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INVESTIGATING THE ASSOCIATION BETWEEN ANEMIA AND MINERAL DYSREGULATION IN CHRONIC KIDNEY DISEASE: EMPHASIS ON IPTH, CALCIUM, AND PHOSPHORUS

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Abstract

Anemia is a frequent complication of CKD chronic kidney disease and may be influenced by mineral metabolism disturbances beyond reduced erythropoietin production. This retrospective study was conducted at the Multan Institute of Kidney Diseases spaniang 1.5 years aim of this study to investigate the relationship between hemoglobin, intact parathyroid hormone (iPTH), calcium, and phosphorus. Demographic and biochemical data were extracted from electronic records, and statistical analysis included Spearman's correlation, Mann–Whitney U tests, and multiple linear regression. The cohort had a mean age of 48.3 ± 16.4 years and was predominantly male (60.9%). Mean hemoglobin was 9.83 ± 2.09 g/dl, with widespread anemia. Hemoglobin was negatively correlated with iPTH ($r = -0.253$, $p < 0.001$) and positively correlated with calcium ($r = 0.292$, $p < 0.001$), while correlation with phosphorus was weak and not significant. Males had significantly higher hemoglobin than females ($p = 0.009$), but no gender differences were observed in mineral parameters. In regression analysis, phosphorus ($B = -0.175$, $p < 0.001$) and calcium ($B = +0.399$, $p < 0.001$) were independent predictors of hemoglobin, whereas iPTH was not significant. The model explained 9.7% of hemoglobin variance. These findings suggest that calcium–phosphorus imbalance, rather than PTH alone, plays a key role in anemia severity in glomerulonephritis, underscoring the importance of mineral management in clinical care.

INTRODUCTION:

Chronic kidney disease (CKD) is tradionally defined using a fixed esmated glomerular filtrate (eGFR) threshold of 60ml/minper1.73m².Though,recent discussions among researchers suggest that this approachmay not adequately account for age-related physiological changes in kidney funcon. Specifically, proposals have emerged to adjust the GFR threshold based on age, advocang for a higher threshold of 75 ml/min per 1.73 m² for younger adults and a lower threshold of 45 ml/min per 11.73 m² for older adults[(1)].Anemia, characterized by a hemoglobin level below 13 g/dL in men and 12 g/dL in women, is a common issue in paents with chronic kidney disease (CKD)[(2)]. Chronic kidney disease (CKD) is a major global health concern and remains a leading cause of morbidity and mortality. In patients with CKD, anemia and disturbances in

mineral metabolism are frequently observed. These include abnormalities in serum intact parathyroid hormone, calcium, and phosphorus levels. Secondary hyperparathyroidism, resulting from disrupted calcium-phosphorus balance, plays a pivotal role in disease progression, cardiovascular risk, and bone-mineral disorders. Anemia in CKD further contributes to reduced quality of life, increased hospitalization, and higher mortality rates. Understanding the prevalence and clinical impact of these complications is crucial for better management and improved outcomes in CKD patients [3].

As chronic kidney disease (CKD) progresses, disturbances in mineral metabolism—particularly involving calcium, phosphorus, serum intact parathyroid hormone 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 from8.5to10.5mg/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 CKD paents, leading to bone diseases and increased cardiovascular risks. Elevated serum phosphorus levels are linked to anemia in CKD paents, but the connecon between anemia and calcium levels is unclear. These imbalances impair quality of life and increase mortality rates due to complicaons like hypocalcemia and hyperphosphatemia. Management of these imbalances is crucial for improving health outcomes (5).In chronic kidney disease (CKD), secondary hyperparathyroidism often emerges as the earliest detectable abnormality in mineral metabolism. The rise in parathyroid hormone (PTH) acts as a compensatory response to counterbalance phosphate retention and diminished production of 1,25-dihydroxyvitamin D, thereby helping to maintain calcium and phosphorus within near-normal ranges. Elevated PTH levels have also been linked to an increased risk of myocardial and coronary heart disease, even in individuals with preserved calcium levels and without advanced renal failure [6]. (iPTH), 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 CKD, the 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 CKD 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 patients with chronic kidney disease (CKD), elevated levels of parathyroid hormone (PTH) have been shown to increase cytoplasmic calcium (Ca^{++}) concentrations. This is particularly evident in uremic individuals, where elevated platelet Ca^{++} levels have been found to correlate with increased plasma PTH concentrations—an effect that can be mitigated through parathyroidectomy (PTX) or treatment with calcitriol. While enhanced calcium influx is considered a key factor in maintaining elevated intracellular calcium levels, studies also indicate that impaired calcium extrusion—due to decreased activity of sarcolemmal Na^{+},K^{+}-ATPase and reduced efficiency of the Na^{+}-Ca^{++} exchanger—may further disrupt cellular calcium homeostasis. Notably, diminished Na^{+},K^{+}-ATPase activity has been consistently observed in uremic conditions associated with CKD[10].

