Original Paper

The Association between Parathyroid Hormone Levels and Hemoglobin in Diabetic and Nondiabetic Participants in the National Kidney Foundation's Kidney Early Evaluation Program

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Key Words

Chronic kidney disease · Anemia · Secondary hyperparathyroidism

Abstract

Background: Both anemia and secondary hyperparathyroidism are reflections of hormonal failure in chronic kidney disease (CKD). While the association of elevated levels of parathyroid hormone (PTH) and anemia has been studied among those with advanced CKD, less is known about this association in mild-to-moderate CKD. **Methods:** In a cross-sectional analysis, the relationship between PTH and hemoglobin levels was investigated in 10,750 participants in the National Kidney Foundation's Kidney Early Evaluation Program with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m². **Results:** In the unadjusted analysis, higher PTH levels were associated with lower hemoglobin levels. However, after multivariable adjustment for age, race, gender, smoking status, education, cardiovascular disease, diabetes, hyperten-

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sion, cancer, albuminuria, BMI, baseline eGFR, calcium, and phosphorus, the direction of association changed. As compared to the first PTH quintile, hemoglobin levels were 0.09 g/dl (95% CI: 0.01–0.18), 0.15 g/dl (95% CI: 0.07–0.24), 0.18 g/dl (95% CI: 0.09–0.26), and 0.13 g/dl (95% CI: 0.07–0.25) higher for the second, third, fourth, and fifth quintiles, respectively. Similarly, each standard deviation increase in natural log transformed PTH was associated with a 0.06 g/dl (95% CI: 0.03–0.09, $p = 0.0003$) increase in hemoglobin. However, a significant effect modification was seen for diabetes ($p = 0.0003$). Each standard deviation increase in natural log transformed PTH was associated with a 0.10 g/dl (95% CI: 0.054–0.138, $p < 0.0001$) increase in hemoglobin, while no association was seen among those without diabetes mellitus.

Conclusion: After multivariable adjustment, there was a small positive association between PTH and hemoglobin among diabetics but not among nondiabetics.

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Introduction

The prevalence of anemia in chronic kidney disease (CKD) increases as renal function declines [1, 2]. Furthermore, the anemia occurs even among those with mild CKD [2] and may not be due to erythropoietin deficiency at these stages [3]. Despite this, one of the mainstays of treatment for the anemia of predialysis CKD has been the use of exogenous erythropoietin-stimulating agents. However, treatment with these agents has been associated with an increased risk of adverse events, including hypertension, stroke, and heart failure, when administered at higher doses [4, 5]. Given that higher hemoglobin concentrations may be associated with improved health-related quality of life scores in predialysis CKD [6], identifying other modifiable and non-modifiable factors in the pathogenesis of anemia is important.

One potential factor may be parathyroid hormone (PTH). In advanced CKD, high PTH levels may cause 'resistance' to erythropoietin by increasing bone marrow fibrosis [7]. Elevated PTH levels may also increase the osmotic fragility of red blood cells, leading to a shortened lifespan [8], or inhibit the proliferation of erythroid precursors [9]. However, other investigators have failed to confirm these results, suggesting other potential mechanisms [10, 11] since surgical or medical correction of hyperparathyroidism has been reported to be associated with an improvement in anemia in advanced CKD [12, 13].

PTH elevations in mild-to-moderate CKD are not as profound as more advanced CKD, and the association with anemia may be different in such a population. Indeed, in vitro, PTH appears to enhance heme synthesis at lower levels, while inhibiting synthesis at higher levels [14]. Furthermore, activation of the PTH receptor in osteoblasts results in the mobilization of hematopoietic stem cells, the precursors of all blood cells [15]. Among patients with primary hyperparathyroidism, circulating levels of these stem cells are elevated with levels directly correlated with PTH. Surgical correction of hyperparathyroidism restored the hematopoietic stem cell levels to those of controls [16]. These findings suggest that PTH may potentially enhance erythropoiesis at lower levels, while it may inhibit the process at higher levels.

We therefore sought to examine the association of PTH with hemoglobin levels in the Kidney Early Evaluation Program (KEEP) participants. KEEP is a free community-based CKD screening program targeting those who are at high risk for CKD [17]. The program is an ideal cohort to examine in this study due to availability of measures, namely hemoglobin and PTH, as well as other potential confounders.

