Effect of secondary hyperparathyroidism on progression of cytopenia in patient with chronic kidney disease on hemodialysis

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Abstract

Background: Chronic Kidney Disease (CKD) commonly affects about 13% of the population, often stemming from various conditions including diabetes, hypertension, and nephrotoxic drugs. A major complication of CKD is Secondary Hyperparathyroidism (SHPT), which disrupts the regulation of Parathyroid hormone, calcium, phosphorus, and vitamin D, and can adversely impact erythropoietin synthesis and bone marrow function. This study aimed to evaluate the impact of SHPT on the development of cytopenia in CKD patients undergoing hemodialysis.

Methods: Conducted at the Baghdad Iraqi Center of Dialysis/Medical City Complex, it analyzed data from 100 patients, with ages ranging from 19 to 80 years. Measurements included urea, creatinine, PTH, vitamin D, ionized calcium, and complete blood counts.

Results: Indicated various correlations between PTH and other blood biomarkers. Notably, a moderate positive correlation existed between PTH and urea levels, as well as with platelet counts, although these were not statistically significant. Weak positive correlations were observed between PTH and parameters like age, hemoglobin, creatinine, and white blood cell counts. Conversely, PTH levels were weakly negatively correlated with estimated Glomerular Filtration Rate (eGFR) and ionized calcium.

Conclusion: The study concluded that while there is an observable association between SHPT and cytopenia in CKD patients on hemodialysis, this association lacks statistical significance. Additionally, the assessment of ionized calcium and PTH levels suggested a prevalence of hypocalcemia, a common issue in advanced CKD and end-stage renal disease cases.

Keywords: Secondary, hyperparathyroidism, progression, cytopenia, chronic kidney disease, hemodialysis

Introduction

Chronic Kidney Disease (CKD) is characterized by a decline in kidney function or kidney damage lasting over three months, often progressing to the need for dialysis or transplantation. Defined by an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m² or by indicators of kidney damage, CKD can be identified via imaging, renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates [1]. Epidemiology: CKD’s true incidence is hard to ascertain due to the asymptomatic nature of early to moderate stages. However, general prevalence is estimated at 10% to 14%, with specific conditions like albuminuria and reduced GFR having lower prevalence [2]. Classification and Staging: The KDIGO classification system details CKD based on cause, GFR, and albuminuria levels, defining stages from G1 to G5, and albuminuria levels from A1 to A3 [3]. Etiology: CKD's primary causes include diabetes mellitus, hypertension, and primary glomerulonephritis. Other contributing factors range from hereditary diseases to systemic conditions affecting kidney structures [4]. Risk Factors: Risk factors for CKD progression are categorized as non-modifiable-such as age, ethnicity, and genetic predispositions-and modifiable, including hypertension, diabetes, and lifestyle factors like smoking and obesity [5]. Pathophysiology: CKD involves progressive kidney fibrosis and destruction, affecting glomeruli, tubules, interstitium, and vessels, leading to conditions such as glomerulosclerosis and tubulointerstitial fibrosis [6]. Evaluation and Management: Assessment includes repeated eGFR tests and monitoring of proteinuria using the albumin-creatinine ratio. Management strategies focus on controlling blood pressure, proteinuria, and other metabolic factors to retard disease progression.
Preparation for renal replacement therapies like dialysis or transplantation is crucial as CKD advances \cite{7,8}. Hyperparathyroidism in CKD: Pathophysiology: Secondary Hyperparathyroidism (SHPT) is a common CKD complication, resulting from disturbed regulation of parathyroid hormone (PTH), calcium, phosphorus, and vitamin D, mainly due to reduced renal function. Elevated PTH levels result from hypocalcemia, hyperphosphatemia, and vitamin D deficiencies, which are prominent as CKD progresses \cite{9}. Clinical Presentation and Management: SHPT often manifests subtly, detected through routine tests. Management involves dietary modifications, phosphate binders, vitamin D analogs, and calcimimetics. In severe cases, parathyroidectomy might be indicated \cite{10}. Effects on Erythropoiesis: SHPT adversely affects erythropoiesis, directly impacting erythropoietin synthesis and leading to conditions such as anemia and thrombocytopenia. Myelofibrosis, often irreversible in hemodialysis patients, can develop, further complicating the CKD condition \cite{11}. Aim of the study to evaluate the effect of Secondary Hyperparathyroidism in development of cytopenia in patient with Chronic Kidney Disease on Hemodialysis.

