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Original Article

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Effects of Serum Calcium and Phosphorus on Anemia Development in Patients with Stage 3b and 4 Chronic Kidney Disease

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Abstract

Objective: The relationship between anemia and bone disease markers was examined to a great extent in patients undergoing renal replacement therapy. The aim of this study was to investigate the relationship between bone disease markers and anemia in a cohort of adult patients without renal replacement therapy.

Materials and Methods: A total of 1279 patients with stage 3b and 4 kidney disease who were admitted to the Nephrology outpatient clinic of the Kayseri Research and Training Hospital between January 1, 2014, and December 31, 2017, formed the study cohort. Logistic and linear regression models were developed to explore the adjusted effects of calcium, phosphorus, parathyroid hormone (PTH), and 25-hydroxyvitamin D concentrations on anemia. Other confounding variables were included in regression equations.

Results: In the adjusted logistic regression model, it was found that the prevalence of anemia was significantly associated with calcium, phosphorus, and PTH levels. An increase of 1 mmol L^{-1} in serum calcium and phosphorus concentrations was associated with a 32% reduction (OR: 0.68; 95% CI: 0.51-0.91; p=0.011) and a 2.4-fold increase (OR: 2.40; 95% CI: 1.40, 4.13; p=0.002) in the prevalence of anemia, respectively. In a receiver operating characteristic analysis for identifying anemia, discriminating power of phosphorus was superior to the other bone disease markers [best cut-off value >1.23 mmol L^{-1}, AUC 0.65 (0.624-0.677)]

Conclusion: Serum calcium and phosphorus levels may contribute to the development of anemia in patients with stage 3b and 4 chronic kidney disease who are not receiving renal replacement therapy.

Keywords: Anemia, bone mineral disorders, calcium, chronic kidney disease, phosphorus

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INTRODUCTION

Anemia is one of the most frequent complications in chronic kidney disease (CKD), and its prevalence ranges between 0% and 95%, depending on the condition of dialysis and severity of CKD. As anticipated, the likelihood of anemia increases when the glomerular filtration rate (GFR) declines (1). Different causes such as poor erythropoietin (EPO) production, absolute or functional iron deficiency, chronic inflammation, and uremic toxin-induced erythropoiesis inhibitors play an important role in the development of anemia in CKD (2). According to the results collected from the cohort studies of hemodialysis patients, hemoglobin levels were individually associated with serum calcium and phosphorus concentrations. Data from the Dialysis Outcomes and Practice Patterns Study indicated that high serum calcium levels were related with high hemoglobin levels, and this relation was independent of vitamin D supplementation and parathyroid hormone (PTH) levels (3). Low calcium values have also been found to be independent determinants of low response to erythropoiesis-stimulating agents in an investigation (4). In recent studies, a meaningful association has been found between high serum phosphorus levels and anemia in individuals with normal and moderately reduced GFR (5, 6).

Moreover, some pathogenic relationships have been proposed between anemia and PTH. These include diminished erythropoiesis due to calcitriol deficiency, and direct or indirect effects of PTH on EPO release along with red blood cell production, survival, and loss (7). For these reasons, PTH has been accepted as a uremic toxin that leads to myelofibrosis and thus inhibits hematopoiesis (8). The evidence presented in the literature about the role of PTH was the amelioration of anemia or decreased EPO requirement by suppressing hyperparathyroidism through surgical correction or vitamin D and its analogues (9, 10).

Vitamin D otherwise has a synergistic effect with EPO in the proliferation and maturation of erythroid progenitor cells (11). Various pathological correlations have been suggested between vitamin D and anemia. Vitamin D receptor activation suppresses the expression of inflammatory cytokines in stromal and accessory cells. It also promotes the lymphocytic release of interleukin-10 (IL-10), which exhibits anti-inflammatory activity. Vitamin D possesses proliferative effects on erythroid progenitors as well. In patients with CKD, vitamin D deficiency may promote cytokine production by stimulating immune cells within the bone marrow microcirculation, thus triggering impaired erythropoiesis. Immune activation involves the reticuloendothelial system giving rise to an increase in hepcidin synthesis and functional iron deficiency. The consequences of this inflammatory cascade are EPO resistance and anemia (12). In conclusion, the link between vitamin D and anemia is seemingly a situation accompanied with anemia of inflammation. The basic mechanism is the direct suppression of hepcidin mRNA expression by vitamin D and the reduction of hepcidin-induced pro-inflammatory cytokines (13).

In the literature, studies examining the relationship between anemia and metabolic bone disease have been usually carried out in hemodialysis patients. However, metabolic bone disease indicators are strictly related, and therefore, it is not easy to discern the individual effects of these indicators on the prevalence of anemia of CKD. The purpose of this study was to investigate the effects of metabolic bone disease markers on the development of anemia in an adult patient population with stage 3b and 4 CKD who are not on dialysis.

