Correlation Between Serum Calcium and Parathyroid Hormone in Chronic Kidney Disease Patients

Wahyudi Pratama Harli, Hasyim Kasyim, Pendrik Tandean, Syakib Bakri, Nur Ahmad Tabri, Arifin Seweng

INTRODUCTION

Chronic kidney disease (CKD) is a medical disorder, according to the Kidney Disease Quality Outcome Initiative (K/DOQI), that involves an impairment in the structure and/or function of the kidneys lasting for more than three months and affecting one’s health.1,2 The diagnosis and stage of the condition are determined by evaluating the existence of albuminuria (or proteinuria) and determining the glomerular filtration rate (eGFR). CKD is characterized by the existence of albuminuria (AER 30 mg/24 hours; ACR > 30 mg/g [> 3 mg/mmol]), irregularities in urine sediment, imbalances in electrolytes, damage to the tubules, abnormalities in kidney tissue, evidence of structural abnormalities in radiological imaging, past kidney transplantation, and a reduction in GFR.1-3

CKD is a global health issue that impacts 5-10% of the world’s population. Many of these people are more likely to experience bone and mineral metabolism disruptions. These disruptions result in abnormal bone formations originally known as renal osteodystrophy (ROD). Patients experiencing these disruptions may exhibit bone discomfort, muscle-tendon rupture, itching, and a high frequency of fractures. Furthermore, compelling data indicates that individuals with ROD have an increased susceptibility to cardiovascular calcification, which is linked to elevated rates of morbidity and mortality. Although there are international and regional protocols in place to reduce the negative clinical outcomes of CKD–mineral and bone disorder (CKD-MBD), the majority of patients with CKD continue to experience the implications of CKD-MBD abnormalities.4

In the advanced phases of CKD, there is a disruption in the levels of calcium, phosphate, parathyroid hormone, and vitamin D. This disruption results in abnormalities in the structure, strength, development, and histology of the bones. CKD-MBD, also known as chronic kidney disease-mineral and bone problem, is identified by the accumulation of calcium in soft tissues, disorders related to the cardiovascular system, and a range of additional symptoms.4,5

Due to poor renal function, there is more phosphorus in the body and less active vitamin D (calcitriol). This results in a cascade of symptoms, including increased parathyroid hormone (PTH) secretion and decreased calcium absorption. Individuals suffering from CKD encounter a reduced ability of the kidneys to efficiently eliminate phosphorus from the blood, resulting in an accumulation of phosphorus in the bloodstream. An outcome of heightened synthesis levels is an augmented production of PTH and an expansion in

ABSTRACT

Introduction: Chronic kidney disease (CKD) is commonly associated with secondary hyperparathyroidism. Elevated phosphorus concentrations and decreased synthesis of active vitamin D (calcitriol) as a direct result of impaired renal function induce a cascade of symptoms, including decreased calcium absorption and increased parathyroid hormone (PTH) secretion. This study aimed to assess the association between calcium levels and PTH levels in patients diagnosed with CKD.

Methods: A cross-sectional observational study was conducted involving a cohort of 80 individuals diagnosed with CKD who met the established criteria. The statistical tests employed in this study were Pearson’s correlation. Statistically significant findings are obtained from these tests when the p-value is below 0.05.

Results: This study demonstrates a correlation between decreased levels of calcium in the blood and increased levels of PTH in persons with impaired kidney function. In eighty patients with CKD stages 3 to 5, regardless of dialysis status, a clear inverse correlation (-0.328, P = 0.000) was observed between parathyroid hormone and serum calcium levels.