There is limited regional data on the relationship between anemia, mineral metabolism, and iPTH levels in CKD patients. Understanding these correlations could help in early intervention strategies to improve clinical outcomes.

Material and Methods:

The Excel sheet with the collected data was exported to SPSS software, where all data analyses were performed. Descriptive statistics provided an overview of demographic, co-morbid, and baseline factors for the overall study sample. Numerical variables were presented as mean and standard deviation, or median and interquartile range, depending on the distribution of data. Categorical variables were presented as absolute and relative frequencies. Further statistical tests were employed to analyze the data.

Results:

Descriptive Statistics

Samples of CKD patients were involved in a retrospective observational cohort study. The average age of respondents was 48.3 +/- 16.4 years with a range (14 -97 years). The cohort was significantly skewed to males (60.9%, n = 521) over females (39.1%, n = 334).

Table 1: Gender Distribution in Sample

GENDER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	521	60.9	60.9	60.9
	2	334	39.1	39.1	100.0
	Total	855	100.0	100.0	

Biochemical profiling displayed significant variation in the parameters of mineral metabolism. The average concentration of serum intact parathyroid hormone (iPTH) was 313.5 +/- 343.1 pg/ml (range: 4.03-3299pg/ml), which represents a high degree of heterogeneity in secondary hyperparathyroidism between individuals. The average calcium count in serum was 8.69 +/- 1.10 mg/dl and serum phosphorus was an average of 5.53 +/- 2.34 mg/dl which shows that there is frequent imbalance being experienced in calcium and phosphorus levels. The average hemoglobin level was 9.83 +/- 2.09 g/dl indicating a high risk of anemia among study participants. Other baseline parameters, such as serum albumin, red blood cell count, BMI, systolic and diastolic blood pressure, are shown in Table 2.

Table 2: Baseline demographic, clinical, and biochemical characteristics of patients with primary glomerulonephritis (N = 855).

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
GENDER	855	1	2	1.39	.488	.449	.084	-1.803	.167
AGE	855	14	97	48.27	16.436	-.081	.084	-.697	.167
PTH	855	4.03	3299.00	313.4846	343.11309	2.797	.084	12.353	.167
CALCIUM	855	4.20	15.00	8.6923	1.10326	-.052	.084	2.735	.167
ALBUMIN	855	1.60	5.00	3.6408	.62344	-.680	.084	.106	.167
PHOSPHORUS	855	1.00	19.70	5.5337	2.34167	1.505	.084	3.996	.167
HEAMOGLOBIN	855	4.00	15.70	9.8323	2.08882	.162	.084	-.218	.167
RBCs	855	1.39	6.67	3.7294	.84825	.410	.084	.228	.167
WEIGHT	855	23.40	139.00	60.0106	15.76840	.610	.084	.724	.167
BP_SYS	855	30.00	230.00	131.7099	19.05188	.002	.084	3.445	.167
BP_DIA	855	15.00	123.00	80.8468	11.71175	-.590	.084	3.299	.167
BMI	855	11.99	924.80	24.5950	31.74994	26.885	.084	759.690	.167
Valid N (listwise)	855								

Correlation Analysis

Since the variables were not normally distributed, non-parametric Spearman correlation was utilized in determining the relationship between hemoglobin and mineral markers. Hemoglobin moderately, but statistically significantly, negatively correlated with iPTH ($r = -0.253$, $p < 0.001$) indicating that the higher the PTH concentrations, the more severe the anemia. There was also a low-to-moderate, statistically significant positive correlation with calcium ($r = 0.292$, $p < 0.001$), such that patients with greater serum calcium also had more hemoglobin. Correlation between hemoglobin and phosphorus was not significant ($r= -0.056$, $p = 0.101$).

Table 3: Spearman's correlation coefficients between hemoglobin and mineral metabolism parameters.

