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Article

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Correlation between anemia and phosphorus metabolism in patients with nondialysis chronic kidney disease

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[Abstract] This study investigated the correlation between anemia and phosphorus metabolism in patients with nondialysis chronic kidney disease (CKD). A total of 196 patients with nondialysis CKD with complete clinical information who were hospitalized in the Department of Nephrology at the Sixth Affiliated Hospital of Kunming Medical University from November 2021 to June 2022 were enrolled. Among these patients, 119 had anemia (anemia group), and 77 did not have anemia (nonanemia group). Univariate logistic regression analysis was performed to analyze the effects of diabetes mellitus (DM), hypertension, and the levels of serum phosphorus, blood calcium, high-sensitivity C-reactive protein (Hs-CRP), and 24-h urinary electrolytes on anemia. Multivariate logistic regression analysis using backward stepwise selection was then performed to further analyze the effect of each factor on anemia. DM, hypertension, the levels of corrected calcium, serum phosphorus, intact parathyroid hormone (iPTH), Hs-CRP, and 24-h urinary phosphorus, and the fractional excretion of phosphorus (FePi) (all $P < 0.05$) were correlated with the incidence of anemia in patients with CKD. Furthermore, there was a 5.82-fold increase, 0.12-fold decrease, and 0.04-fold increase in the risk of anemia for every 1-mmol/L increase in serum phosphorus (OR = 6.82, 95% CI: 1.32–35.11), 1-mmol/L increase in 24-h urinary phosphorus (OR = 0.88, 95% CI: 0.81–0.91), and 1-mg/dL increase in Hs-CRP (OR = 1.04, 95% CI: 1.01–1.07), respectively. The FePi and serum phosphorus and Hs-CRP levels were independent risk factors, and the 24-h urinary phosphorus level was an independent protective factor for anemia in patients with nondialysis CKD.

Keywords: chronic kidney disease (CKD), anemia, phosphorus metabolism, inflammation.

Introduction

Anemia is one of the most common complications of chronic kidney disease (CKD), and a reduced erythropoietin (EPO) level is the main cause of renal anemia, especially in patients undergoing dialysis. However, in addition to insufficient EPO production, ion metabolism also plays an

important role in anemia in patients with CKD. In patients with CKD, disorders of calcium and phosphorus metabolism usually occur in CKD stage 3, and anemia occurs in even earlier stages of CKD [1]. Therefore, the level of serum phosphorus lacks clinical value for guiding the diagnosis and management of complications in patients with early-stage CKD. Is there any other phosphorus metabolism-related indicator that may be altered in the early stage of CKD? The fractional excretion of phosphorus (FePi) begins to change in the early stages of CKD [2], but its relationship with anemia has not yet been reported. In this study, we collected data from patients with nondialysis CKD and analyzed the effects of phosphorus metabolism and related indicators on anemia to provide a theoretical basis for the early clinical management of anemia in patients with CKD.

Materials and methods

Study population

Patients with CKD with complete clinical information who were admitted to the Department of Nephrology at the Sixth Affiliated Hospital of Kunming Medical University from November 2021 to June 2022 were enrolled in this study. The inclusion criterion was patients who met the staging criteria for CKD in the Evaluation and Management of Chronic Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines [3]. The exclusion criteria were as follows: (1) age < 18 years; (2) combined bone malignancy; (3) combined severe infection; (4)

history of gastrointestinal bleeding in the last 3 months; (5) hematologic disorders; (6) primary parathyroid disease; (7) parathyroidectomy/renal transplantation; (8) pregnancy; and (9) incomplete clinical information. The relevant demographic characteristics, medication history, and laboratory test results of the individuals included in this study were collected. Patients with CKD were divided into anemia and nonanemia groups according to the World Health Organization (WHO) definition of anemia [4] (hemoglobin < 130 g/L in men and hemoglobin < 120 g/L in women).

Methods

Ethical approval

This study was approved by the ethics committee of the Sixth Affiliated Hospital of Kunming Medical University (approval number: 2021 kmykdx65107). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. All enrolled patients provided signed consent for participation in the research. Written informed consent for publication was obtained from all enrolled patients or their legal guardians. All patient data will be maintained with strict confidentiality, with robust measures implemented to safeguard against unauthorized disclosure or leakage of sensitive information.