Conclusion: Patients with CKD showed a significant inverse correlation between their blood serum calcium levels and PTH levels. Hence, it is imperative to assess the concentrations of blood calcium and PTH in individuals with CKD and a glomerular filtration rate below 60 ml/min/1.73 m2.
parathyroid cells. Hyperparathyreodism is known to lower serum calcium levels using physicochemical binding and inhibiting alpha-hydroxylase activity, leading to a decline in 1,25(OH)2D (calcitriol) levels. Hypocalcemia can occur due to diminished calcium absorption in the gastrointestinal tract, caused by reduced calcitriol levels. A decline in calcitriol levels is observed in individuals with CKD, a consequence of renal damage or a reduction in renal mass. Moreover, there is a decrease in the expression of the vitamin D receptor, which acts as the site where calcitriol binds to exert its physiological effects. This will magnify the consequences of a lack of calcitriol.5-8

Hyperparathyreodism secondary is a common complication of CKD. Secondary hyperparathyreodism arises from an imbalance in the body’s mineral levels, resulting in increased concentrations of PTH in the bloodstream and growth of the parathyroid glands. An investigation was conducted by Dias C. et al. on 163 non-dialysis CKD patients to establish a negative correlation between PTH levels and serum calcium concentration; therefore, as serum calcium levels lowered, increased PTH levels. Additionally, in the highest PTH quartile (>9.5pg/mL), the mean calcium concentration was found to be the lowest (9.30 ± 0.55 mg/dL). In considering the critical role calcium plays in stimulating PTH synthesis, hypocalcemia in CKD will increase serum PTH. Research has demonstrated that secondary hyperparathyreodism contributes to the occurrence of vascular calcification, cardiovascular disease, and renal osteodystrophy.9-10

Blood calcium and PTH levels were assessed in persons with CKD to achieve this. Subsequently, the data was examined to determine the association between blood calcium levels and PTH levels in the setting of CKD. The main aim of this study is to investigate the possible relationship between PTH levels and serum calcium in persons with CKD. The findings of this study have the potential to establish serum calcium levels as a treatment measure for individuals with CKD-MBD, in addition to providing a benchmark for subsequent studies in this area of research.

**METHODS**

**Study design and population**

This inquiry is a cross-sectional observational study, serving as a sub-analysis of the CKD-MBD study in 2021. Patients at Dr. Wahidin Sudirohusodo Hospital in Makassar, South Sulawesi, Indonesia, who were undergoing outpatient or inpatient care and had CKD stages 3, 4, and 5 (including non-dialysis and dialysis) were included in this study. The hospital has been a tertiary referral hospital since May 2021. The participants in the study were selected from a population that met the predetermined criteria. This study had 80 samples that fulfilled the stated criteria for inclusion and exclusions.

**Inclusion and exclusion criteria**

The study included patients who were diagnosed with CKD stages 3, 4, and 5, including those who were not on dialysis and those who were on dialysis. The patients were required not to have TB or cancer, and they should not be using calcium supplements or phosphates-binding drugs.

**Clinical data and sample collection**

The sample collection process was conducted in a consecutive manner until the required number of samples was attained, as determined by medical record data. Subsequently, PTH and calcium levels were sampled on patients who qualified the inclusion criteria and provided their consent to participate as study subjects. Intact serum PTH levels were measured using the CMIA (chemiluminescent microparticle immunoassay) method.11 The normal range of PTH levels in the general population is less than 65 pg/ml. However, the reference range for PTH levels has been elevated to 150-300 pg/ml in persons with CKD. This adjustment is attributed to decreased phosphate excretion and bone’s heightened resistance to the effects of PTH in individuals with CKD.8,11 Meanwhile, the typical range for calcium levels in the plasma of healthy people is 8.5 to 10.5 mg/dL.7,12

**Statistical analysis**

The data analysis was performed using SPSS version 25 (Armonk, NY: IBM Corp.). This study’s analytical approach included descriptive methodologies and statistical testing. The statistical tests used in this study were Pearson’s correlation. In statistical analysis, test findings are considered significant if the p-value of the test is less than 0.05.