Methods

Study Participants

KEEP methods have been described previously [17]. Participants were eligible to participate if they were ≥ 18 years old and had a personal history of diabetes or hypertension or a first-degree relative with CKD, diabetes, or hypertension. For the purpose of this analysis, patients on dialysis or with a history of kidney transplant or dialysis were excluded. The KEEP database from November 1, 2005 through December 11, 2010 was examined. Since PTH levels were only measured among those with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² [18, 19], the analysis was limited to this eGFR range among those with PTH and hemoglobin values recorded. Therefore, a total of 10,750 participants were included in this analysis. Participants in KEEP signed consent that information collected at screening can be used for research purposes. Analyses involving KEEP data have been approved by the Human Subjects Committee at the Minneapolis Medical Research Foundation (#03–2262).

Patient Characteristics

Age, sex, race, education level, health insurance coverage, tobacco use, and physician care were derived from patient reports. Blood pressure, height, and weight were measured by trained personnel. BMI was calculated as weight (kg) divided by height (m²). Diabetes was defined as self-reported history of hyperglycemia or diabetes mellitus, use of glucose-lowering medications, fasting blood glucose ≥ 126 mg/dl, or non-fasting blood glucose ≥ 200 mg/dl. Cardiovascular disease was defined as self-reported history of heart angina, heart attack, heart bypass surgery, heart angioplasty, stroke, heart failure, abnormal heart rhythm, or coronary heart disease. Hypertension was defined as self-reported history of hypertension, use of antihypertensive medications, or blood pressure $\geq 130/85$ mm Hg.

Laboratory Data

Calcium, phosphorus, and intact PTH were measured as previously described [18, 19]. Specifically, PTH was analyzed using the Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, www.usa.siemens.com). This assay measures both whole PTH and PTH fragments [20]. eGFR was estimated using the CKD Epidemiology Collaboration equation [21]. Albuminuria was defined as a spot urine albumin-creatinine ratio ≥ 30 mg/g (and included those with a ratio > 300). Hemoglobin levels were measured from samples sent to a central laboratory.

Statistical Methods

Baseline characteristics were compared across PTH quintiles by the χ^2 test or ANOVA, as appropriate. Multivariable linear regression was used to examine the effects of PTH on hemoglobin. PTH was modeled as a categorical and continuous (per standard deviation increase in natural log transformed PTH) predictor. Models were adjusted for age, sex, race, smoking status, high school education (yes/no), health insurance (yes/no), diabetes (yes/no), cardiovascular disease (yes/no), hypertension (yes/no), cancer (yes/no), albuminuria (yes/no), BMI, baseline eGFR, calcium, and phosphorus. Prespecified, multiplicative interaction terms were constructed to evaluate for the effects of diabetes, gender, albuminuria (yes/no), and eGFR category (≤ 45 vs. > 45 ml/min/1.73 m²) using PTH as a continuous predictor. Interactions found to be statistically significant were presented in stratified form, and a linear association by strata was confirmed using PTH as a categorical predictor. A two-tailed p value < 0.01 was considered statistically significant to adjust for multiple comparisons.

Results

A total of 10,750 participants were included in the analysis. Baseline characteristics are provided in table 1. The majority of the participants were female (69.2%) and white (68.8%), and almost half (47.4%) of the participants had diabetes. Participants in the highest PTH quintiles were more likely to be black and had less than a high school education. They also had a higher prevalence of hypertension, cardiovascular disease, and albuminuria and were more likely to have seen a nephrologist. Participants in the highest PTH quintiles generally had lower calcium, eGFR, and hemoglobin levels as well as a higher BMI.

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Table 1. Baseline data across PTH quintiles

