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INFLUENCE OF CALCIUM AND PHOSPHORUS ON ANEMIA IN PATIENTS WITH RENAL FAILURE FROM SOUTH PUNJAB PAKISTAN

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Abstract

Anemia is a frequent complication of kidney failure, mainly due to reduced erythropoietin production, with mineral metabolism disturbances potentially playing a contributing role. This retrospective study, conducted over 2.5 years at Multan Institute of Kidney Diseases, examined the relationship between hemoglobin levels, calcium, and phosphorus in patients with renal failure secondary to glomerulonephritis. Demographic and biochemical data were obtained from the hospital's electronic management system, and analyses included Spearman's correlation, the Mann–Whitney U test, and multiple linear regression. The cohort had a mean age of 48.3 ± 16.4 years and was predominantly male (60.9%). The mean hemoglobin level was 9.83 ± 2.09 g/dL, indicating a high prevalence of anemia. Phosphorus showed a weak, non-significant correlation with hemoglobin, whereas males had significantly higher hemoglobin levels than females ($p = 0.009$). No significant gender differences were found in calcium or phosphorus levels. Multivariable regression analysis identified phosphorus ($B = -0.175$, $p < 0.001$) and calcium ($B = +0.399$, $p < 0.001$) as independent predictors of hemoglobin, collectively explaining 9.7% of its variance. These findings indicate that calcium–phosphorus imbalance may exacerbate anemia severity in kidney failure, highlighting the importance of mineral regulation as part of comprehensive anemia management.

INTRODUCTION:

Anemia is a frequent and clinically significant complication of kidney failure, classically linked to reduced erythropoietin production. Recent evidence indicates that disruptions in mineral metabolism particularly calcium and phosphorus imbalance may also impact hemoglobin levels in patients with chronic kidney disease (CKD). CKD is traditionally defined by an estimated

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glomerular filtration rate(eGFR) below 60ml/min/1.73m^2.However,this fixed threshold may not account for normal age-related changes in kidney function. To improve accuracy, some experts advocate for age-adjusted definitions, with higher cut-offs (75 ml/min/1.73 m^2) for younger adults and lower ones (45 ml/min/1.73 m^2) for older individuals [1].

Renal failure can lead to significant metabolic and hematologic complications. Among these, anemia and disturbances in mineral metabolism, including serum levels of intact parathyroid hormone, calcium, and phosphorus, are common. Secondary hyperparathyroidism due to dysregulated phosphorus and calcium homeostasis plays a crucial role in the progression of renal dysfunction and associated complications [2]. Anemia, characterized by a hemoglobin level below 13 g/dL in men and 12 g/dL in women, is a common issue in patients with chronic kidney disease (CKD)[3]. Serum calcium concentration is carefully regulated 45%of calcium is bound to plasma proteins, 15% to anions, and 40% to a free or ionized state. Normal total serum calcium levels range from 8.5to10.5mg/dL. The metabolism of calcium and phosphorus is interconnected, with hormones such as parathyroid hormone and calcitonin managing calcium levels through intricate feedback mechanisms [4]. Mineral bone disorders significantly impact patients with renal failure, leading to bone diseases and increased cardiovascular risks. Elevated serum phosphorus levels are linked to anemia in renal failure patients, but the connection between anemia and calcium levels is unclear. These imbalances impair quality of life and increase mortality rates due to complications like hypocalcemia and hyperphosphatemia. Management of these imbalances is crucial for improving health outcomes[5].As chronic kidney disease (CKD) progresses, disturbances in mineral metabolism particularly involving calcium, phosphorus, and anemia can lead to a decline in quality of life and an increased risk of morbidity and mortality due to cardiovascular complications, bone disorders, and other systemic effects[7].

Additionally, serum calcium levels, which are normally maintained within a narrow physiological range, play a vital role in the progression of chronic kidney disease (CKD). In patients with renal failure, tightly regulated balance between calcium and phosphorus controlled by hormones such as parathyroid hormone and calcitonin is disrupted, resulting in complex metabolic disturbances [8]. Previous research has emphasized the critical role of mineral and bone disorders in patients with renal failure, outcomes demonstrating that imbalances in calcium and phosphorus metabolism contribute significantly to the development of bone disease and elevate the risk of cardiovascular complications [9]. In kidney disease elevated intracellular calcium results not only from increased influx but also from impaired extrusion, linked to reduced Na+,K+-ATPase activity and decreased Na+-Ca++ exchanger efficiency both commonly observed in uremia[10].