**RESULTS**

**Study population**

80 CKD subjects were examined in total, of which 42 were male (52.5%), and 38 were female (47.5%). The dataset consisted of people between 18 and 65, with an average age of 48.8 ± 12.65 years. The range of calcium levels is from 5.4 mg/dL to 11.4 mg/dL, with an average of 8.08 ± 1.05 mg/dL (table 1). The levels of PTH ranged from 9.05 pg/mL to 392.3 pg/mL, with a mean of 99.02 ± 93.44 pg/mL (table 1).

The present study employed stratification of CKD patients into five stages (stages 3, 4, and 5) without dialysis, in addition to stage 5 patients who received hemodialysis. The research variables examined in this study were blood calcium levels and parathyroid hormone. These variables were reported as both median and mean values.

Among non-dialysis patients, the stratification analysis revealed a consistent trend of declining serum calcium levels and increasing PTH levels as CKD progressed from stages 3 to 5. Patients diagnosed with stage 5 CKD who are receiving dialysis exhibited restoration of calcium levels and PTH levels to a normal state. This phenomenon can be attributed to the influence of hemodialysis, which serves as a confounding variable that can disrupt calcium homeostasis.

**Correlation between serum calcium and PTH levels in CKD**

An inverse correlation (P = 0.000, R = -0.328) was observed within serum calcium and PTH levels in eighty individuals with CKD stages 3, 4, and 5, irrespective of dialysis status. This finding was statistically significant (Figure 1).

**Comparison of serum calcium and PTH levels based on the stage of CKD**

Based on the CKD stage, there was an inverse correlation between blood calcium levels and PTH in stages 3 and 5 with...
Table 1. Characteristics of Research Subjects (N=80)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.05 (5.4 -11.40)</td>
<td>8.08 ± 1.05</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>59.7 (9.05-392.3)</td>
<td>99.02 ± 93.44</td>
</tr>
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</table>

Note: PTH, Parathyroid Hormone.

DISCUSSION

Analysis of the relationship between serum calcium levels and PTH

The study found a significant inverse correlation (P = 0.000, R = -0.328) between serum calcium levels and PTH levels in CKD patients at stages 3–5 of dialysis. This meant that a drop in serum calcium levels was linked to increased PTH levels, which meant the kidneys were not working either. Calcium homeostasis is disrupted in CKD patients as LFGe levels fall while PTH levels rise. In CKD, increased PTH acts as a compensatory mechanism for hypocalcemia. Dialysis patients' ability to excrete phosphate, produce calcitriol, and maintain calcium balance is reduced. This disorder promotes the development of secondary hyperparathyroidism if left untreated. However, some treated patients develop bone abnormalities associated with overemphasizing bone turnover, a condition known as adynamic bone disease.13–16

According to a study by Sah et al., an inverse correlation (r = -0.340) was found between PTH and serum calcium levels in 70 non-dialysis CKD stage 1–5 patients and 50 healthy patients. This means that the PTH variables and serum calcium levels are unrelated in a straight line. Even in stages I and II of CKD, there is an increase in mean serum PTH levels associated with a decline in mean serum calcium levels from early to advanced CKD stages. Arora et al. examined the correlation between PTH levels and mineral status in patients at stage 5 of dialysis who had end-stage renal disease (ESRD). Serum PTH and serum calcium were found to have an inverse linear relationship in sixty patients with ESRD who were at least 18 years old. (P ≤ 0.001; r = −0.805).17,18

A cross-sectional analysis was performed by Ennis et al. on laboratory data obtained from 2028 patients with CKD, of which 505 were African American (AA) races who utilized CKD laboratory services in the United States. Serum concentrations of calcium (Ca), phosphorus (P), 25-hydroxyvitamin D (25-D), and plasma PTH were compared between AA and non-AA races. The current investigation established a negative correlation between serum calcium levels and parathyroid hormone, whereby reduced serum calcium levels led to increased PTH levels in both the AA and non-AA groups.19

Rastogi et al. investigated the effects of dialysis on intact PTH, blood calcium, and phosphorus levels in individuals diagnosed with CKD. The mean age of the predialysis (n = 50) and post-dialysis (n =
Comparison of serum calcium and PTH levels based on CKD stage