PTH quintiles (pg/ml)	1st quintile ≤41 (n = 2,204)	2nd quintile >41–59 (n = 2,164)	3rd quintile >59–80 (n = 2,171)	4th quintile >80–114 (n = 2,091)	5th quintile >114 (n = 2,140)	p value for trend
Mean age ± SD	69.8±10.4	70.1±10.7	71.3±10.5	71.5±10.6	71.1±11.9	<0.0001
Male, %	32.1	32.4	32.2	33.4	32.2	0.7035
Race, %						<0.0001
White	76.5	73.5	68.9	66.8	57.5	
Black	14.1	17.1	20.7	24.8	33.2	
Other	9.4	9.4	10.4	8.5	9.3	
Smoker, %						0.9810
Never	59.3	60.2	59.4	60.3	59.5	
Quit	35.7	34.6	35.6	34.8	35.1	
Current	5.0	5.2	5.0	4.9	5.4	
High school education, %	86.2	85.3	82.5	82.5	78.7	<0.0001
Health insurance, %	92.3	90.8	91.6	91.2	90.8	0.1743
Prior nephrology care, %	8.8	7.3	7.6	10.7	16.7	<0.0001
Comorbidities						
Diabetes, %	52.1	43.6	45.4	45.7	49.8	0.3996
Cardiovascular disease, %	40.0	39.2	43.2	44.6	50.7	<0.0001
Cancer, %	19.9	21.1	21.2	21.6	21.3	0.2534
Hypertension, %	91.4	91.6	91.7	93.5	95.7	<0.0001
Albuminuria, %	16.1	17.0	22.2	26.1	38.2	<0.0001
Physical measurements						
Mean systolic BP ± SD, mm Hg	135.8±19.4	137.2±19.5	137.4±20.7	137.9±20.0	139.1±21.7	<0.0001
Mean BMI ± SD	29.7±6.1	29.6±5.9	29.6±6.1	30.3±6.5	31.3±7.1	<0.0001
Laboratory measurements						
eGFR, ml/min/1.73 m ²	49.6±8.4	49.6±8.3	48.7±8.8	47.3±9.4	41.9±12.3	<0.0001
eGFR category >45	75.2	74.2	71.4	64.2	46.4	<0.0001
Hemoglobin, g/dl	13.4±1.5	13.4±1.4	13.3±1.5	13.2±1.5	12.8±1.6	<0.0001
Calcium, mg/dl	9.8±0.5	9.7±0.4	9.6±0.4	9.6±0.5	9.5±0.6	<0.0001
Phosphorus, mg/dl	3.74±0.58	3.70±0.56	3.69±0.59	3.65±0.58	3.67±0.69	<0.0001

Upon multivariable adjustment, the direction of association of PTH with hemoglobin changed. As compared to the first PTH quintile, hemoglobin levels were 0.09 g/dl (95% CI: 0.01–0.18), 0.15 g/dl (95% CI: 0.07–0.24), 0.18 g/dl (95% CI: 0.09–0.26), and 0.13 g/dl (95% CI: 0.07–0.25) higher for the second, third, fourth, and fifth quintiles, respectively (table 2). Similarly, each standard deviation increase in natural log transformed PTH was associated with a 0.06 g/dl (95% CI: 0.03–0.09, p = 0.0003) increase in hemoglobin.

When using PTH as a continuous predictor, a significant effect modification was seen for diabetes (p for interaction = 0.0003) and the eGFR category (p for interaction = 0.001), but not for gender (p for interaction = 0.05) or albuminuria (p for interaction = 0.85) when accounting for multiple comparisons. For each standard deviation increase in natural log transformed PTH, hemoglobin increased by 0.1 g/dl (95% CI: 0.01–0.14, p < 0.0001) among diabetics but not among nondiabetics [0.01 g/dl (95% CI: –0.03 to 0.05, p = 0.83)]. A linear relationship of PTH and hemoglobin among diabetics was confirmed using PTH as a categorical variable (data not shown). Similarly, for each standard deviation increase in natural log transformed PTH, hemoglobin increased by 0.07 g/dl (95% CI: 0.03–0.1, p = 0.0003) among those with an eGFR >45 but not among those with an eGFR ≤45, [–0.2 g/dl (95% CI: –0.07 to 0.03), p = 0.36]. However, when using PTH as a categorical predictor, no linear asso-

Table 2. Linear regression of PTH with hemoglobin levels

	1st quintile	2nd quintile	3rd quintile	4th quintile	5th quintile
Beta coefficient (95% CI)					
Unadjusted	ref	0.03–0.06, 0.12)	–0.05 (–0.14, 0.04)	–0.17 (–0.26, –0.08)	–0.57 –0.66, –0.48)
Adjusted	ref	0.09 (0.01, 0.18)	0.15 (0.07, 0.24)	0.18 (0.09, 0.260)	0.13 (0.07, 0.25)

Adjusted for age, sex, race, smoking status, high school education (yes/no), health insurance (yes/no), cardiovascular disease (yes/no), diabetes (yes/no), hypertension (yes/no), cancer (yes/no), albuminuria (yes/no), BMI, baseline eGFR, calcium, and phosphorus.

ciation of PTH with hemoglobin was seen, and the direction of the association was similar for both strata (data not shown). Therefore, the association of PTH and hemoglobin was not modified by eGFR status.

