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Original Paper

The Association between Parathyroid Hormone Levels and the Cardiorenal Metabolic Syndrome in Non-Diabetic Chronic Kidney Disease

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Key Words
Chronic kidney disease · Hyperparathyroidism · KEEP · Metabolic syndrome

Abstract
Aims: The relationship between parathyroid hormone (PTH) and the cardiorenal metabolic syndrome was examined among non-diabetic persons with chronic kidney disease (CKD). ***Methods:*** In a cross-sectional analysis, the relationship between PTH levels and the cardiorenal metabolic syndrome was investigated in 3,215 non-diabetic participants in the National Kidney Foundation-Kidney Early Evaluation Program (KEEP 2.0) found to have CKD (eGFR <60 ml/min/1.73 m^2). ***Results:*** In unadjusted analyses, the prevalence of the cardiorenal metabolic syndrome increased along increasing PTH quartiles (31.7, 33.8, 37.3, and 48.7%, respectively, p for trend <0.0001). After multivariate adjustment, as compared to the first PTH quartile, odds of the cardiorenal metabolic syndrome were 16% ($p = 0.18$), 35% ($p = 0.006$), and 80% ($p < 0.0001$) higher for the second, third, and fourth quartiles, respectively. When taken as a continuous predictor, each standard deviation increase of natural log transformed PTH was associated with

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26% ($p < 0.0001$) higher odds of the cardiorenal metabolic syndrome. The association of PTH with the cardiorenal metabolic syndrome was not modified by age or gender (p for interaction was not significant for both modifiers). ***Conclusions:*** Among an outpatient non-diabetic population with CKD, higher PTH levels were associated with a higher prevalence of the cardiorenal metabolic syndrome.

Introduction

The cardiorenal metabolic syndrome is associated with insulin resistance and is a risk factor for chronic kidney disease (CKD), independent of the presence of overt diabetes [1, 2]. Furthermore, CKD is itself associated with development of insulin resistance [3–7] as evidenced by a greater incidence of diabetes in more advanced stages of CKD [8]. Mechanisms behind the association between CKD and insulin resistance (e.g. pre-diabetes) are likely multifactorial and include anemia [4], metabolic acidosis [6], vitamin D deficiency [3], as well as elevations of parathyroid hormone (PTH) (e.g. secondary hyperparathyroidism; 2HPT) [5, 7]. The presence of insulin resistance [9] has been described in early to moderately advanced CKD wherein anemia [10], metabolic acidosis, and even vitamin D deficiency [9] would not be expected to be as prevalent or severe. However, elevations in PTH can occur in early stages of CKD [11] and may contribute to insulin resistance.

Clinical studies in non-CKD populations [12, 13] suggest that elevations in PTH are associated with insulin resistance and impaired insulin release, reinforcing its independent role among patients with more advanced stages of CKD [5, 7]. Furthermore, among patients with advanced CKD, control of PTH with phosphate binders [5] or parathyroidectomy [7] may improve insulin secretion, further supporting a role for 2HPT in the progression of diabetes. While studies in non-CKD populations examining the association of PTH and pre-diabetes have provided conflicting results [14–17], less is known about this association in the general CKD population.

We sought to examine the association between increasing levels of PTH and the cardiorenal metabolic syndrome in pre-diabetic CKD participants in the Kidney Early Evaluation Program (KEEP 2.0) conducted by the National Kidney Foundation (NKF). The KEEP is a national screening program for CKD that represents a large, diverse CKD cohort with measures of PTH and both physical and biochemical components of the metabolic syndrome [18, 19].

Methods

Study Participants

KEEP recruitment methods and screening protocols have been described previously [18, 19]. Eligibility criteria included age ≥18 years, a personal history of 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 <60 ml/min/1.73 m^2 had additional testing for calcium, phosphorus, and intact PTH and were selected for inclusion. Patients with a history of diabetes were also excluded. The final study cohort included 3,215 participants.

Study Variables

Parathyroid Hormone. The intact PTH assay was performed using Immulite 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, Calif., USA), a 2-site chemiluminescent enzyme-labeled immunometric assay. The intra-assay coefficient of variation was 4.2–5.7% and the inter-assay coefficient of variation ranged from 6.3 to 8.8%.