This study comprised a total of 80 individuals diagnosed with CKD. Among them, 20 patients were selected to represent each stage of CKD, ranging from stage 3 to stage 5, both with and without dialysis. Individuals diagnosed with stage 3 CKD had a significant inverse correlation between their blood calcium and PTH levels (P = 0.041, R = -0.461). Similar findings were observed in individuals with stage 5 CKD who were not doing dialysis (P = 0.025, R = -0.500) and those undergoing dialysis (P = 0.018, R = -0.524). During stage 4 of CKD, the research did not find any statistically significant connection between the levels of calcium in the blood and the levels of PTH (P = 0.256, R = -0.266). However, a negative correlation between the variables under investigation was still seen. One drawback of this study is its small sample size (50) groups, consisting of 100 patients, was 50.34 years and 51.88 years, respectively. The risk of intact PTH was found to be 2.82-fold greater in patients with calcium levels below 8.5 mg/dL compared to those with calcium levels between 10.5 and 8.5 mg/dL (odds ratio [OR], 2.82; 95% confidence interval [CI], 1.13–7.01; P = 0.02).20

CKD is recognized as a distinct and autonomous risk factor for the development of cardiovascular disease (CVD). Hence, it is imperative to employ suitable preventive and therapeutic approaches to reduce the incidence and fatality rates associated with cardiovascular disease (CVD). CKD is also associated with a significant correlation between impaired mineral metabolism and cardiovascular disease. According to prior research, hyperphosphatemia, elevated calcium-phosphorus product (Ca x P), and hyperparathyroidism have been identified as non-traditional risk factors that may contribute to an increased likelihood of cardiovascular mortality and morbidity. A recent meta-analysis underscores the significance of this crucial association. The guidelines for controlling mineral metabolism were released by K/DOQI in 2003. The recommended ideal thresholds for intact calcium (Ca), phosphorus (P), calcium-phosphorus product (Ca x P), and PTH levels are as stated below: The values are as stated: The values are as follows: 8.4–9.5 mg/dl, 3.5–5.5 mg/dl, less than 55 mg/dl, and 150–300 pg/ml, respectively.21

The CORES Study examined 16,173 hemodialysis (HD) patients from six Latin American nations to investigate the potential association between their calcium, phosphorus, and PTH levels and their mortality rates from all causes of cardiovascular disease. The study followed these patients for 18 years, during which they underwent hemodialysis treatment for a maximum of 54 months. The study’s results show that serum albumin-corrected calcium (CaAlb) levels below 9.5 mg/dL and above 10.5 mg/dL were linked to a higher risk of death from any cause. A lower level of calcium-albumin (CaAlb) concentration, specifically below 9.0 mg/dL, is associated with an elevated risk of mortality from cardiovascular disease, leading to an increased heart rate. Furthermore, it was observed that those with low levels of high-sensitivity troponin (less than 150 pg/mL) and high levels (greater than 500 pg/mL and greater than 300 pg/mL) experienced an elevated heart rate, leading to increased risks of both all-cause death and cardiovascular mortality.22

![Figure 3. Correlation between serum calcium levels and PTH in patients with stage 4 CKD (n= 20), with Pearson's correlation test.](image)

![Figure 4. Correlation between serum calcium levels and PTH in patients non-dialysis stage 5 CKD (n: 20), with pearson's correlation test.](image)
ORIGINAL ARTICLE

CKD who have had dialysis, specific interventions are required. The study by Jean et al. examined the immediate physiological impacts of administering dialysate calcium (DCa) to maintain blood calcium and PTH levels within the range of 150 to 300 pg/mL. Increasing DCa levels from 1.25 to 1.5 mmol/L and subsequently from 1.5 to 1.75 mmol/L resulted in a simultaneous increase of 2.2% and 1.7% in calcium levels. At the same time, phosphatemia levels went down by 7% and 9%, total alkaline phosphatase (t-ALP) levels went down by 10% and 12%, and PTH levels went down by 50% and 62%. The reduction in DCa levels from 1.75 to 1.5 mmol/L and 1.5 to 1.25 mmol/L resulted in a decrease in calcium levels of 2.5% and 1.7%, respectively. In addition, there was an increase in phosphatemia by 11% and 12%, t-ALP by 12% and 10%, and a significant rise in PTH by 138% and 175%.