Discussion

This study examines the association of PTH with hemoglobin in a large community-based sample of predialysis CKD patients. On unadjusted analysis, we found an inverse relationship of PTH with hemoglobin. However, after multivariable adjustment, the direction of association changed in that higher PTH levels were associated with a modest increase in hemoglobin. Furthermore, the association was stronger and significant only among diabetics.

Prior studies in KEEP have demonstrated a greater prevalence of anemia among diabetics with CKD and at earlier stages [22]. Erythropoietin levels have shown to be lower in diabetics than among nondiabetics prior to the development of significant CKD, indicating an effect of diabetes on the production of this hormone [23, 24]. However, others have demonstrated a greater prevalence of anemia among diabetics with CKD despite similar erythropoietin levels to nondiabetics [25]. Thus, other factors may additionally be contributing to the anemia of CKD in diabetics.

The osteoblast has recently been described to be an important promoter of hematopoiesis [26]. Diabetes impairs osteoblast function [27] and is associated with a greater prevalence of adynamic bone disease in CKD patients [28]. A depressed osteoblast number and function in diabetic CKD may thus impair hematopoiesis, and higher PTH levels may be protective against this [29]. Indeed, osteoblast-specific constitutive activation of the PTH receptor results in an expansion of hematopoietic stem cells in vivo [26], possibly via the insulin growth factor (IGF) pathway [30].

IGF-1 may affect erythropoiesis via different pathways. Similar to erythropoietin, IGF-1 inhibits apoptosis of erythroid progenitor cells [31]. IGF-1 may additionally enhance the proliferation of erythroid progenitor cells at later stages of maturation [31, 32]. IGF-1 levels are lower in diabetic than nondiabetic CKD, and lower levels have been shown to be associated with anemia in diabetic but not nondiabetic CKD [25]. Thus, higher PTH levels may result in higher IGF-1 levels in diabetics, leading to higher hemoglobin levels. Unfortunately, IGF-1 levels are not measured in KEEP and this hypothesis requires further study.

There are other potential explanations for our findings. When controlling for eGFR, calcium, and phosphorus, participants with higher PTH level measurements may be more likely to be vitamin D deficient. However, vitamin D deficiency is associated with anemia in CKD [33] and thus unlikely to explain this association. Conversely, these patients are more probable to receive vitamin D therapy, which leads to higher hemoglobin levels. Neither

vitamin D therapy nor vitamin D levels were recorded in KEEP, thus further studies are required to address these issues.

KEEP also did not record other important predictors of anemia such as folate, vitamin B12, and iron levels. The latter may also be an important confounder in this study. It has been postulated that iron may be an important regulator of fibroblast growth factor-23 (FGF-23) [34, 35]. Since FGF-23 may regulate PTH secretion [36], adjusting for the effects of iron and/or FGF-23 would enhance our study, particularly since the secretion of FGF-23 may be modified by diabetic status [37]. However, FGF-23 and iron parameters were not measured in KEEP, and this too requires additional study.

Many of the patients, particularly of those with diabetes, were presumably treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as most (>90%) had hypertension. Angiotensin II is an important regulator of erythropoiesis by directly stimulating erythroid progenitors and enhancing erythropoietin secretion [38]. Consequently, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with a reduction in hematocrit in a variety of populations, including the CKD population [39]. Unfortunately, KEEP did not record class-specific medications, and the inability to adjust for the confounding effect of these agents is another limitation to our study.

Strengths of the current study include the use of a wide, community-based, national CKD sample with available measures of PTH and hemoglobin. However, there are several limitations beyond the non-measured parameters mentioned above. First, the cross-sectional nature of this study does not imply the direction of the association nor does it imply causation. Second, the lack of important confounders, both known and unknown ones, limit the conclusions of an independent effect of PTH. Third, single measurements of both the predictor and main outcome variable may have led to a misclassification bias in the results. Fourth, the relative change in hemoglobin per change in PTH was rather modest and may be within the normal variability of the assay. Fifth, overadjustment in the multivariable model may have occurred, biasing our results. Finally, although we described a biologic plausibility of the effect modification for diabetes, this is the first study to directly examine such modification, and thus the subgroup analysis should be interpreted with caution. Despite these limitations, we feel our findings are unique and both add to the literature examining the association of PTH and hemoglobin levels in CKD and provide a rationale for further prospective studies along these lines.

In conclusion, in a large community-based sample of CKD, higher PTH levels were associated with higher hemoglobin levels among diabetics but not among nondiabetics. The mechanisms behind this association require additional study.

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