Methods
The study conducted at the Iraqi Center of Hemodialysis at Baghdad Medical City Complex aimed to investigate the impacts of secondary hyperparathyroidism on patients with end-stage renal disease undergoing hemodialysis. This analytical cross-sectional study took place from February to October 2023, enrolling both male and female participants who met the inclusion criteria of having secondary hyperparathyroidism and being on hemodialysis for over three months. The study excluded individuals with primary hyperparathyroidism, bone marrow disorders, or hepatitis B and C. Ethical clearance was obtained from the University of Baghdad's College of Medicine, Department of Clinical Chemistry, the Iraqi Board for Medical Specialization, and the Ministry of Health and Environment. Additionally, oral consent was acquired from all participants involved in the study. The patient cohort comprised 100 individuals with a mean age of 48.8 years, ranging from 19 to 80 years. The sample collection was meticulously executed, with 5 ml of venous blood drawn from each patient's antecubital fossa using a disposable syringe. The blood was then segregated into different aliquots for various tests: 1.5 cc was deposited into an EDTA tube for complete blood count (CBC) analysis, and 3.5 cc into a serum separator tube. The serum samples were left to clot at room temperature for 20-30 minutes before being centrifuged at 4000 RPM for 10 minutes using a GENEX centrifuge to separate the serum. The clear serum was then allocated into three aliquots for subsequent biochemical analyses.

Biochemical assessments were conducted using specific instruments and methodologies:
1. Parathyroid hormone (PTH) levels were measured using a Cobas e411 analyzer based on a sandwich principle, which involved a dual incubation process to form a sandwich complex that was measured photometrically.
2. Vitamin D levels were assessed through a competition-based assay on the same analyzer, involving multiple incubations to accurately measure 25-hydroxyvitamin D levels in the serum.
3. Blood urea and serum creatinine were quantified using a Cobas c111 analyzer, employing enzymatic and colorimetric methods respectively.
4. Serum ionized calcium was measured using an EXIAS electrolyte analyzer, ensuring high-quality testing through integrated solutions and quality control measures.

A Sysmex XP-300 Automated Hematology Analyzer was used for the CBC, employing direct current detection with complex algorithms to count and differentiate cells. Statistical analysis of the collected data involved descriptive statistics to summarize continuous and categorical variables. Correlations between PTH levels and other biomarkers were examined using Spearman's rank correlation coefficient, while univariate linear regression was employed to calculate beta coefficients. A p-value of less than 0.05 was considered statistically significant for all tests. The study also incorporated the CKD-EPI equation for accurate estimation of glomerular filtration rate (GFR), accounting for variables such as age, gender, and race.

Results
In this study, a cohort of 100 cases with CKD were involved. The mean age of the participants was 48.8 years with a standard deviation of 12.7 years. The age range observed in the study was between 19.0 and 80.0 years. Regarding gender distribution, the study included 61 males, accounting for 61.0% of the cases, and 39 females, making up 39.0% of the cases. The sex ratio, which is the ratio of males to females, was calculated to be 1.6, as in Table 1.

Table 1: Description of Patient’s demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases, N = 100¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>48.8±12.7</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>48.0 (41.0-58.0)</td>
</tr>
<tr>
<td>Range</td>
<td>19.0-80.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>61 (61.0%)</td>
</tr>
<tr>
<td>Females</td>
<td>39 (39.0%)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1.6</td>
</tr>
</tbody>
</table>

¹Mean±SD; Median (IQR); n (%)

The mean urea level was 136.0±3.85 mg/dL, and the median value was 134.5 (interquartile range: 106.0 to 160.5 mg/dL). Creatinine levels exhibited a mean of 8.5±0.27 mg/dL, with a median of 8.1 (interquartile range: 6.6 to 10.2 mg/dL). Estimated glomerular filtration rate (eGFR) displayed a mean of 5.7±0.24 ml/min and a median of 5.3 (interquartile range: 3.9 to 6.8 ml/min) indicating a stage V CKD. In terms of the CBC parameters, the mean hemoglobin level was 7.5±0.23 g/dL, with a median of 8.1 (interquartile range: 6.2 to 9.0 g/dL). White blood cell count exhibited a mean of 5.3±0.16 cells/μL and a median of 5.1 (interquartile range: 4.1 to 6.4 cells/μL). Platelet count displayed a mean of 161.9±64 cells/μL, with a median of 153.0 (interquartile range: 121.8 to 201.5 cells/μL). In addition to the kidney function and CBC parameters, the study also evaluated ionized calcium and parathyroid hormone levels. The mean ionized calcium level was 1.0±0.02 mmol/L, with a median of 1.0 (interquartile range: 0.9 to 1.1 mmol/L), showing a relatively narrow range. On the other hand, parathyroid hormone exhibited substantial variability, with a mean of 433.7±33.72 pg/mL and a median of 351.5 (interquartile range: 197.8 to 538.5 pg/mL). The observed range for parathyroid hormone levels was extensive, spanning from 38.0 to 1,516.0 pg/mL, as in Table 2.
In this study investigating the correlation between parathyroid hormone (PTH) and various blood biomarkers, Spearman’s rank correlation coefficient (rho) and P-values were utilized. Among the parameters analyzed, a moderate positive correlation was observed between PTH and urea levels (rho = 0.17, P=0.09), and a moderate positive correlation with platelet count (rho = 0.14, P=0.16). Weak positive correlations were found between PTH and age (rho = 0.08, P=0.41), hemoglobin (rho = 0.09, P=0.38), and very weak positive correlations with creatinine (rho = 0.04, P=0.67) and WBC count (rho = 0.03, P=0.76). However, PTH showed weak negative correlations with eGFR (rho = -0.06, P=0.56) and ionized calcium (rho = -0.12, P=0.25). Overall, while some associations were present, they generally demonstrated weak strength and lacked statistical significance. As in Table 3.