Definition of the Cardiorenal Metabolic Syndrome. The definitions included (1) pre-diabetes: a fasting blood glucose level >100 mg/dl (ATP III criteria) without diabetes; (2) hypertension: average systolic blood pressure >129 mm Hg or diastolic blood pressure >84 mm Hg (ATP III criteria), or a self-reported history of hypertension, or treatment with blood pressure-lowering medication; (3) obesity: body mass index ≥30 (WHO criteria); (4) dyslipidemia: triglyceride level >150 mg/dl (ATP III criteria) or cholesterol >200 mg/dl, and (5) proteinuria: albumin to creatinine ratio >29 mg/g (WHO criteria). Participants with three or more components were defined as having the metabolic syndrome.

Other Laboratory Measurements and Patient Characteristics. Age, sex, race, education, health insurance coverage, and timing of last physician visit were defined by self-report. Diabetes was defined as self-reported drug treatment or increased blood glucose, defined as a glucose level of ≥126 mg/dl (≥7.0 mmol/l) if fasting or >200 mg/dl (≥11.1 mmol/l) if non-fasting. Calcium and phosphorus levels were determined using the Architect c8000 (Abbott Laboratories, Abbott Park, Ill., USA) with Arsenazo-III (Stanbio Laboratory, Boerne, Tex., USA) dye for calcium and ammonium molybdate for phosphorus. Calcium levels were not corrected as albumin levels were not available in KEEP. eGFR was calculated by using the isotope dilution mass spectrometry-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation: (175 × [serum creatinine (mg/dl)$^{-1.154}$] × [age (years)$^{-0.203}$]) × (0.742 for women) × (1.21 for African Americans), as previously described [20]. Proteinuria was defined as a spot urine albumin to creatinine ratio ≥30 mg/g.

Statistical Methods

Univariate associations of clinical and demographic variables were compared across quartiles of PTH using ANOVA for continuous variables and the χ^2 for categorical variables. PTH was found to be skewed and was natural log transformed when examined as a continuous predictor. Subsequently, multivariate logistic regression was used to evaluate the association between PTH (modeled both continuously and categorically across PTH quartiles) and the metabolic syndrome. 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, eGFR, high-school education (yes/no), health insurance coverage (yes/no), and seeing a physician in the past year (yes/no). Multiplicative interaction terms were used to assess effect modification for gender and age (≥60 vs. <60 years) [16–17]. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics by PTH quartiles are depicted in table 1. Persons in the highest PTH quartile were older and more frequently male and black. Additionally, those in the highest quartile were less likely to have graduated high school and less likely to have seen a physician in the prior year. Smoking and reported health insurance coverage were similar across quartiles. With regard to the metabolic syndrome components, the prevalence of pre-diabetes or insulin resistance, obesity, hypertension, and albuminuria occurred more frequently across increasing PTH quartiles, while dyslipidemia remained the same. Overall, the prevalence of the cardiorenal metabolic syndrome increased across PTH quartiles (fig. 1).

In the fully adjusted model, as compared to the first PTH quartile, odds of the cardiorenal metabolic syndrome were 16% ($p = 0.18$), 35% ($p = 0.006$), and 89% ($p < 0.0001$) higher in the second, third, and fourth quartiles, respectively (table 2). When examining PTH as a continuous predictor, each standard deviation increase of natural log-transformed PTH was associated with 26% (95% CI 16–37%) higher odds of the metabolic syndrome. No significant interaction was seen for age or gender (p for interaction was not significant for each modifier).

The NKF-KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines define 2HPT by CKD stages: >70 pg/ml in CKD stage 3, >110 pg/ml in CKD stage 4, and >300 pg/ml in CKD stage 5 [21]. Using the guidelines, KEEP screening activities in this cohort detected 2HPT in 54.9% of participants with metabolic syndrome, compared to 44.9% of participants without metabolic syndrome ($p < 0.0001$).

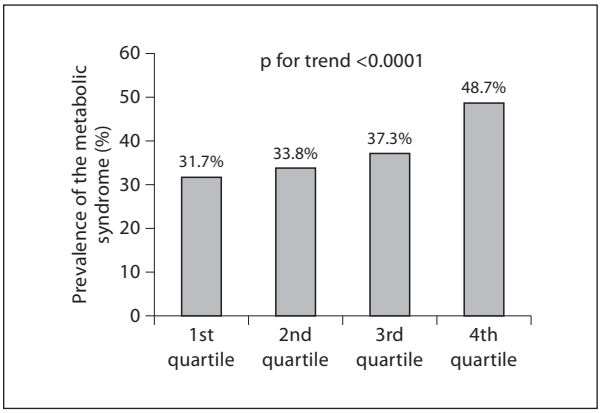

Fig. 1. Unadjusted prevalence of the cardiorenal metabolic syndrome across increasing PTH quartiles.

