

Association of Dialysis Adequacy and Estimated Kidney Function with Mineral Metabolism Parameters in Patients Undergoing Peritoneal Dialysis

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Introduction. In terminal CKD, imbalance of calcium and phosphate can lead to complications such as skeletal and cardiovascular involvements. Disturbances in mineral metabolism are common among patients with advanced CKD and may be influenced by dialysis adequacy and estimated kidney function. We aimed to evaluate selected serum mineral metabolism parameters and their associations with dialysis adequacy and estimated kidney function in patients undergoing PD.

Methods. This cross-sectional study included 85 adult patients undergoing PD. eGFR was calculated using the CKD-EPI equation, and urea Kt/V was used as a measure of dialysis adequacy. An independent-samples t-test was used to compare calcium and phosphate levels between patients with Kt/V < 1.7 and those with Kt/V ≥ 1.7.

Results. The mean age was 55.91 ± 16.45 years, and 52.9% were male. The mean serum calcium level differed significantly according to the number of daily PD exchanges ($P = .034$). Tukey's post-hoc analysis showed a significant difference between patients receiving two and three exchanges per day ($P = .048$), with a higher mean calcium concentration in patients receiving two exchanges per day. Serum calcium showed a modest positive correlation with eGFR, while serum phosphate showed significant inverse correlations with urea Kt/V and eGFR. No significant differences in serum calcium or phosphate were observed between patients with Kt/V < 1.7 and those with Kt/V ≥ 1.7.

Conclusions. These findings suggest an association between dialysis adequacy, estimated kidney function, and selected biochemical parameters of mineral metabolism. However, the cross-sectional design does not permit causal inference.

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INTRODUCTION

Chronic kidney disease (CKD) involves a variety of pathophysiological processes with abnormal renal function and progressive decline in glomerular filtration rate.^{1,2} Disturbances in mineral metabolism are particularly common in advanced CKD and

include abnormalities in serum phosphate, calcium, PTH, vitamin D metabolism, and bone turnover.



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These abnormalities are important components of CKD-mineral and bone disorder (CKD-MBD) and have been associated with cardiovascular complications and adverse outcomes. Studies over the last 20 years have shown the impact of biochemical changes on the survival and quality of life of patients with CKD-MBD.^{3,4} Prevention and correction of hyperphosphatemia is a major goal of the treatment of CKD-MBD, so special attention must be given to phosphate balance.⁵ In terminal chronic kidney disease most patients have hyperphosphatemia, elevated parathyroid hormone (PTH) levels, elevated levels of Fibroblast Growth Factor 23 (FGF23), and low vitamin D levels because the calcium (Ca) and phosphate (Ph) control mechanisms are disrupted and inadequate. Previous studies have shown this imbalance disturbs the regulation of calcium and phosphorus levels in the blood which can lead to complications such as skeletal, cardiovascular, and sometimes, severe extracellular soft tissue involvement.^{3,6,7} High serum phosphate is the most important risk factor for cardiovascular disease. Therefore, control of serum phosphate levels should be considered one of the most important therapeutic goals in patients with CKD.^{5,8} A retrospective study conducted by Liu *et al.* indicated that serum calcium level of ≥ 9.5 mg/dL, serum phosphate levels of either ≥ 6.5 mg/dL or < 3.5 mg/dL and alkaline phosphatase (ALP) level of ≥ 100 IU/L were correlated with increased mortality, but higher serum levels of PTH did not have any association with increased mortality.⁹

Renal replacement therapy in patients with CKD consists of dialysis which has two forms: hemodialysis (HD) and peritoneal dialysis (PD). Xianglei Kong *et al.* documented that serum Ca and Ph levels were statistically higher ($P < .05$) in the HD patients in comparison with those of PD patients, but serum PTH level was statistically higher in the PD patients in comparison with those of HD patients ($P = .03$).¹⁰

PD may influence mineral metabolism through several mechanisms, including dialysis adequacy, residual kidney function, and the composition of the dialysis solution. In particular, the calcium concentration of the dialysate may influence calcium balance and PTH regulation. Glucose

concentration affects ultrafiltration and volume management, while icodextrin-containing solutions may provide sustained ultrafiltration during long dwell periods. These factors may indirectly influence the management of mineral metabolism abnormalities in PD patients.^{11,12}

Given the above, most studies of mineral metabolism disorders have been performed in patients undergoing hemodialysis, and fewer studies have been conducted in patients undergoing PD.