Main Points

- There are very few studies on whether serum calcium or phosphorus levels may contribute to anemia in CKD patients.
- It should be kept in mind that calcium and phosphorus imbalances may play a role in the development of anemia in patients with chronic kidney disease who have not yet received dialysis.
- In these patients, increasing serum calcium or lowering phosphorus in terms of anemia treatment may be one of the clinical study subjects in the upcoming processes.

MATERIALS AND METHODS

Study Design and Setting

This was designed as a single-center and retrospective observational cohort study, which was carried out between January 1, 2014, and December 31, 2017. Patients admitted to the Nephrology outpatient clinic of the Kayseri Research and Training Hospital were included in the study. They had similar features regarding applied procedures, referral characteristics, and follow-up durations. The final analysis was implemented in 1279 subjects. Approval of the instutional review board was waived due to anonymized and retrospective nature of the data.

Inclusion and Exclusion Criteria

Male and female patients over 18 years of age who were followed up for at least six months were included in the study. Patients were also evaluated as appropriate for the study if serum calcium, phosphorus, creatinine, and hemoglobin levels were examined at least once within 120 days of the first calcium measurement. Patients who had estimated glomerular filtration rate (eGFR) >45 and <15, and who had the highest serum calcium concentration of 0.5% and the lowest 0.5% in the distribution were excluded from the study to reduce the effect of outliers. The other exclusion criteria were blood transfusion or organ transplantation, cancer, bleeding, pregnancy, hematological or autoimmune disorders, and liver or lung disease, which may have the confounding effects on the development of anemia.

Data Sources and Laboratory Measurements

Data such as age, sexuality, comorbid conditions, and laboratory values were gathered from the hospital's electronic files. eGFR levels were measured corresponding to the MDRD formula using the earliest detected creatinine values within 120 days of basal calcium measurement. The autoanalyzer automatically calculated mean corpuscular volume (MCV) and red cell distribution width (RDW) values showing the dimensions of red blood cells. Serum calcium and phosphorus levels were treated both as continuous and nominal variables.

The main predictor variables were serum calcium and phosphorus concentrations, and the primary outcome variable was the presence of anemia as a nominal variable along with hemoglobin levels as a continuous variable. According to the World Health Organization definition, hemoglobin <13 g dL^{-1} for men and <12 g dL^{-1} for women was regarded as anemia.

Statistical Analysis

Continuous variables were expressed as mean (SD) or median (inter-quartile range) if data distribution was appropriate. Normal distribution was investigated by the Shapiro-Wilk test. Categorical variables were presented as a percentage. The comparison of the variables in the groups with and without anemia was performed by Student-t, Wilcoxon, or chi-square test. The relationship between serum calcium or phosphorus and anemia was assessed cross-sectionally by using linear and logistic regression models. The analysis was made only once in each patient.

First, the raw effects of the predictor variables on the outcome variable were evaluated. Later, logistic regression models were created by using bone disease indicators (corrected calcium, phosphorus, PTH, 25(OH)D_3). Second, demographic and clinical confounding variables that may be associated with anemia (age, sex, body mass index, diabetes, hypertension, eGFR, urinary protein-creatinine ratio, MCV, RDW, transferrin saturation, vitamin D or vitamin D analogue and angiotensin-converting enzyme inhibitors use) were entered to the regression equation. Finally, albumin and C-reactive protein (CRP) were included in the model to eliminate the confounding effects of systemic inflammation. Multivariate linear regression model was also generated in a fully adjusted manner. Adjusted regression coefficients and ORs were produced with 95% confidence intervals. Goodness of fit of the models was established by standardized Pearson chi-squared test in logistic regression and coefficients of the determinants in linear regression. Patients with missing data were omitted from primary analyses, and these data were not imputed. The complete data of 1279 patients were obtained for multivariate analyses. We also performed a receiver operating characteristic (ROC) curve analysis to compare the accuracy of calcium, phosphorus, PTH, and 25(OH)D_3 for predicting anemia. Nonparametric methods were utilized to compare area under the ROC curves. We reported sensitivity, specificity, and cut points leading to the best balance of sensitivity and specificity for each measure. The Youden index, which was defined as the minimal distance of the ROC curve to the point (0,1) of the graph, was used to identify the optimal ROC-derived cut-off levels.

Statistical analyses were performed using STATA statistical software version 14 (StataCorp, College Station, TX, USA). Two-sided p values of less than 0.05 were considered statistically significant.

RESULTS

A total of 23,657 patient were screened from the records. Of them, 22,378 were removed from the study because they did not satisfy the inclusion criteria (Figure 1). Finally, analyses were performed in 1,279 subjects whose data were thoroughly accessible. The mean age was 65.5 years, and the percentage of women was 49.9%; 63.9% of the subjects had diabetes mellitus, and hypertension was present in 88.3% of the entire population. Table 1 presents the demographic and clinical characteristics of the patients according to anemia status.