This study aimed to identify disturbances in mineral metabolism, specifically serum calcium and phosphorus that may serve as potential predictors of anemia severity in patients with primary glomerulonephritis. It also sought to determine the prevalence and severity of anemia in this population and to evaluate its association with serum calcium and phosphorus levels. By exploring these associations, the study provides insights into the role of mineral imbalance in the hematological complications of glomerulonephritis and highlights its importance in guiding clinical management.

MATERIAL AND METHODS

This retrospective observational cohort study was conducted over a 2.5-year period at Multan Institute of Kidney Diseases. It included adult patients aged 18 years and above who were diagnosed with renal failure. Patients with acute kidney injury , severe infections, recent blood transfusions, or those receiving bone marrow suppressive therapies ,malignancies were excluded. Data were analyzed using SPSS, with descriptive statistics used to summarize baseline characteristics and appropriate statistical tests applied to evaluate correlations and associations.

Descriptive Statistics:

This study enrolled patients with renal failure with a mean age of 48.3 ± 16.4 years and a male predominance of 60.9%. Biochemical assessment

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revealed considerable variability in mineral metabolism, characterized by frequent and pronounced disturbances in calcium (8.69 ± 1.10 mg/dl) and phosphorus (5.53 ± 2.34 mg/dl) levels. The mean hemoglobin level was low (9.83 ± 2.09 g/dl), reflecting a high prevalence of anemia in this population.

Correlation Analysis

Subsequently the variables did not follow a normal distribution , the non-parametric Spearman correlation test was used to assess the association between hemoglobin and mineral parameters. A statistically significant positive correlation was found between hemoglobin and calcium ($r = 0.292$, $p < 0.001$), indicating that higher serum calcium levels were associated with higher hemoglobin concentrations. In contrast, no significant correlation was observed between hemoglobin and phosphorus ($r = -0.056$, $p = 0.101$). A summary of all correlation results is presented in Table 2, and the relationships between hemoglobin, calcium, and phosphorus are further illustrated through scatterplots (Table no.1).

Table1: Spearman's correlation coefficients between hemoglobin and mineral metabolism parameters.

Spearman's rho		HEAMOGLOBIN	PHOSPHORUS	CALCIUM
HEAMOGLOBIN	Correlation Coefficient	1.000	-.253**	.292**
	Sig. (2-tailed)	.	.000	.000
	N	855	855	855
PHOSPHORUS	Correlation Coefficient	-.253**	1.000	0.191**
	Sig. (2-tailed)	.000	.	.000
	N	855	855	855
CALCIUM	Correlation Coefficient	.292**	-.191**	1.000
	Sig. (2-tailed)	.000	.000	0.000