General information

General information, including name, sex, age, height, weight, history of smoking, alcohol consumption, medication history, and medical history, was collected from the patients. Clinical and biochemical data for hemoglobin (Hb), creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), albumin (Alb), alkaline phosphatase (ALP), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood calcium, serum phosphorus, blood potassium, blood magnesium, blood sodium, blood chloride, intact parathyroid hormone (iPTH), 24-h urinary volume, 24-h urinary electrolytes, etc., were also collected. Moreover, FePi was calculated as follows: FePi = [24-h urinary phosphorus (mmol/L) × 1000]/[1440 (min) × serum phosphorus (mmol/L) × eGFR] × 100%. Additionally, the corrected blood calcium level was calculated as follows: corrected blood calcium level (mmol/L) = total serum calcium (mmol/L) + [40 - serum albumin (g/L)] × 0.02.

Laboratory index testing

The included patients fasted for more than 8 hours at night, and venous blood was collected from patients on an empty stomach early the next morning and sent for testing. Moreover, a 24-h urine sample was also retained during hospitalization and sent for testing the next day. Serum phosphorus, high-sensitivity C-reactive protein (Hs-CRP), and 24-h urinary electrolyte levels were examined with an automatic biochemical

analyzer (Bayer Model 1650).

Statistical analysis

The measurement data were first tested for normality. The data that conformed to a normal distribution are expressed as ($\bar{x} \pm s$) and were compared via t tests, whereas the data with a skewed distribution are expressed as the median (25th quartile, 75th percentile) [M (1/4, 3/4)] and were compared via the Mann–Whitney U test. Count data are expressed as n (%) and were compared via the chi-square test. Factors independently associated with anemia were analyzed via binary logistic regression. Differences were considered statistically significant at $P < 0.05$. Because the 24-h urinary protein and iPTH levels were not measured in some patients, the missing values were converted into and replaced by the mean values. SPSS 23.0 was used to perform all of the statistical analyses.

Results

A total of 196 patients were included in this study, including 129 (65.8%) males and 67 (34.2%) females. The patients were divided into anemia and nonanemia groups on the basis of their hemoglobin levels, and the incidence of anemia in the total patient population was approximately 60.71%. No statistically significant differences were observed in sex, age, the use of vitamin D and its analogs, smoking history, mean corpuscular volume (MCV), or ALP level between the two groups ($P > 0.05$). In contrast, the two groups presented significant differences in the presence

of diabetes mellitus (DM), the presence of hypertension, the use of ACEIs/ARBs, the use of FePi, and the levels of hemoglobin, serum iron, serum phosphorus, corrected blood calcium, calcium–phosphorus products, iPTH, Hs-CRP, 24-h urinary protein, 24-h urinary phosphorus, and 24-h urinary calcium ($P < 0.05$) (Table 1).

Table 1. Clinical and biochemical characteristics of the study population according to the presence or absence of anemia

