher BMI was associated with higher PTH levels largely among those with lower albumin levels and higher white blood cell counts [6]. Investigators have speculated that these markers may represent the presence of the malnutrition and inflammation syndrome often present in more advanced stages of CKD. Although KEEP lacks measures of nutrition, we have incorporated the presence of microalbuminuria as a surrogate marker of inflammation [11]. We report no effect modification with the presence of microalbuminuria on the association of PTH and BMI. It is likely that the presence of microalbuminuria in our population may not have been a surrogate for low albumin and elevated white blood count, possibly explaining the lack of effect modification in our analysis. Furthermore, given that none of the parameters tested are true surrogate markers for inflammation or nutrition, it is difficult to draw any definitive conclusions from either analysis. Further studies enriched in measures of inflammation and nutrition are required to further address this issue.

Although the effects of a chronically elevated PTH on the skeleton are well known, it is also important to note that adipose tissue appears to be an important regulator of bone formation independent of PTH and vitamin D [20]. Here, adipocyte-derived cytokines and signaling may directly and indirectly affect osteogenesis. Furthermore, it is additionally possible that these factors may either contribute to PTH resistance at the skeletal level or negatively affect skeletal anabolism, both leading to a compensatory rise in PTH levels. However, the regulatory effect of adipose tissue on bone formation is quite complex [20]; and the interplay with PTH requires further study.

Although the scope of this discussion has centered on obesity leading to higher PTH levels, it is also possible that higher PTH levels may contribute to increased adiposity [21]. However, the finding of a reduction in PTH levels with nonsurgical weight loss [22] argues against this. Although it is an intriguing hypothesis, the cross-sectional nature of this analysis precludes determination of temporality.

As stated above, nonsurgical weight loss has been associated with a reduction in PTH levels [22], suggesting an additional modality to treat 2HPT in CKD. With surgical weight loss, hyperparathyroidism may persist or worsen, possibly because of malabsorption of calcium and vitamin D [23,24]. However, with adequate replacement, PTH levels may still improve. Furthermore, the potential for improvement appears to be greater with laparoscopic gastric banding as compared with gastric bypass [23].

Strengths of this study include the large sample size and measurement of multiple potential confounding variables. The study does have important limitations. First, as stated above, the cross-sectional nature precludes determination of temporality. Second, KEEP lacked measures of nutrition, inflammation, and vitamin D; so we are unable to fully account for the effects of these parameters. Finally, given the variability in measurements such as PTH and microalbuminuria, using single measurements could have led to misclassifications. Despite these limitations, we feel that the results of this study are valuable and add to the body of literature regarding BMI and PTH levels in CKD.

In conclusion, we found that increasing BMI was associated with elevations in PTH levels in a large, diverse CKD population. Given that increased body weight is potentially modifiable, strategies designed toward weight loss may provide additional tools in the management of 2HPT in overweight CKD patients.

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