Figure 1(a): Scatterplots showing correlation between (a) hemoglobin and calcium

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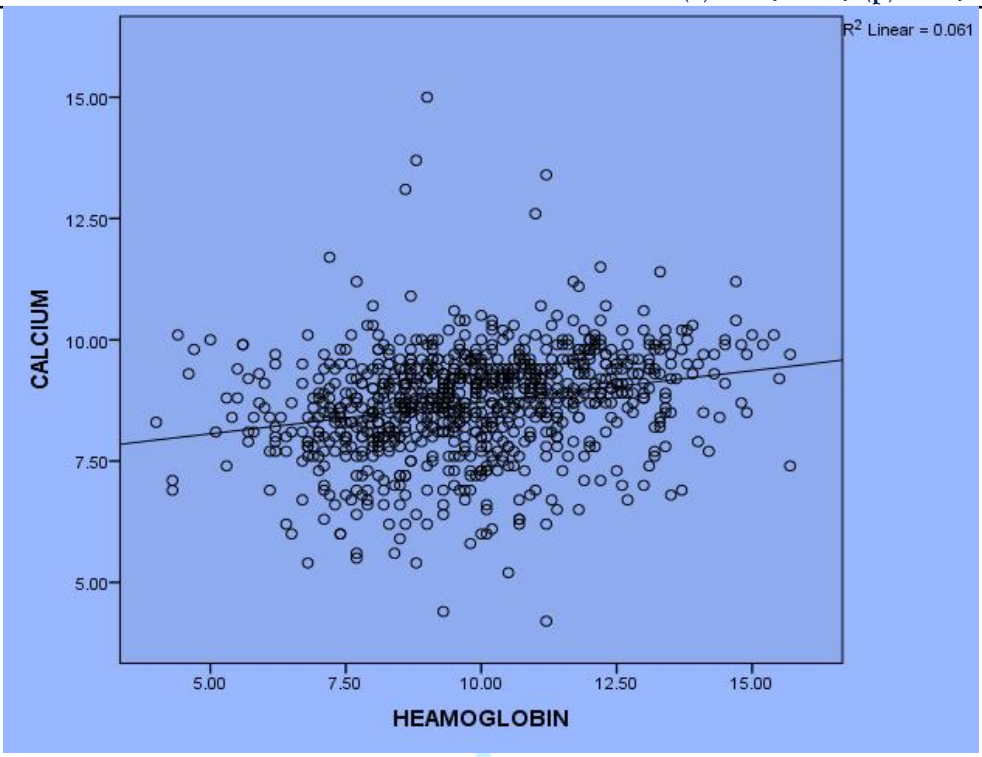

Regression Analysis

A multiple linear regression according to predicting the hemoglobin concentration was constructed based on the independent prediction of mineral parameters. The dependent variable was hemoglobin and serum iPTH, calcium and phosphorus as independent variables. The complete regression model was statistically significant (F (3, 851) = 30.43, p < 0.001) and all of the variance in hemoglobin levels was explained (Adjusted R 2 = 0.094).

Table 2: ANOVA for Predictors of Hemoglobin

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	360.952	3	120.317	30.426	0.000[b]
Residual	3365.197	851	3.954	—	—
Total	3726.149	854	—	—	—

a Dependent Variable: Hemoglobin

b Predictors: (Constant), Calcium, Phosphorus

In the multivariable analysis, serum phosphorus emerged as a significant independent negative predictor of hemoglobin (B = –0.175, p < 0.001), while serum calcium was identified as a significant independent positive predictor (B = +0.399, p < 0.001).

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Table 3: Multiple linear regression analysis

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	7.288	.612		11.903	.000
	PHOSPHORUS	0.175	.030	0.19	5.833	.000
	CALCIUM	0.399	.063	0.211	6.313	.000
a. Dependent Variable: HEAMOGLOBIN						

The regression analysis identified significant predictors of hemoglobin levels among patients. The constant term was 7.288 ($p < 0.001$), representing the baseline hemoglobin value when all predictors were held at zero. Serum phosphorus was a significant negative predictor ($B = -0.175$, $\beta = -0.196$, $t = -5.833$, $p < 0.001$), indicating that higher phosphorus levels were associated with lower hemoglobin concentrations. Conversely, serum calcium was a significant positive predictor ($B = +0.399$, $\beta = +0.211$, $t = 6.313$, $p < 0.001$), meaning that higher calcium levels were associated with higher hemoglobin levels.