Variables	Total (n = 196)	No anemia (n = 77)	Anemia (n = 119)	P value
Age, years	57.00 (48.0, 70.00)	56.00 (46.00, 67.00)	59.00 (50.00, 1.00)	0.121
Women, %	34.20	31.20	46.10	0.474
Smoking, %	41.80	42.90	41.20	0.816
Diabetes mellitus, %	35.20	26.00	41.20	0.030
Hypertension, %	76.50	68.80	81.50	0.041
Erythropoiesis-stimulating agents use, %	17.30	1.30	27.70	0.001
Vitamin D use, %	19.90	23.50	14.30	0.143
Vitamin D analogs use, %	9.20	6.50	10.90	0.294
ACEI/ARB use, %	31.6	45.50	22.70	0.001
Serum creatinine, μmol/L	186.5 (122.0, 409.0)	122.0 (101.00, 174.0)	329.0 (174.0, 533.0)	<0.001
Hemoglobin, g/L	117.36 ± 29.28	146.15 ± 15.52	98.57 ± 19.07	<0.001
MCV, fl	92.65 (88.90, 95.50)	92.80 (88.45, 96.35)	92.60 (89.10, 94.90)	0.785
Serum iron	12.41 ± 5.95	15.36 ± 5.37	10.49 ± 5.53	<0.001
Albumin-corrected serum calcium, mmol/L	2.22 (2.15, 2.29)	2.25 (2.18, 2.30)	2.19 (2.10, 2.28)	0.001
Serum phosphorus, mmol/L	1.23 (1.08, 1.47)	1.14 (1.00, 1.29)	1.29 (1.14, 1.56)	<0.001
Ca × P, $mmol^2/L^2$	2.71 (2.38, 3.19)	2.59 (2.25, 2.87)	2.84 (2.51, 3.43)	<0.001
Serum intact PTH, ng/L	126.3 (63.30, 249.80)	87.6 (57.6, 193.1)	180.4 (73.1, 312.4)	0.001
Serum albumin, g/L	38.30 (33.50, 42.20)	41.60 (38.00, 45.20)	36.70 (32.20, 39.30)	<0.001
Serum alkaline phosphatase, U/L	78.00 (59.00, 103.00)	77.00 (59.50, 97.50)	78.00 (59.00, 112.20)	0.394
Serum hsCRP, mg/L	2.64 (0.84, 10.92)	1.53 (0.62, 3.35)	4.40 (0.95, 19.58)	<0.001
24-h urinary protein excretion, g	1.13 (0.38, 2.81)	0.67 (0.38, 2.18)	1.68 (0.37, 3.28)	0.042
24-h urinary phosphorus excretion, mmol	9.54 (6.82, 14.63)	12.95 (9.31, 19.00)	8.46 (5.80, 12.42)	<0.001
24-h urinary calcium excretion, mmol	0.60 (0.30, 1.08)	0.93 (0.54, 1.43)	0.45 (0.19, 0.85)	<0.001
Fractional phosphorus excretion, %	0.18 (0.10, 0.31)	0.12 (0.89, 0.21)	0.21 (0.12, 0.34)	<0.001

Data are expressed as percentages, means ± SDs, or medians (interquartile ranges). Differences were considered statistically significant when $p < 0.05$.

Analysis of predictive factors for anemia in CKD patients

Univariate logistic regression analysis demonstrated that DM (P =

0.031), hypertension (P = 0.043), corrected blood calcium (P = 0.003), serum phosphorus (P < 0.001), iPTH (P = 0.011), Hs-CRP (P = 0.004), 24-h urinary phosphorus (P < 0.001), and FePi (*P* = 0.002) are predictive factors for anemia in patients with CKD. Factors with P < 0.05 in the univariate regression, as well as age and sex, were included in the further multivariate logistic regression analysis, which was performed via backward stepwise selection. The results demonstrated that the risk of anemia increased by 5.82-fold for every 1-mmol/L increase in serum phosphorus (OR = 6.82, 95% CI: 1.32–35.11) and decreased by 0.12-fold for every 1-mmol/L increase in 24-h urinary phosphorus (OR = 0.88, 95% CI: 0.81–0.91). Moreover, 33.35-fold and 0.04-fold increases in the risk of anemia were observed in patients for each 1% increase in FePi (OR = 34.346, 95% CI: 1.231–963.365) and a 1-mg/dL increase in Hs-CRP (OR = 1.04, 95% CI: 1.01–1.07), respectively. DM (P = 0.030) was an independent risk factor for anemia in CKD patients (Table 2).

Table 2. Results of the univariate and multivariate logistic regression analyses of the influence of variables on patients with CKD with anemia and without anemia.