When serum metabolic bone disease markers were considered, calcium and 25(OH)D_3 were lower, and phosphorus levels were higher in patients with anemia. Women were more anemic than men, and iron saturation and eGFR along with albumin levels were lower in anemic patients. In addition, anemic patients were using more iron preparations.

According to the unadjusted logistic regression model, the increase in corrected calcium levels decreased the prevalence of anemia, whereas an increase in phosphorus and PTH levels increased the prevalence of anemia. Age, female sex, and transferrin saturation had a statistically significant impact on the frequency of anemia. High levels of albumin were also found to reduce the anemia frequency (Table 2).

Corresponding to the logistic regression model where only metabolic bone disease variables were involved, the increase in corrected calcium levels, likewise, decreased the odds of anemia, whereas the increase in phosphorus levels increased the odds of anemia (Table 2). There was no significant difference in the statistical significance levels and odds values compared with the crude analysis. In the second model, which consisted

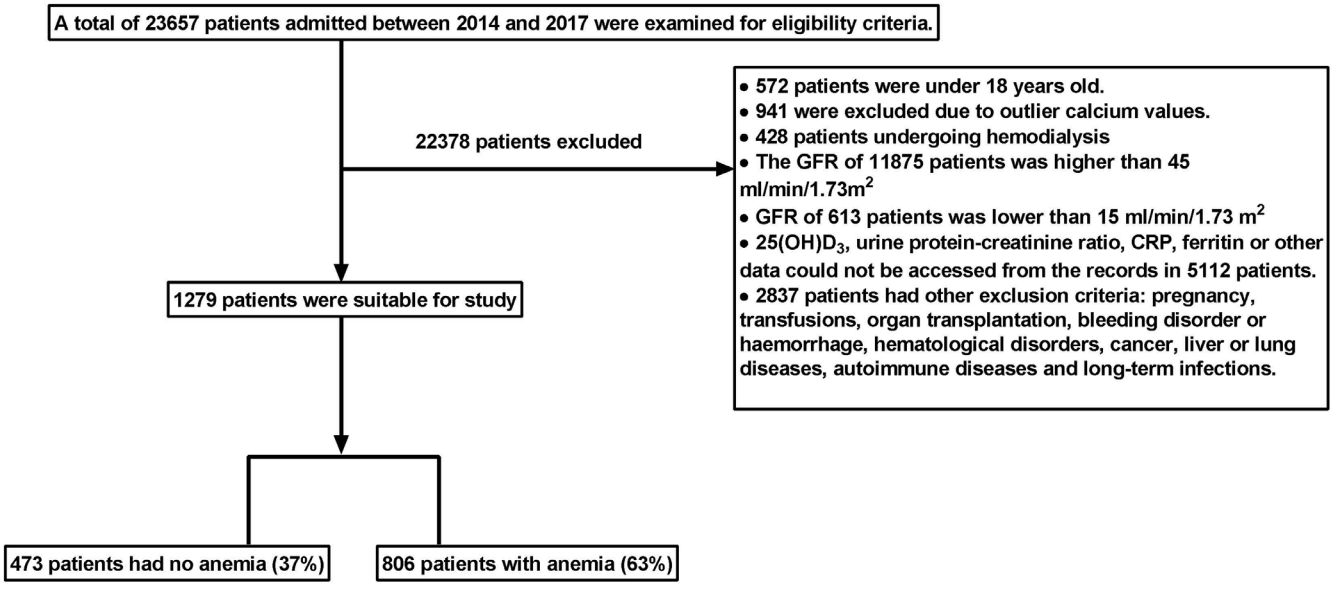

Figure 1. Flow chart of study cohort. Anemia was defined as hemoglobin <120 g L^{-1} for females and <130 g L^{-1} for males.