The linear regression model using the provided blood parameters (age, urea, creatinine, eGFR, hemoglobin, platelets, WBC, and ionized calcium) does not appear to be a good fit for predicting parathyroid hormone levels. The model lacks statistical significance, as indicated by the p-values for individual coefficients and the F-statistic for the overall model. Moreover, the adjusted R-squared suggests that the independent variables do not explain a substantial portion of the variance in the dependent variable. As in Fig 1.
Discussion

The study at the Iraqi Center of Hemodialysis at Baghdad Medical City Complex focused on the complexities surrounding secondary hyperparathyroidism (SHPT) and its association with cytopenia in patients with chronic kidney disease (CKD) on hemodialysis. SHPT, characterized by elevated parathyroid hormone (PTH) levels in response to disturbed mineral metabolism, notably low calcium and high phosphorus levels, has a multi-faceted impact on patients’ hematological profile. Data revealed that the average age of the study participants was 48 years, consistent with regional studies by AlhajimSA [12] and AwadSM [13], and slightly younger than CKD populations in Brazil [14] and Western countries [15, 16]. This age discrepancy may reflect differing healthcare system efficiencies, early disease detection capabilities, and management strategies across regions which influence the progression to dialysis. Gender distribution within the study showed a predominance of males, aligning with findings across various geographical settings, suggesting possible biological, hormonal, or socio-cultural factors influencing disease prevalence [17, 18]. Ionized calcium levels averaged at 1.0 mmol/L, indicating prevalent hypocalcemia, a common issue in advanced CKD stages due to a decline in 1,25-dihydroxyvitamin D synthesis. This insufficiency leads to SHPT as the body attempts to compensate for low calcium absorption and high phosphorus levels, which further exacerbate PTH secretion [19, 20]. The PTH levels varied significantly, ranging from 38.0 to 1,516.0 pg/mL, illustrating the challenge in managing this parameter within recommended ranges to avoid complications like adynamic bone disease [21].

Hematological findings showed mean hemoglobin levels at 7.5±0.23 g/dL, indicative of anemia, a common complication in CKD due to decreased erythropoietin production by the failing kidneys [22]. Despite this, white blood cell and platelet counts remained within normal ranges, suggesting no immediate cytopenic conditions, contrary to the potential risks associated with hemodialysis and myelosuppression [23]. Interestingly, the study highlighted a positive correlation between PTH levels and blood cell counts; however, this relationship did not reach statistical significance, possibly due to the multifactorial nature of hematological changes in CKD patients undergoing dialysis. Elevated PTH is known to impact bone marrow function, potentially leading to anemia and thrombocytopenia, a condition exacerbated by inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α stimulated by high PTH levels [24, 25]. Despite these findings, the analysis was unable to establish a significant predictive model for PTH levels based on hematological parameters. This might be attributed to the limited sample size or the complex interactions between SHPT, CKD pathology, and other individual patient factors, suggesting that larger, multi-centered studies could provide more definitive insights. Moreover, the presence of myelofibrosis in both primary and secondary hyperparathyroidism indicates a potential universal mechanism through which PTH levels may influence bone marrow function, independent of CKD. This observation warrants further exploration into the role of uremic toxins and other CKD-related factors in contributing to bone marrow pathology [26, 27]. The study reaffirms the complex interplay between SHPT and hematological abnormalities in CKD patients on hemodialysis, it also highlights the need for meticulous management of mineral metabolism and PTH levels to mitigate their adverse effects on bone and blood cell production. Ongoing research and clinical vigilance are crucial to enhance understanding and improve outcomes for this vulnerable patient population.

Conclusion

The following conclusions were reached as a consequence of the study's findings: The study's average age was 48 years, with a higher male-to-female ratio, as indicated by the demographic analysis. The evaluation of ionised calcium and PTH levels in the study population revealed hypocalcemia, which is a prevalent occurrence in advanced CKD and end-stage renal disease. Despite the fact that this study demonstrated a correlation between SHPT and cytopenia, the association was not statistically significant.

Conflict of Interest

Not available

Financial Support

Not available

References


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