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.018 (0.998–1.038)	0.083	1.002 (0.973–1.031)	0.916
Gender			-	
Male	1.249 (0.679–2.300)	0.474	0.683 (0.300–1.555)	0.364
Female	Reference		Reference	
Smoking			-	
Yes	0.933 (0.522–1.668)	0.816	-	
No	Reference		-	
DM			-	
Yes	1.995 (1.066–3.733)	0.031	2.554 (1.096–5.951)	0.030
No	Reference		Reference	

HP				
Yes	1.997 (1.023–3.896)	0.043	2.008 (0.817–4.933)	0.129
No	Reference		Reference	
Vitamin D or its analogs use				
Yes	1.889 (0.921–3.876)	0.083		
No	Reference			
Albumin-corrected serum calcium	0.044 (0.005–0.356)	0.003	0.162 (0.008–3.147)	0.229
Serum phosphorus	11.918 (3.745–37.930)	<0.001	6.817 (1.323–35.114)	0.022
iPTH	1.002 (1.001–1.004)	0.011	1.000 (0.999–1.001)	0.513
ALP	1.006 (0.998–1.014)	0.123	-	-
Hs-CRP	1.048 (1.015–1.081)	0.004	1.038 (1.007–1.071)	0.016
24-h urinary protein excretion	1.000 (1.000–1.000)	0.275	-	-
24-h urinary phosphorus excretion	0.877 (0.832–0.925)	<0.001	0.867 (0.811–0.928)	< 0.001
FePi	32.002 (3.610–283.699)	0.002	34.346 (1.231–963.365)	0.037

HP: hypertension; DM: diabetes mellitus; iPTH: serum intact PTH; FePi: fractional excretion of phosphorus. Differences were considered statistically significant when $P < 0.05$.

The differences in the serum phosphorus levels among the CKD stages were statistically significant (see Table 3). As shown in Figure 1, the serum phosphorus levels began to increase gradually after CKD stage 3, and there were significant intragroup differences. As shown in Figure 2, the FePi gradually increased as the CKD stage progressed, and the difference between the groups was statistically significant. Compared with the change in the serum phosphorus level, the significant change in the FePi occurred earlier in CKD stage 2 patients.

Table 3. Comparison of serum phosphorus levels by CKD stage

	CKD Stage					P value
	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5	
Serum phosphorus, mmol/L	1.25 (1.06, 1.35)	1.15 (0.99, 1.38)	1.12 (1.01, 1.38)	1.25 (1.09, 1.41)	1.58 (1.36, 1.89)	<0.001
FePi, %	0.08 (0.06, 0.10)	0.09 (0.05, 0.13)	0.12 (0.09, 0.19)	0.17 (0.13, 0.28)	0.34 (0.24, 0.44)	<0.001

The crude OR and adjusted OR of the serum phosphorus level for anemia and those for FePi for anemia calculated by the univariate and multivariate logistic regression models revealed that the OR increased

with increasing levels of serum phosphorus and FePi (Table 4 and Figure 3).

Table 4. Adjusted ORs (95% CIs) of the serum phosphorus level and FePi for anemia in various logistic models

Variables	OR (95% CI)	
	Crude	Adjusted
Serum phosphorus (mmol/L)	11.918 (3.745–37.930)[a]	5.089 (1.254–20.646)[c]
Q1	(Reference)	(Reference)
Q2	2.826 (1.015–5.146)[c]	1.995 (0.731–5.441)
Q3	2.210 (1.001–4.879)	1.628 (0.587–4.516)
Q4	9.143 (3.462–24.147)[a]	4.679 (1.429–15.326)[c]
FePi (%)	32.002 (3.610–283.699)[b]	7.702 (0.539–110.001)
Q1	(Reference)	(Reference)
Q2	1.780 (0.799–3.864)	1.600 (0.574–4.459)
Q3	3.625 (1.562–8.412)[c]	4.026 (1.317–12.312)[c]
Q4	4.471 (1.882–10.620)[a]	2.609 (0.823–8.271)

On the basis of the quartiles, the ORs of serum phosphorus and FePi were obtained via univariate logistic regression. Then, they were adjusted for age, sex, smoking history, the presence of DM, the presence of hypertension, the use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), the use of vitamin D and its analogs, the albumin level, the corrected calcium level, the serum iron level, the PTH level, and the 24-h urinary protein level with multivariate logistic regression to obtain adjusted ORs for the serum and urinary phosphorus levels. The lowest quartiles of the serum phosphorus level and FePi were used as reference values. [a] $P < 0.001$, [b] $P < 0.01$, and [c] $P < 0.05$. (Figure 3 and Figure 4)

figure 1:

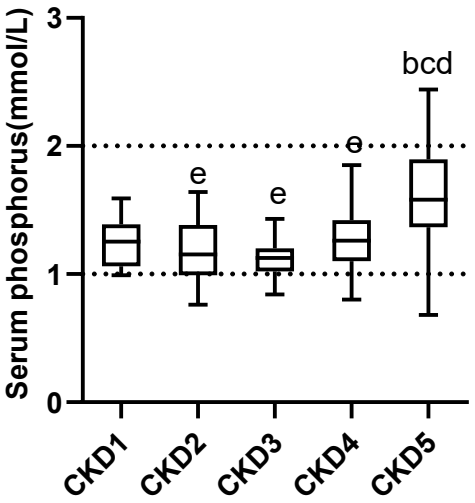
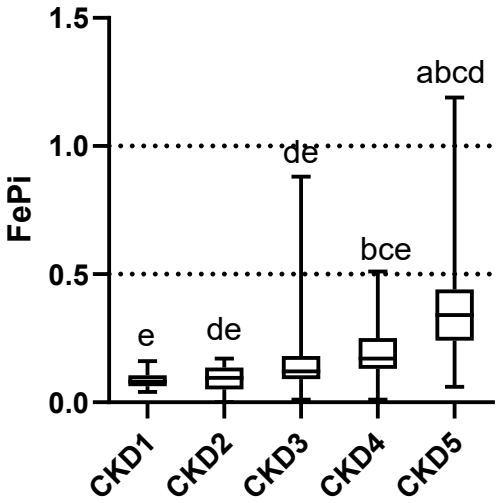


figure 2:

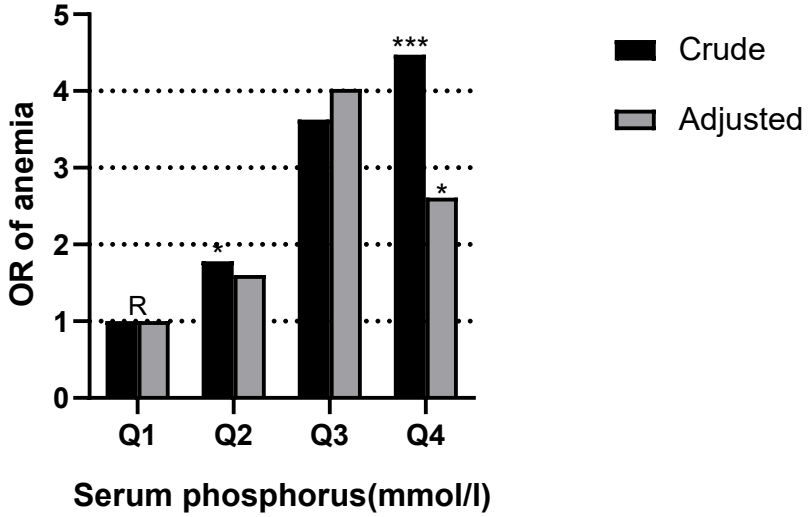


a represents CKD stage 1; b represents CKD stage 2; c represents CKD stage 3; d represents CKD stage 4; e represents CKD stage 5

Figure1： Crude OR of serum phosphorus in relation to anemia.

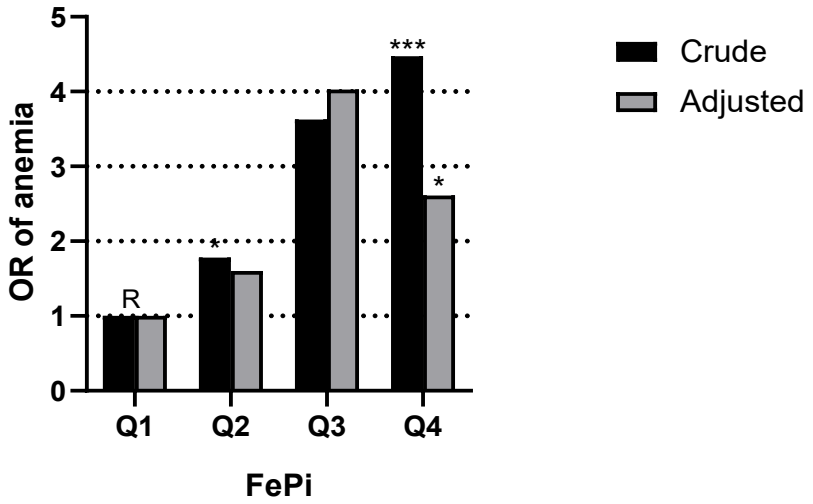
Figure2： Crude OR of FePi in relation to anemia.