Previous research has confirmed that hemodialysis affects the hemodynamics of serum calcium levels and PTH. Based on the previous research, we conclude that various factors can influence serum calcium levels in the dialysis phase of CKD, including phosphate elimination during dialysis and the presence of dialysate calcium concentration used for hemodialysis. The limitation of this study is that we were unable to analyze a number of additional factors that might impact serum calcium levels, which are restricted by this study.

CONCLUSION

The study revealed a significant negative correlation between serum calcium levels and PTH levels in individuals with CKD. More precisely, a decrease in calcium levels was shown to occur simultaneously with an increase in PTH levels, which is linked to a decline in kidney function. Future investigations on individuals with CKD and a GFR below 60 ml/min/1.73 m2 should include serum calcium and PTH level assessments. The treatment for hypocalcemia in patients with CKD consists of administering calcium carbonate, calcitriol, and vitamin D to prevent the occurrence of secondary hyperparathyroidism.

size, which may introduce bias towards the samples at this stage. Hence, further investigation, including a more extensive sample size, is important to thoroughly comprehend the correlation between blood calcium levels and PTH levels in stage 4 CKD.

Differentiation of CKD stages using research variables

Our analysis revealed an association between the research variables, specifically calcium and PTH levels, and the stages of CKD. The study involved a sample size of 80 CKD patients, with 20 individuals representing each stage ranging from CKD stage 3 to 5, including those on dialysis. The results showed that as the CKD stage went up or kidney function went down from CKD stage 3 to 5 in people who weren't on dialysis, calcium levels went down, and PTH levels went up. In the context of CKD stage 5 dialysis, it was shown that the variables of calcium levels and PTH did not exhibit a significant drop or rise, respectively. This lack of significant change might be attributed to the patient's prior exposure to hemodialysis, which served as a confounding factor in the analysis. Hyperphosphatemia is a condition characterized by elevated levels of phosphate in the blood. This condition has been found to affect serum calcium levels by causing a physicochemical binding process, which reduces calcium levels. Furthermore, it has been found that hyperphosphatemia hinders the function of alpha-hydroxylase 1, an enzyme involved in the formation of 1,25-dihydroxyvitamin D (1,25(OH)2D). Consequently, this suppression of alpha-hydroxylase 1 activity decreases the levels of 1,25(OH)2D. The extent of phosphate removal differs among various dialysis techniques. Phosphate removal during traditional hemodialysis, administered three times weekly for a duration of four hours per session, typically varies between 600 and 900 mg per dialysis session, resulting in a weekly elimination of approximately 1800 to 2700 mg. To restore normal calcium levels in individuals with CKD who have had dialysis, specific interventions are required.

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AUTHORS’ CONTRIBUTION
Conceptualization: Wahyudi Pratama Harli, Hasyim Kasym
Data curation: Hasyim Kasym
Investigation: Wahyudi Pratama Harli, Nur Ahmad Tabri
Methodology: Hasyim Kasym, Arifin Seweng
Project administration, Software, Formal analysis, Visualization, Writing—original draft: Wahyudi Pratama Harli
Resources: Hasyim Kasym, Nur Ahmad Tabri
Supervision: Pendrik Tandean, Syakib Bakri
Validation: Pendrik Tandean, Hasyim Kasym
Writing—review & editing: Pendrik Tandean, Syakib Bakri

ETHICAL APPROVAL
The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, (Ethical code No. 714/UN4.6.4.5.31/PP36/2023). Prior to any intervention, all participants provided written informed consent. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

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REFERENCES