Table 1. Characteristics of study population by anemia status

Variables	Anemia (no) (n=473)	Anemia (yes) (n=806)	Total (n=1279)	p
Age, years	64.74 (7.93)	65.91 (7.86)	65.48 (7.90)	0.011
Sex (female)	210 (44.4%)	428 (53.1%)	638 (49.9%)	0.003
Diabetes mellitus	290 (61.3%)	527 (65.4%)	817 (63.9%)	0.143
Hypertension	411 (86.9%)	718 (89.1%)	1129 (88.3%)	0.240
Body mass index, kg m^{-2}	23.66 (3.77)	23.70 (3.57)	23.69 (3.64)	0.853
Hemoglobin, g L^{-1}	132.62 (9.47)	105.04 (8.10)	115.24 (15.87)	<0.001
MCV, fl	91.08 (3.94)	90.27 (6.31)	90.57 (5.57)	0.012
RDW, %	13.78 (1.26)	13.97 (1.41)	13.90 (1.36)	0.016
Serum ferritin, pmol L^{-1}	122.63 (52.34)	124.44 (51.35)	123.77 (51.70)	0.545
Transferrin saturation (≤20)	255 (53.9%)	496 (61.5%)	751 (58.7%)	0.007
Albumin-corrected serum calcium, mmol L^{-1}	2.29 (0.40)	2.22 (0.40)	2.25 (0.40)	0.003
Serum phosphorus, mmol L^{-1}	1.31 (0.23)	1.35 (0.21)	1.34 (0.22)	0.003
Serum intact PTH, ng L^{-1}	157.99 (56.22)	165.16 (57.13)	162.51 (56.88)	0.030
Serum 25(OH)D_3, nmol L^{-1}	28.2 (21.0, 41.2)	26.2 (18.0, 40.2)	27.2 (18.7, 40.7)	0.015
Serum albumin, g L^{-1}	40.09 (2.84)	39.60 (2.84)	39.78 (2.85)	0.003
Albumin (≤40 g L^{-1})	185 (39.1%)	378 (46.9%)	563 (44.0%)	0.007
Serum CRP, nmol L^{-1}	23.8 (16.2, 36.2)	25.7 (17.1, 37.1)	24.8 (16.2, 37.1)	0.169
eGFR, mL min^{-1} 1.73 m^{-2}	23.84 (4.79)	23.17 (4.76)	23.42 (4.78)	0.015
Urine protein/creatinine ratio, mg $mmol^{-1}$	50.0 (25.3, 86.1)	56.1 (28.7, 93.5)	54.0 (27.1, 92.0)	0.053
Erythropoiesis-stimulating agents use	0 (0.0%)	118 (14.6%)	118 (9.2%)	<0.001
Iron supplement use	99 (20.9%)	225 (27.9%)	324 (25.3%)	0.006
Vitamin D use	26 (5.5%)	24 (3.0%)	50 (3.9%)	0.025
Vitamin D analogues use	61 (12.9%)	120 (14.9%)	181 (14.2%)	0.324
ACEI/ARB use	180 (38.1%)	269 (33.4%)	449 (35.1%)	0.090

Data are presented as Mean (SD), Median (Q1, Q3), or N (%)
ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; MCV: mean corpuscular volume; RDW: red cell distribution width; CRP: C-reactive protein; PTH: parathyroid hormone; eGFR: estimated glomerular filtration rate

of demographic, clinical, and laboratory variables other than albumin and CRP, there was no effect of age.

In the fully adjusted model with inflammatory markers, 1 mmol L^{-1} increase in serum calcium and phosphorus concentration was associated with a 32% reduction (OR: 0.68; 95% CI: 0.51-0.91; p=0.011) and a 2.4-fold increase (OR: 2.40; 95% CI: 1.40, 4.13; p=0.002) in the prevalence of anemia, respectively. Figure 2 shows the odds ratios of variables with 95% confidence intervals in nominal levels.

Figure 3a and 3b show the alteration of the predicted anemia probability relative to the calcium and phosphorus values as a continuous variable in fully adjusted logistic regression models. Figure 3c and 3d demonstrate the adjusted effects of calcium and phosphorus on the hemoglobin levels in multiple linear regression model. Correspondingly, the tendency of anemia declined, and the hemoglobin values increased with increasing calcium levels, whereas the rise in phosphorus increased the possibility of anemia and the hemoglobin values decreased.

ROC curves showed that all biomarkers were marginally accurate in predicting anemia (Figure 4, Table 3). As a continuous variable, calcium and phosphorus resulted in the areas under the curves (AUCs) for anemia of 0.55 (95% CI: 0.52, 0.58) and 0.65 (95% CI: 0.62, 0.68), respectively (Figure 4). Also, PTH and 25(OH)D_3 had an AUC of 0.54 (95% CI: 0.50, 0.56) and 0.54 (95% CI: 0.51, 0.57), respectively. AUC of phosphorus was significantly higher compared with the three other bone disease markers measures (Table 3). No difference was observed between calcium, PTH, and 25(OH)D_3.

DISCUSSION

The objective of this study was to explore the relationship between anemia and metabolic bone disease markers in patients with stage 3b and 4 CKD. The results of the analysis showed that serum calcium and phosphorus levels were associated with hemoglobin concentrations. As the calcium levels increased the frequency of anemia increased, and there was an inverse relationship between phosphorus and hemoglobin levels. These relationships were independent of other bone disease markers or

Table 2. Odds ratios (95% confidence intervals) of anemia with various confounders in various logistic regression models*