figure 3:



(* P < 0.05, ** P < 0.01, *** P < 0.001).

figure 4:



(* P < 0.05, ** P < 0.01, *** P < 0.001).

Figure3： Multivariable-adjusted OR of serum phosphorus in relation to anemia.

Figure4： Multivariable-adjusted OR of FePi in relation to anemia.

Discussion

Anemia is the most common complication and early complication of CKD, and the incidence of CKD in patients with anemia is approximately 2–7 times greater than that in the general population. Anemia not only aggravates the progression of renal dysfunction in patients with CKD but is also an independent risk factor for concomitant cardiovascular disease [5, 6]. Previous studies have confirmed that[7] renal anemia is an associated factor in the development of left ventricular hypertrophy in patients with CKD, which can increase the probability of adverse cardiovascular events in patients. Therefore, the diagnosis and treatment of anemia are essential for the prognosis and survival of patients with CKD. Previous studies on anemia in patients with CKD have focused mainly on insufficient EPO production and a lack of raw materials for EPO

production. Very little attention has been given to the effect of phosphorus metabolism on anemia in patients with CKD. In this study, we collected data from patients with nondialysis CKD and demonstrated that the FePi was an independent risk factor, whereas 24-h urinary phosphorus was an independent protective factor for anemia in these patients. These findings have not been previously reported in the literature. CKD impairs phosphorus excretion due to reduced renal unit mass. Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) are overproduced in the early stages of CKD to prevent an increase in the serum phosphorus concentration [8]. Both PTH and FGF23 increase urinary excretion of phosphorus, and in contrast to FGF-23, PTH is associated with serum calcium due to the relative activation of the calcium-sensing receptor (CaSR). Indeed, PTH limits the gastrointestinal absorption of calcium because it decreases 1,25-dihydroxyvitamin D levels. This negative feedback maintains serum calcium and phosphorus within normal ranges in individuals with normal renal function. However, the progression of renal disease can lead to a failure of this balance, and hypocalcemia, hyperphosphatemia, and tertiary hyperparathyroidism may develop. FGF-23 is involved in pathways affecting hemoglobin levels and can cause a direct decrease in renal EPO secretion and blockade of red lineage progeny in the G2 phase of the cell cycle. Thus, an increase in FGF-23 levels impairs the differentiation of red lineage cells and their apoptosis [9]. In

patients with CKD, hyperphosphatemia tends to appear at approximately CKD stage 3 [10]. Even in patients with a normal serum phosphorus level, serum phosphorus is associated with endothelial dysfunction [11], vascular calcification, atherosclerosis [12], and other outcomes, including accelerated CKD progression [13] and increased risk of death [14]. Thus, phosphate homeostasis in humans is determined primarily by renal excretion rather than the serum phosphorus level [15]. Moreover, basic studies have confirmed that phosphate homeostasis, rather than the serum phosphate level, is associated with clinical outcomes [16]. Thus, compared with the serum phosphorus level, the FePi level exhibited greater early clinical value, as we demonstrated in this study, in which the FePi level began to change in CKD stage 2 patients. Bech et al. also demonstrated that the FePi changed early in patients with CKD and used it as a more economical alternative to fibroblast growth factor-23 (FGF-23) [2]. Bellasi et al. also demonstrated that, in nondialysis patients with normal serum phosphorus levels in CKD stages 3–5, more than 75% of patients had a higher-than-normal FePi [17]. Given the early clinical value of the FePi, is it clinically feasible to improve the prognosis of patients with CKD by performing phosphorus interventions to alter the FePi, even in the presence of a normal serum phosphorus level? Block et al. [18] performed a study on 148 patients with CKD who had a GFR of 20–45 mL/min/1.73 m^2 and demonstrated that, compared with those in the placebo group, the 24-h