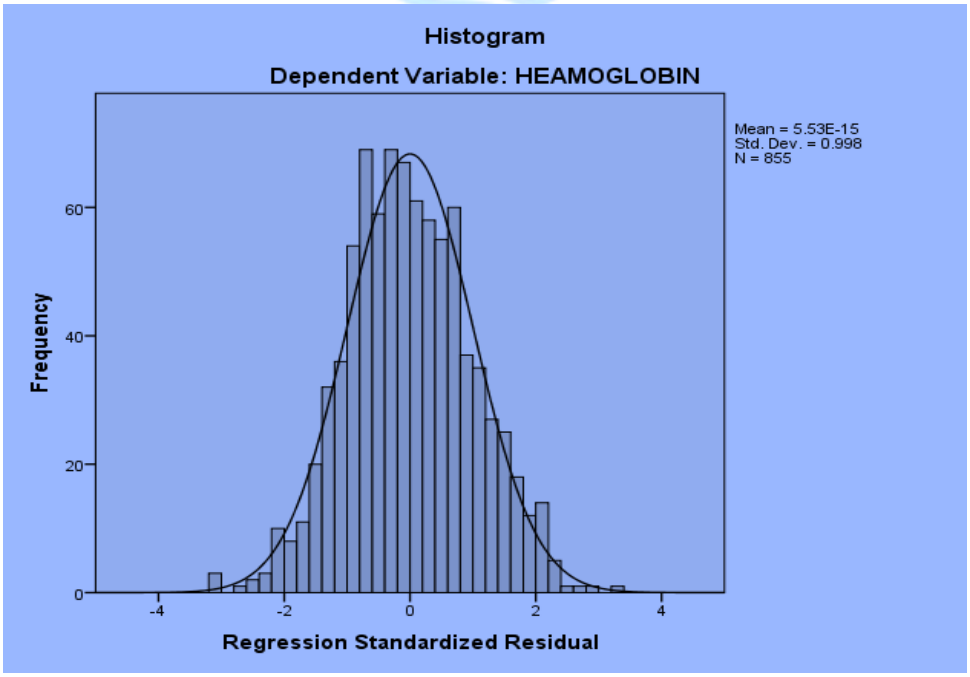

Figure 2: Regression diagnostics: (a) histogram of standardized residuals,

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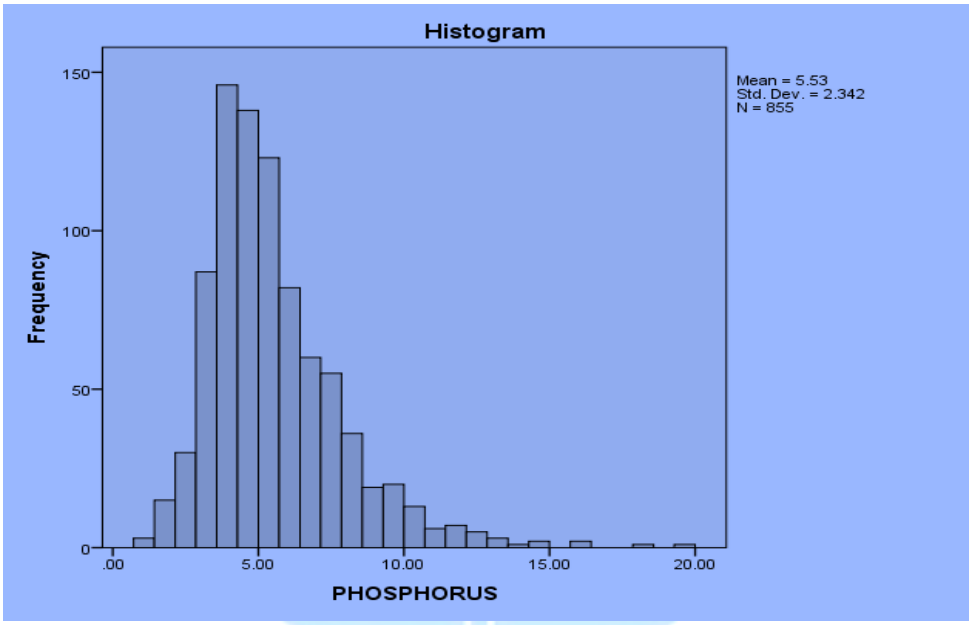

Figure 3: Regression diagnostics: (a) histogram of standardized residuals

Regression diagnostics, including histogram and P–P plots of standardized residuals, confirmed appropriate model fit and absence of major violations of linearity or normality assumptions.

Discussion

Anemia is a well-recognized and clinically significant complication among patients with renal failure. It is primarily attributed to inadequate production of erythropoietin by the diseased kidneys, but other factors—including disturbances in mineral metabolism—also play a crucial role. In this study, patients with renal failure secondary to primary glomerulonephritis exhibited a high prevalence of anemia, accompanied by marked abnormalities in calcium and phosphorus levels. These findings align with previous evidence indicating that disrupted mineral homeostasis contributes to the severity of anemia in chronic kidney disease. Elevated phosphorus and reduced or imbalanced calcium levels can impair erythropoiesis, increase oxidative stress, and contribute to chronic inflammation, thereby worsening anemia.