	Crude effects			Model 1			Model 2			Model 3		
Variables	**OR**	**%95 CI**	**p**	**OR**	**%95 CI**	**p**	**OR**	**%95 CI**	**p**	**OR**	**%95 CI**	**p**
Albumin-corrected serum calcium, mmol L^{-1}	0.654	0.493-0.867	0.003	0.654	0.493-0.869	0.003	0.666	0.498-0.891	0.006	0.682	0.509-0.915	0.011
Serum phosphorus, mmol L^{-1}	2.212	1.316-3.718	0.003	2.209	1.311-3.723	0.003	2.426	1.412-4.167	0.001	2.403	1.396-4.134	0.002
Serum intact PTH, ng L^{-1}	1.002	1.000-1.004	0.030	1.002	1.000-1.004	0.040	1.002	1.000-1.004	0.031	1.002	1.000-1.004	0.040
Serum 25(OH)D_3, nmol L^{-1}	0.995	0.988-1.002	0.158	0.995	0.988-1.002	0.172	0.996	0.989-1.003	0.293	0.996	0.989-1.003	0.283
Age, years	1.019	1.004-1.034	0.011				1.016	1.001-1.031	0.043	1.017	1.001-1.032	0.031
Sex (female)	1.418	1.129-1.781	0.003				1.408	1.110-1.785	0.005	1.418	1.117-1.801	0.004
Diabetes mellitus	1.192	0.942-1.508	0.143				1.253	0.982-1.600	0.070	1.274	0.997-1.629	0.053
Hypertension	1.231	0.870-1.741	0.241				1.207	0.841-1.732	0.307	1.211	0.844-1.739	0.299
Transferrin saturation (<20)	1.368	1.087-1.721	0.008				1.393	1.097-1.769	0.006	1.391	1.094-1.767	0.007
Serum ferritin, pmol L^{-1}	1.001	0.998-1.003	0.545				1.001	0.998-1.003	0.600	1.001	0.998-1.003	0.637
eGFR, mL min^{-1} 1.73 m^{-2}	0.971	0.948-0.994	0.015				0.975	0.952-1.000	0.047	0.974	0.950-0.998	0.035
Urine protein/ creatinine ratio, mg $mmol^{-1}$	1.002	1.000-1.005	0.075				1.002	1.000-1.005	0.099	1.002	1.000-1.005	0.091
Iron supplement use	1.463	1.117-1.916	0.006				1.512	1.144-1.999	0.004	1.503	1.135-1.989	0.004
Vitamin D use	0.528	0.299-0.930	0.027				0.545	0.301-0.985	0.045	0.522	0.288-0.947	0.032
Vitamin D analogues use	1.181	0.848-1.646	0.324				1.132	0.802-1.597	0.481	1.122	0.795-1.585	0.512
ACEI/ARB use	0.815	0.644-1.033	0.091				0.844	0.660-1.078	0.174	0.852	0.666-1.089	0.201
Serum albumin (g/L)	0.940	0.903-0.979	0.003							0.935	0.896-0.975	0.002
Serum CRP (nmol/L)	1.004	0.996-1.011	0.360							1.004	0.996-1.012	0.300

*Continuous variables per one-unit increase
GFR: glomerular filtration rate; PTH: parathyroid hormone; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker

factors leading to anemia. Calcium and phosphorus are firmly linked variables and may have separate effects on bone marrow through distinct pathways. We think that the results of our research are noteworthy in this aspect.

There is not enough information about the relationship between anemia and serum calcium or phosphorus levels in CKD patients. In our study, the odds of anemia reduced by 32% for every 1 mmol/L increment in corrected serum calcium after the effects of other confounding variables was adjusted with multivariate regression models, and the odds increased by 140% for every 1 mmol L^{-1} increment in serum phosphorus levels. Another remarkable finding was that ferritin levels were not significantly associated with anemia. This may be related to ferritin measurement faults formerly mentioned in the assessment of iron stores (14).

Phosphorus was independently associated with anemia according to our study. It does not support the assumption that other metabolic bone disease markers such as vitamin D or PTH mediates this relationship. An idea has been suggested that uremic polyamine metabolism could lead to anemia in CKD. Polyamines are uremic toxins that suppress erythropoiesis. Excessive levels of polyamine induced by high phosphorus levels may clarify the relationship between phosphorus and anemia (15). Furthermore, hyperphosphatemia is associated with substantially increased erythropoietin resistance. One of the responsible mechanisms may be the shift to the right of oxygen-hemoglobin dissociation curve that results in down regulation of erythropoietin receptors (16).