urinary phosphorus in the group treated with phosphate-binding agents was reduced by 22%. In a placebo-controlled clinical trial of patients with nondialysis CKD, Block et al. [19] also demonstrated that ferric citrate significantly reduced FGF23 and serum phosphate levels in patients with elevated baseline serum phosphate levels (≥4.5 mg/dL) but not in patients with low baseline serum phosphate levels. In addition to controlling serum phosphate and FGF23 levels, iron citrate may have beneficial effects on CKD-associated anemia by increasing the levels of hemoglobin, ferritin, and transferrin saturation [20]. However, in patients with CKD who have normal or near-normal serum phosphorus levels, phosphate-binding agents promote the progression of vascular calcification [18]. Moreover, a meta-analysis also revealed that, in patients with nondialysis CKD in stages 2–5, the effects of sevelamer, lanthanum, and iron-based phosphate binding agents on the cardiovasculature, vascular calcification, and skeletal outcomes compared with those of placebo or conventional treatment were uncertain. Because they may lead to constipation and iron-based binding agents may lead to diarrhea [21], the safety and efficacy of using phosphate-binding agents in patients with CKD remain unclear. Thus, additional large-sample multicenter studies in the future may be needed to validate this conclusion.

This study demonstrated that the serum phosphorus level was an independent risk factor for anemia in patients with nondialysis CKD.

Previous studies have also demonstrated that patients with CKD have a greater chance of developing anemia when they have a high serum phosphorus concentration [22-25]. Furthermore, a study of patients who underwent dialysis and renal transplant reported that hyperphosphatemia was independently associated with anemia [26]. The mechanisms by which hyperphosphatemia leads to anemia in patients with CKD have been explained as follows: (1) a high serum phosphorus level may lead to increased polyamine production, which inhibits erythropoiesis [27]; (2) a high serum phosphorus level leads to the calcification of blood vessels, including renal arteries, which might ultimately lead to EPO deficiency and anemia [28]; and (3) hyperphosphatemia can also decrease vitamin D synthesis, resulting in hypocalcemia and elevated PTH levels, which could, in turn, directly inhibit erythropoiesis and induce hemolysis and bone marrow fibrosis in patients with CKD [29-32]. However, no relationship between PTH and anemia was demonstrated in the present study, which is consistent with the findings of Mauro et al. [22]. Therefore, there is no evidence that secondary hyperparathyroidism has direct effects on anemia, and it may exert its effect indirectly through other minerals.

In addition, this study demonstrated that the serum phosphorus and Hs-CRP levels affected the development of anemia simultaneously and independently. By adjusting for age, sex, the presence of DM, the presence of hypertension, and other confounding factors affecting anemia in the

logistic regression model, it was observed that the serum phosphorus and Hs-CRP levels were independent risk factors for anemia in patients with CKD. Briefly, the risk of anemia increased by 5.82-fold per 1-mmol/L increase in serum phosphorus (OR = 6.817, 95% CI: 1.323–35.114) and by 0.038-fold per 1-mg/dL increase in Hs-CRP (OR = 1.038, 95% CI: 1.007–1.071). Patients with CKD are known to have a chronic microinflammatory state, and the serum phosphorus level plays an important role in maintaining the inflammatory state in these patients. Clinical studies have demonstrated that phosphorus overload is independently associated with proinflammatory factors [33, 34]. However, the underlying mechanisms by which serum phosphorus stimulates inflammation remain unclear, but because the important steps of the inflammatory pathway are regulated by phosphorylation processes, it can be hypothesized that a high serum phosphorus level may trigger a phosphorylation-driven inflammatory signaling cascade [35-38]. Thus, it can be inferred that management with the purpose of maintaining the serum phosphorus level within the appropriate range may suppress the inflammatory response and thus indirectly ameliorate anemia.

CRediT statement

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Writing—review and editing: Liao X.;Li A.;Lu Y,X.

Disclosure statement

The authors report that there are no competing interests to declare.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Lu Y,X, upon reasonable request.

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