Correlations

			HEAMOGLOBIN	PHOSPHORUS	PTH	CALCIUM
Spearman's rho	HEAMOGLOBIN	Correlation Coefficient	1.000	-.253**	-.056	.292**
		Sig. (2-tailed)	.	.000	.101	.000
		N	855	855	855	855
	PHOSPHORUS	Correlation Coefficient	-.253**	1.000	.229**	-.191**
		Sig. (2-tailed)	.000	.	.000	.000
		N	855	855	855	855
	PTH	Correlation Coefficient	-.056	.229**	1.000	-.262**
		Sig. (2-tailed)	.101	.000	.	.000
		N	855	855	855	855
	CALCIUM	Correlation Coefficient	.292**	-.191**	-.262**	1.000
		Sig. (2-tailed)	.000	.000	.000	.
		N	855	855	855	855

**. Correlation is significant at the 0.01 level (2-tailed).

All the correlations of all the study variables are displayed in Table 2. The relationship between hemoglobin and iPTH has an inverse trend, and that between hemoglobin and calcium has a positive one, which can be visualized on a scatterplot (Figure 1a and Figure 1b).

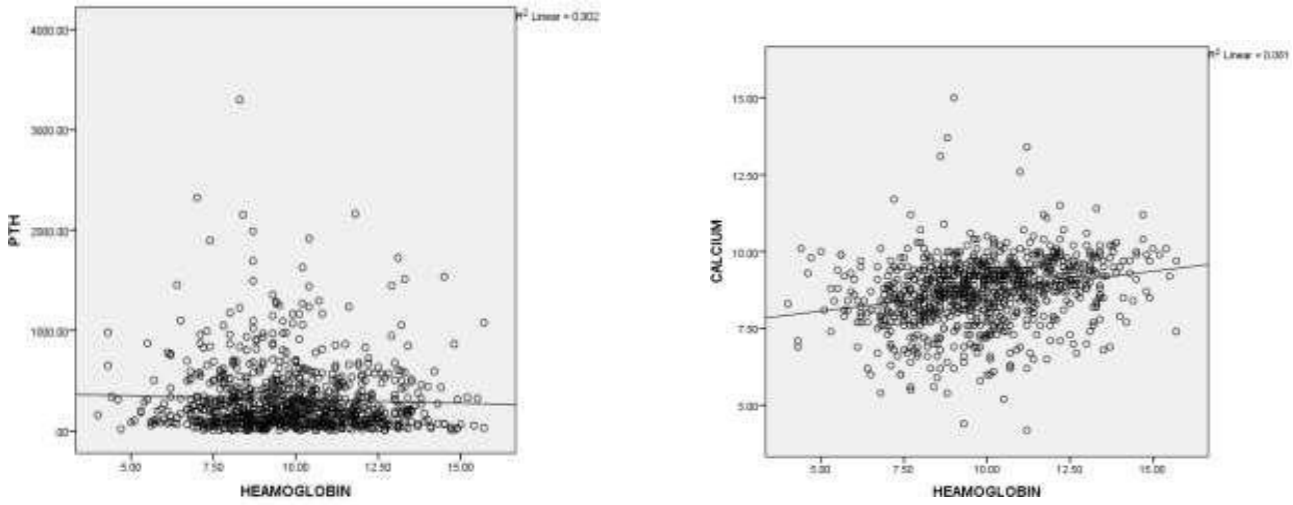

Figure 1(a&b) Scatter plots showing correlation between (a) HB and iPTH, and(b) HB and calcium.

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 4: ANOVA Matrix

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	360.952	3	120.317	30.426	.000[b]
	Residual	3365.197	851	3.954		
	Total	3726.149	854			

a. Dependent Variable: HEAMOGLOBIN

b. Predictors: (Constant), PTH, CALCIUM, PHOSPHORUS

In the multivariable analysis:

Serum phosphorus was identified as a significant independent negative predictor of hemoglobin (B = –0.175, p < 0.001).Serum calcium was a significant independent positive predictor (B = +0.399, p < 0.001).iPTH did not retain independent predictive value (B ≈ 0, p = 0.514) when calcium and phosphorus were included in the model.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	7.288	.612		11.903	.000
	PHOSPHORUS	-.175	.030	-.196	-5.833	.000
	CALCIUM	.399	.063	.211	6.313	.000
	PTH	.000	.000	.022	.652	.514

a. Dependent Variable: HEAMOGLOBIN

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 (Figure 2).