A possible relationship between serum calcium and anemia is also an issue that has been seldom focused so far. It was recognized a long time ago that calcium is needed for *in vitro* proliferation and differentiation of erythropoietin-induced erythroid progenitor cells (17). The increased erythropoietin levels for any reason, e.g. hypoxia-induced, not merely enhances erythropoi-

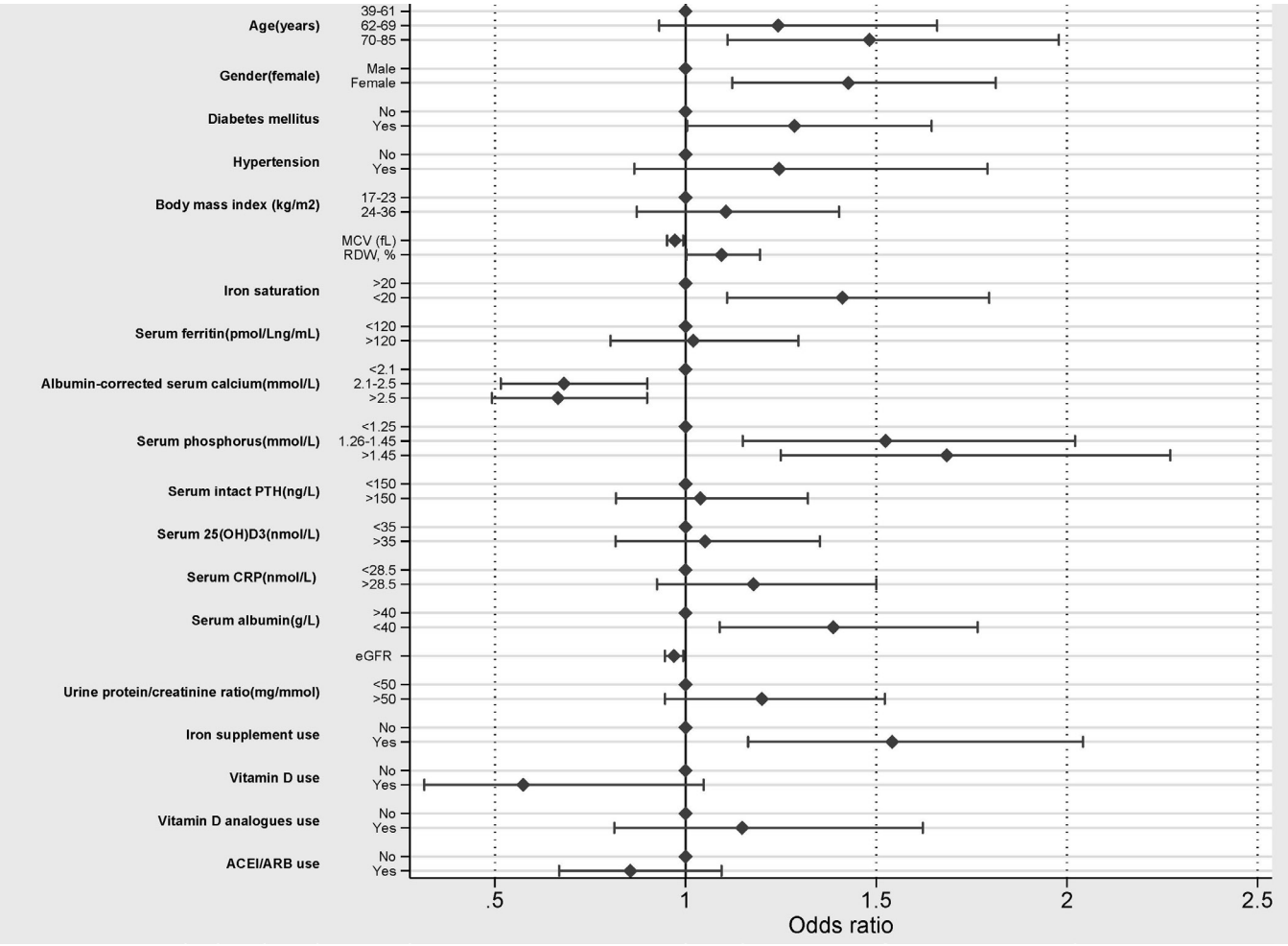

Figure 2. Forest plot of completely adjusted OR for anemia. Age, sex, body mass index, diabetes, hypertension, ferritin, iron saturation, MCV, RDW, eGFR, urine protein/creatinine ratio, iron supplement use, treatment with vitamin D, vitamin D analogues, or ACEI/ARB, serum albumin and CRP. Erythropoiesis-stimulating agent excluded from models.

Table 3. Area under the receiver operating characteristic curve, sensitivity, specificity, and predictive values for anemia using specific bone disease biomarkers and cut-off values*

	AUC (95% CI)	AUC p	Cut-off value	Sensitivity	Specificity	PPV	NPV
Calcium, mmol L^{-1}	0.552(0.524-0.579)[a]	0.002	≤2.17	51.36	58.99	68.1	41.6
Phosphorus, mmol L^{-1}	0.65(0.624-0.677)[b, c]	<0.001	>1.23	80.52	40.38	69.7	54.9
PTH, ng L^{-1}	0.536(0.50-0.563)	0.033	>117.19	78.04	28.96	65.2	43.6
25(OH)D_3, nmol L^{-1}	0.541(0.513-0.568)	0.013	≤20.71	34.86	75.05	70.4	40.3