Table 1. Baseline demographic, clinical, and laboratory data by PTH quartiles

	1st PTH quartile (3–48 pg/ml) (n = 809)	2nd PTH quartile (>48–70 pg/ml) (n = 808)	3rd PTH quartile (>70–101 pg/ml) (n = 796)	4th PTH quartile (>101–500 pg/ml) (n = 802)	p for trend
Demographics					
Age, years	66.0 ± 12.5	67.3 ± 12.2	69.0 ± 11.5	69.8 ± 13.1	<0.0001
Age >60 years, %	69.3	72.9	79.4	79.2	<0.0001
Male, %	27.9	29.0	31.3	31.9	0.0248
Race, %					<0.0001
White	79.8	75.4	72.8	62.9	
Black	11.4	13.5	19.6	27.4	
Other	8.8	11.1	7.6	9.7	
Prior or current smoking, %	40.5	40.5	38.2	40.6	0.3954
High-school education, %	86.7	88.1	85.6	82.0	0.0016
Health insurance, %	91.5	89.8	90.6	90.2	0.2518
Seen by physician in past year, %	70.8	71.7	77.1	81.7	<0.0001
Physical measurements					
Systolic BP, mm Hg	134.1 ± 20.2	136.1 ± 19.5	136.3 ± 19.8	137.1 ± 20.2	0.0213
Diastolic BP, mm Hg	77.5 ± 11.6	78.3 ± 11.5	78.4 ± 12.1	78.6 ± 12.5	0.2957
Pulse pressure, mm Hg	56.7 ± 17.1	57.8 ± 17.0	58.0 ± 16.8	58.6 ± 17.6	0.1502
Body mass index	28.5 ± 5.9	28.5 ± 5.5	28.8 ± 5.5	30.0 ± 6.2	<0.0001
Laboratory parameters					
Cholesterol, mg/dl	201.8 ± 40.8	203.0 ± 43.0	201.4 ± 41.4	199.5 ± 43.8	0.4145
Triglycerides, mg/d	166.9 ± 96.8	170.0 ± 99.4	164.5 ± 102.4	165.1 ± 93.7	0.6724
eGFR, ml/min/1.73 m^2	51.0 ± 7.9	51.1 ± 7.9	49.8 ± 8.1	44.6 ± 11.5	<0.0001
Metabolic syndrome components					
Dysglycemia, %	9.9	8.7	10.8	12.1	0.0365
Hypertension, %	84.9	87.8	90.1	93.2	<0.0001
Obesity, %	33.0	32.1	36.2	44.4	<0.0001
Dyslipidemia, %	69.6	69.2	66.3	70.4	0.4725
Proteinuria, %	11.6	13.7	17.9	28.9	<0.0001
Cardiorenal metabolic syndrome, %	31.7	33.8	37.3	48.7	<0.0001

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Table 2. The association between PTH and the cardiorenal metabolic syndrome

		Odds ratio	95% CI	p value
Model 1	1st PTH quartile (ref.)	1.00		
	2nd PTH quartile	1.10	0.90–1.36	0.36
	3rd PTH quartile	1.29	1.05–1.58	0.02
	4th PTH quartile	2.05	1.67–2.52	<0.0001
Model 2	1st PTH quartile (ref.)	1.00		
	2nd PTH quartile	1.13	0.93–1.39	0.22
	3rd PTH quartile	1.36	1.10–1.68	0.005
	4th PTH quartile	2.19	1.78–2.70	<0.0001
Model 3	1st PTH quartile (ref.)	1.00		
	2nd PTH quartile	1.16	0.93–1.43	0.18
	3rd PTH quartile	1.35	1.09–1.67	0.006
	4th PTH quartile	1.89	1.51–2.36	<0.0001

Model 1: unadjusted; model 2: adjusted for age, race, and gender; model 3: adjusted for age, race, gender, smoking, alcohol use, eGFR, calcium, phosphorus, high-school education (yes/no), health insurance coverage (yes/no), and seeing a physician in the past year (yes/no).