Furthermore, the significant positive association between hemoglobin and calcium, and the inverse trend with phosphorus, underscores the complex interplay between mineral metabolism and hematological parameters. While erythropoietin deficiency remains the primary driver of anemia in renal failure, these results highlight the importance of considering mineral disturbances as modifiable contributors. Optimizing calcium–phosphorus balance through dietary control, phosphate binders, or other interventions may support better anemia management and improve patient outcomes. These findings emphasize the need for a more integrated approach to care in patients with chronic kidney disease, targeting both traditional and nontraditional risk factors.

This Positive correlation between hemoglobin andcalcium, phosphorous,is consistent with previous research which identified that an elevated may

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suppress erythropoiesis due to the mechanism of bone marrow fibrosis, impaired erythroid progenitor cell activity, and shorter red blood cell life [13].The anemia which is rather associated with a mal-regulation of calcium and phosphorus. Increased phosphorus and hypocalcemia are established triggers of secondary hyperparathyroidism, and their independent prognostic role in this study further supports their more immediate causal relationship in the determination of anemia severity [14].

The positive association between calcium and hemoglobin levels is clinically meaningful. Elevated calcium may support erythropoiesis through the suppression of excessive parathyroid hormone activity, which is often elevated in chronic kidney disease. By reducing iPTH overactivity,calcium helps create a more favorable environment for red blood cell production and improves the bone marrow's responsiveness to erythropoietic signals. This mechanism may partly explain the observed positive predictive value of calcium in relation to hemoglobin levels in patients with renal failure[15]. These results indicate that phosphate control and maintenance of normal calcium may be a beneficial addition to standard therapy with EPO and iron in anemia treatment. Our findings are consistent with previous research in CKD populations. For example, Wu et al. (2022) reported that elevated phosphorus levels were linked to an increased risk of anemia and a poorer response to erythropoiesis-stimulating agents, whereas maintaining calcium balance showed a positive association with hemoglobin levels. This supports the role of mineral homeostasis in influencing anemia outcomes[16]. Dialysis cohorts have also found secondary hyperparathyroidism to contribute to anemia, but that this would be attenuated when calcium and phosphorus were properly treated. Contrarily, some previous studies noted iPTH as a direct factor of the severity of anemia [17]. This discrepancy could be attributed to variations in the patient populations (non-dialysis CKD vs. dialysis CKD.

The identified gender difference in hemoglobin levels, whereby the male population had higher hemoglobin levels as compared to the female population, is in line with the differences in the female sex during the healthy body when it comes to the difference in baseline hemoglobin and has been extensively reported among CKD and non-CKD populations. Nonetheless, the absence of gender differences in the mineral parameters indicates that mineral dysregulation in glomerulonephritis is gender-independent to a large extent.The significance of the findings of this study with respect to clinical practice is significant. First, they highlight the necessity to consider monitoring of mineral metabolism as an adjunctive therapy in the anemia management regimen of the patients with primary glomerulonephritis [18]. The treatment algorithms in use today tend to focus more on the iron status, inflammation, and ESA therapy yet are against realizing the importance of calcium and phosphorus. Second, that optimization of calcium/phosphorus balance, via dietary phosphate restriction, phosphate binders, or calcium supplement, could be a complementary approach in the control of anemia [19]. Third, the low explanatory power of the regression model (Adjusted R^2 = around 0.094) confirms that anemia in CKD is multifactorial, and includes contributions of inflammation, iron deficiency, erythropoietin deficiency, and uremic toxins, in addition to mineral metabolism [20].

Conclusion: In conclusion, this study highlights a strong association between anemia and altered mineral metabolism in patients with renal failure. Both calcium and phosphorus were identified as independent predictors of hemoglobin levels, emphasizing the clinical importance of maintaining mineral balance in managing anemia. Future prospective studies that also assess iron metabolism, inflammation, and treatment interventions are needed to better understand causal pathways and improve anemia management in this population.

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