*Optimal cut-off values were determined with Youden index.
[a]Phosphorus vs Calcium, p<0.001
[b]Phosphorus vs PTH, p<0.001
[c]Phosphorus vs 25(OH)D3, p<0.001
PPV: positive predictive value; NPV: negative predictive values; AUC: area under the receiver operating curve; PTH: parathyroid hormone

esis, but also provokes eryptosis by increasing intracellular calcium. This leads to a rapid recycling of iron and culminates in efficient reticulocytosis (18). However, it has been noted that there is a disorder in the pathways that carries intracellular calcium out of the cell in CKD. This pathology leads to excess calcium accumulation within the cell, and a considerable amount of this calcium remains adhered to the cytoplasmic proteins or is stored in the endoplasmic reticulum (19). This may justify the hypothesis that changes in serum calcium concentrations may limit erythropoietin-mediated calcium movement to erythroid cells.

Experimental and clinical studies have presented the evidence that secondary hyperparathyroidism suppresses erythropoi-

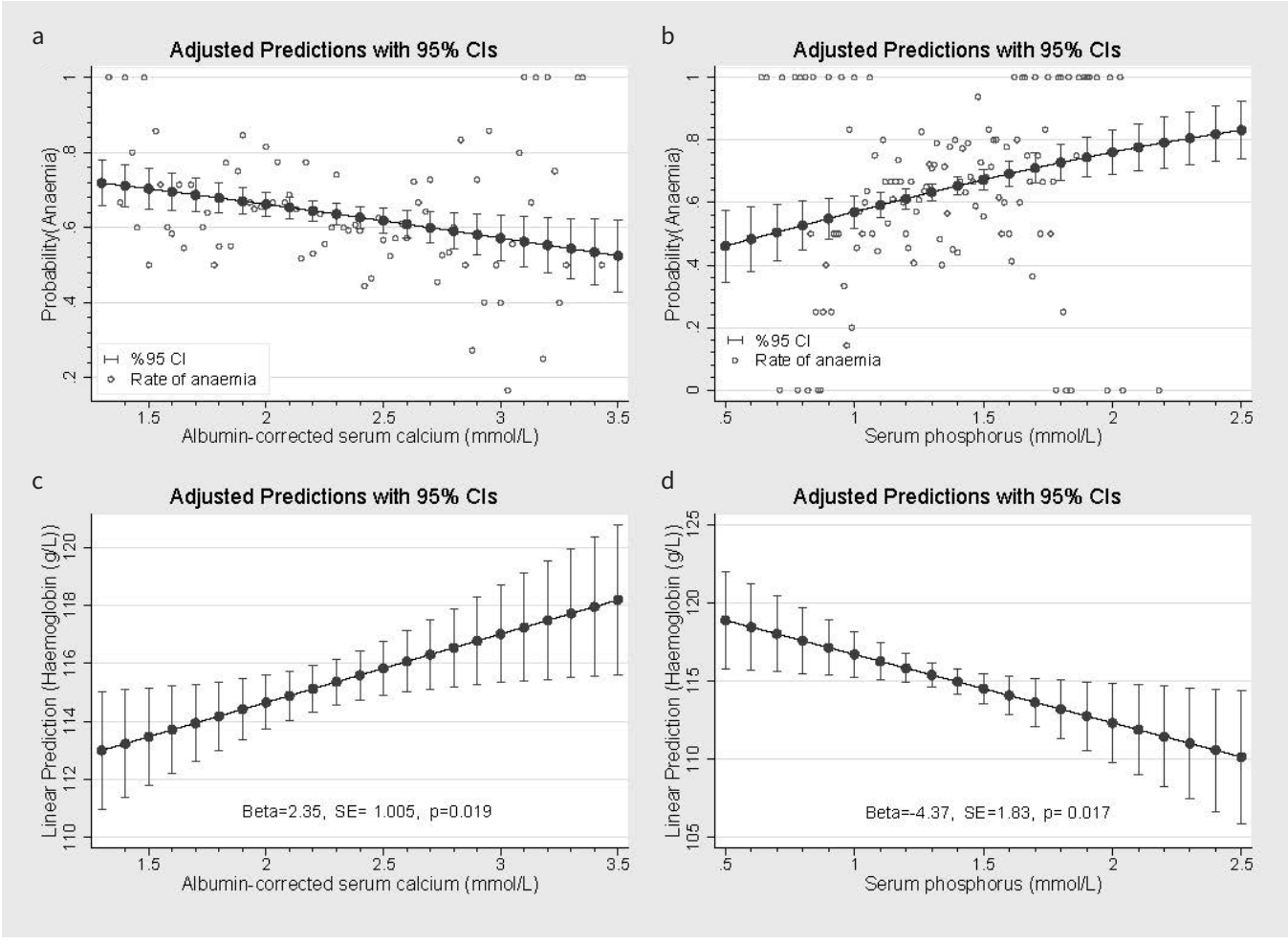

Figure 3. a-d. a) Adjusted effects of serum calcium concentrations on predicted probability of anemia. b) Adjusted effects of serum phosphorus concentrations on predicted probability of anemia. c) Adjusted linear prediction of serum hemoglobin levels according to calcium levels. d) Adjusted linear prediction of serum hemoglobin levels according to phosphorus levels. Logistic and linear regression models adjusted for age, sex, body mass index, diabetes, hypertension, ferri-tin, iron saturation, MCV, RDW, eGFR, urine protein/creatinine ratio, iron supplement use, treatment with vitamin D, vitamin D analogues, or ACEI/ARB, serum albumin, and CRP. Erythropoiesis-stimulating agent using were excluded from models.