Discussion

Our study demonstrates that increasing PTH levels are associated with an increased prevalence of the metabolic syndrome among non-diabetic participants with CKD in the NKF-KEEP. Our findings extend data from non-CKD populations wherein insulin resistance has been reported among persons with primary hyperparathyroidism [13] as well as data in more advanced stages of CKD wherein surgical or medical correction of 2HPT improves glycemic control [5, 7]. Thereby, our data support the premise that higher PTH levels in CKD are associated with insulin resistance and pre-diabetes, and more likely presence of the metabolic syndrome. While the results of this study suggest that elevated PTH levels are associated with the cardiorenal metabolic syndrome in CKD, the cross-sectional nature and available measures in KEEP preclude determination of the mechanism behind this association.

Studies in non-CKD populations examining the association of PTH and pre-diabetes and the cardiorenal metabolic syndrome have provided conflicting results, with the largest studies suggesting an association only in older men [16, 17]. While the reason why gender and age modifications occurred is not clear, the association in older men was seen only at extreme PTH levels comparable to the third and fourth quartiles in this study, suggesting that the higher PTH levels in CKD might explain the more uniform finding without gender or age modifications. The addition of elevated PTH levels in CKD [9] in this pre-diabetic population may also have contributed to the stronger association.

The association of PTH and the cardiorenal metabolic syndrome could alternatively be explained by vitamin D deficiency [22, 23]. However, data from NHANES indicate that low 25-hydroxyvitamin D levels are confounded not only by obesity, but also by older age, African-American and Hispanic race, and female gender [24]. Vitamin D levels are decreased in obesity, possibly through increased sequestration in adipose tissue [25], leading to less vitamin D-mediated suppression of PTH release [26]. The association of vitamin D deficiency and insulin resistance and diabetes has been well documented [9, 27–29] and remains even

after adjustment for anthropomorphic surrogates of adiposity, such as waist circumference [27]. However, when more sensitive measures of adiposity are used in statistical models, the association with vitamin D and insulin resistance is markedly attenuated and no longer significant [27]. Furthermore, studies among large diverse populations have suggested that overt vitamin D deficiency (<15 ng/ml) is uncommon in CKD and largely restricted to those with GFR <30 ml/min/1.73 m^2 [29, 30] who make up <10% of the KEEP population with CKD [31]. Additionally, other studies have found that the association of PTH and the cardiorenal metabolic syndrome is independent of vitamin D [15, 16]. KEEP did not measure vitamin D, and thus future studies among CKD patients measuring vitamin D are required to further address this issue. Another possible explanation is fetuin-A. Higher PTH is associated with higher fetuin-A, an inhibitor of vascular calcification. High fetuin-A levels are also associated with insulin resistance and higher risk for diabetes. The latter relationship may be mediated by adiponectin [32].

It is possible that the metabolic abnormalities associated with the metabolic syndrome may lead to PTH elevations. We have previously reported that obesity is associated with elevated PTH levels in KEEP [33]. As mentioned above, obesity may result in increased sequestration of vitamin D in adipose tissue, leading to higher PTH levels. Additionally, the adipocytokine leptin directly inhibits the 1α-hydroxylase enzyme, leading to lower 1,25-OHD_3 [34, 35] upregulating PTH release. Data from the bariatric surgery literature have shown that morbidly obese individuals prior to bariatric surgery can manifest 2HPT, possibly due to vitamin D deficiency [36]. Furthermore, after surgery with repleted levels of 25- and 1,25-dihydroxyvitamin D, a form of hyperparathyroidism due to vitamin D resistance can be observed, reinforcing the complicated relationship between PTH, vitamin D, and obesity [37].

In conclusion, our data support a strong association between 2HPT and the metabolic syndrome in pre-diabetic individuals with CKD. Limitations of this study include the cross-sectional nature of this analysis, precluding determination of temporality and causality. Additionally, KEEP lacks measures of vitamin D and more accurate and/or sensitive measures of adiposity/body fat to fully evaluate the effects of PTH as an independent predictor of the metabolic syndrome. Finally, single measurements of PTH and other measures may have led to misclassification. In view of these findings, prospective studies examining the role of 2HPT on preventing the development of the metabolic syndrome are warranted.

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Disclosure Statement

The authors have no conflicts of interest.

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