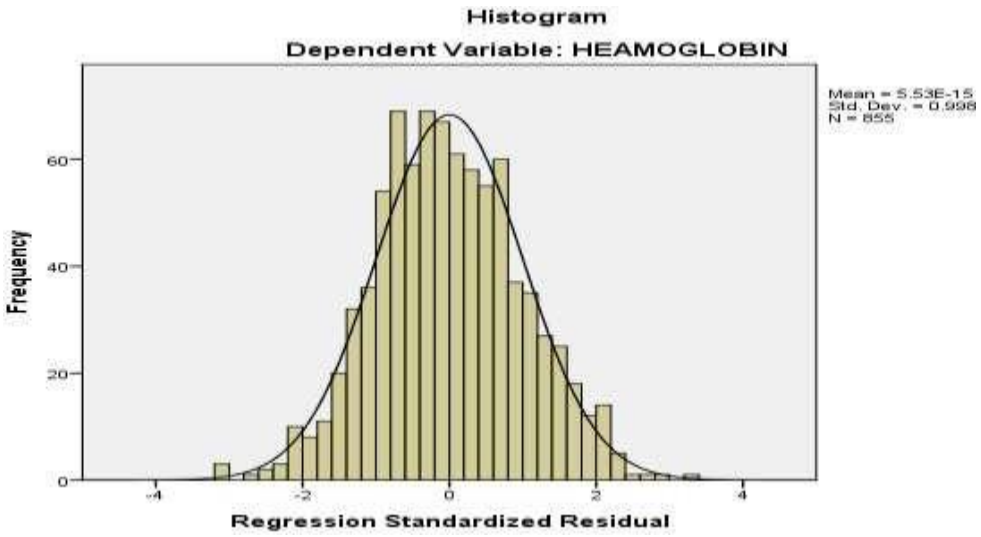

Figure 2: Regression diagnostics: (a) histogram of standardized residuals, and

Discussion

The study aimed to examine the relationship between anemia, disturbances of mineral metabolism, and, in particular, iPTH, calcium, and phosphorus, in a large group of patients with primary glomerulonephritis biopsy-proven. The results point back that anemia is excessively common in the group of people and any anomalies in calcium-phosphorus homeostasis are significantly related to anemia in this group [(11)]. More precisely, it was found that higher concentrations of phosphorus alone were predictors of hemoglobin and higher calcium alone was a predictor of hemoglobin levels [(12)]. In bivariate analysis, however, iPTH was inversely correlated with hemoglobin but did not persist into multivariable analysis, lending support to the hypothesis that this association could be intermediated by abnormalities of mineral metabolism.

Interpretation of Findings

This negative correlation between hemoglobin and iPTH is consistent with previous research which identified that an elevated iPTH level may suppress erythropoiesis due to the mechanism of bone marrow fibrosis, impaired erythroid progenitor cell activity, and shorter red blood cell life [(13)]. The p-value of iPTH decreases in the multivariable model, indicating a lack of significance that may be resulting due to an indirect effect of iPTH on 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 negative effect of phosphorus on hemoglobin levels, independent of phosphorus, is notable. Hyperphosphatemia has been shown to contribute to anemia of CKD via several mechanisms, involving inhibition of erythropoietin receptor signaling, oxidative stress, and resistance to erythropoiesis-stimulating agents (ESAs). In contrast, the positive predictive value of calcium can be attributed to its action in suppressing iPTH overactivity by extension promoting erythropoiesis [(15)]. These results indicate that phosphate control and maintenance of normal calcium may be a beneficial addition to standard therapy with ESA and iron in anemia treatment with glomerulonephritis.

Comparison with Previous Studies

Our findings are in line with other studies done in populations with CKD. According to Wu et al. 2022, the higher concentration of phosphorus was the association of anemia risk and worse ESA response compared to the associative positive effect of the calcium balance exposure to hemoglobin [(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, or mixed causes of kidney disease and biopsy-proven glomerulonephritis in our study) and/or variation in assays used to measure iPTH.

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.

Clinical Implications

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].

Strengths and Limitations:

The study's strengths include a relatively large sample size of biopsy-confirmed glomerulonephritis cases, simultaneous evaluation of mineral parameters in relation to anemia, and the use of hospital-based electronic records, which minimized recall bias and ensured completeness of laboratory data. However, the retrospective design limits the ability to establish causal relationships, and the absence of key confounders such as iron indices, markers of inflammation, and the use of ESA or phosphate binders may have influenced the associations observed. Additionally, variability in iPTH assays and the low explanatory power of the regression model could have introduced bias, while the single-center design restricts the generalizability of the findings to the broader CKD population.

Conclusion

In conclusion, this study indicates that anemia among patients with chronic kidney disease substantially linked with impaired mineral metabolism. Serum phosphorus and calcium were found to be independent determinants of hemoglobin concentration, but although iPTH appeared to be a negative correlate, it was not significant in the multivariable analysis. These data show the necessity to consider calcium-phosphorus balance when anemia of glomerulonephritis is managed. Prospective investigations to include iron metabolism and inflammatory markers along with treatment options should be conducted to help to define causal mechanisms and maximize treatment regimes.

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