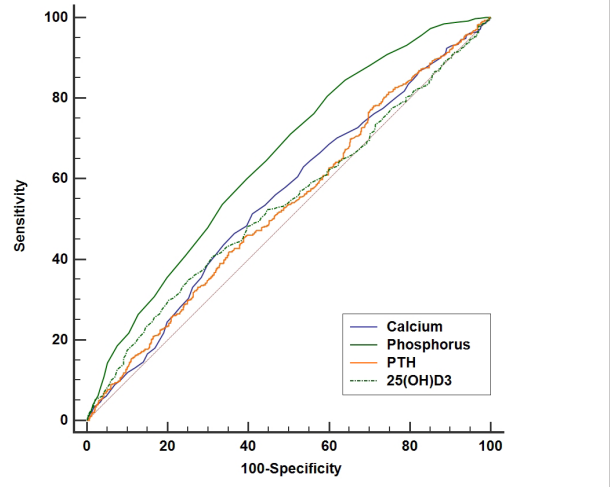

Figure 4. Receiver operating characteristic curves for bone disease biomarkers for predicting anemia.

esis and leads to erythropoietin resistance (20). In our study, we identified a statistically meaningful positive relationship between PTH and anemia development in accordance with the literature, while this result was not supported in a recent study (21). Perhaps other mechanisms that influence bone mineral balance may contribute to the development of anemia in hyperparathyroidism.

Vitamin D deficiency has also been suggested to contribute to the development of anemia in non-dialysis patients with mild to moderate renal damage (22). In addition, 25(OH)D_3 levels were found to be positively associated with erythropoietin response in hemodialysis patients (23). Furthermore, there are reports that the use of vitamin D or analogues may contribute to the recovery of anemia or reduction in EPO doses in hemodialysis patients (24). In our study, we did not find a significant relationship between vitamin D and anemia, probably because of the exclusion of patients with inflammation.

Vitamin D is a remarkably potent pleiotropic hormone and its receptors are virtually located in all human cells. It has been suggested that the 1,25 $(OH)_2$ D_3 molecule directly triggers erythropoiesis. However, the evidence reported in the literature so far is that it prevents anemia with its anti-inflammatory properties (25, 26). In fact, there are many common points between anemia in CKD and anemia in inflammation. From this point of view, recent studies have established a negative linear relationship between CRP, a marker of inflammation, and hemoglobin levels (27). Another study yields evidence that low 25(OH)D_3 and elevated CRP levels were independently related with low hemoglobin concentrations in non-dialysis kidney disease subjects (28). Some studies have also determined that albumin levels in patients with CKD are lower in those with anemia compared with those without anemia and that low serum albumin is an indicator of impaired erythropoietin response in patients with chronic hemodialysis (29, 30). In our study, serum albumin was also independently associated with anemia in multivariate analysis.

To our knowledge, the diagnostic accuracy of bone disease markers on anemia development has not been investigated in CKD patients. In our study, except for the moderate effect of phosphorus levels, other markers had minimal effect in discriminating the presence of anemia. Although there is statistical significance in multivariate regression models, ROC analysis results suggest that this significance does not appear to have relevant clinical implications.

We accept that this study includes some weaknesses. Except for a single-center and retrospective study, it was carried out in the Central Anatolia region, a geographical area where racial characteristics are dispersed homogeneously in CKD cases. Therefore, it can be interpreted that the findings may be questionable in terms of generalization and should be verified in separate populations. Another limitation of this study is that the factors that may affect the outcome variables such as serum erythropoietin, plasma FGF-23, IL-6 levels, and active smoking could not be obtained from records. In contrast, a strong aspect of this study is that the number of samples is comparably high enough to strengthen the statistical power and involve individuals in similar disease stages, and the patients are under regular follow-up of the nephrology department.

CONCLUSION

This study postulates that circulating calcium and phosphorus levels could be individually related to anemia in patients with chronic renal damage who do not require dialysis. Long-term studies and clinical trials assessing the effects of treatment methods that increase serum calcium or decrease phosphorus might be performed in order to examine alternative potential explanations of this relationship.

Ethics Committee Approval: Ethics committee approval was not received for this study due to the retrospective and anonymized nature of the study.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflict of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

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