Furthermore, the relationship between dialysis adequacy and serum phosphate is clinically relevant because phosphate removal may occur through both peritoneal and residual renal clearance. Previous studies have suggested an association between phosphate clearance and measures of urea clearance in PD patients.¹³

The present study therefore aimed to evaluate selected serum mineral metabolism parameters, including calcium, phosphate, PTH, ALP, and vitamin D, and to determine their associations with dialysis adequacy and estimated kidney function in patients undergoing PD.

MATERIALS AND METHODS

This cross-sectional study has been verified by Isfahan University of Medical Sciences with ethical code "IR.MUI.MED.REC.1398.618" and was conducted in April 2020.

The study was conducted at Alzahra Hospital, affiliated with Isfahan University of Medical Sciences, Iran.

The study population consists of both male and female peritoneal dialysis patients from Alzahra Hospital who were chosen based on inclusion and exclusion criteria. Eighty-five patients who verified the inclusion criteria were selected.

Inclusion criteria include patients over the age of 18 who have been on peritoneal dialysis for at least 3 months and patients who have complete file information and tests.

Exclusion criteria include the patients who recorded any febrile infections in their medical records in the previous month, a history of metabolic disorders related to calcium and phosphate imbalances, and the patients who needed an acute change in the peritoneal dialysis solution in the

past month.

The data collected included variables of age, gender, underlying disease leading to renal failure, the type of peritoneal dialysis solutions, daily dialysis frequency, the serum levels of calcium, phosphate, parathyroid hormone, alkaline phosphatase, vitamin D, urea KT/V (which is considered a valid adequacy parameter concerning small solute clearance), and estimated Glomerular Filtration Rate (eGFR).¹⁴

The underlying causes of kidney disease were classified according to the diagnoses documented in the patients' medical records and included hypertension, diabetes mellitus, vesicoureteral reflux, polycystic kidney disease, nephrolithiasis, neurogenic bladder, glomerulonephritis, congenital kidney disease, trauma, and unknown/unspecified causes.¹⁵

All variables were extracted from the patient's medical record and laboratory tests.

Estimated GFR was calculated using the CKD-EPI equation and was considered an estimate of kidney function. In this study, eGFR was not considered equivalent to directly measured residual kidney function in patients receiving PD. Daily peritoneal dialysis exchanges included 2 to 6 times. Also, the type of peritoneal dialysis solutions included types 1.5, 2.5, and 4.25% glucose solutions and Extraneal solutions.

The last measured values of Serum levels of Ca, Ph, PTH, ALP, and Vitamin D were considered in the study. Furthermore, a 24-hour urinalysis test was used to calculate the patient's KT/V. Direct measurements of residual renal clearance and daily urine output were not systematically available for all participants and therefore could not be incorporated into the present analysis.

Statistical Analysis

Descriptive information for variables is expressed as mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables.

One-way analysis of variance was used to compare the mean of calcium, phosphate, PTH, ALP, and Vit D in patients according to the type of peritoneal dialysis solution and the number of peritoneal dialysis exchanges per day.

In cases in which analysis of variance was

significant, Tukey's post-test was used to identify the subgroups whose means were significantly different as well. Pearson correlation coefficient was also used to investigate the relationship between variables and dialysis adequacy and renal function. The Independent t-test was used to compare the mean serum levels of calcium and phosphate depending on the total KT/V < 1.7 and ≥ 1.7 . All statistical operations were performed using SPSS software at an error level of $P < .05$.

RESULTS

The average age of participants was (55.91 ± 16.45) years. In this study, about 53% of subjects were male, and hypertension was the most common cause of chronic kidney disease. The present study also showed that 42.4% (36) patients were with total KT/V < 1.7 and 57.6% (49) subjects ≥ 1.7 (Table 1).

One-way analysis of variance resulted in the mean serum levels of calcium, phosphate, PTH, ALP, and vitamin D were not different significantly depending on the type of peritoneal dialysis solution ($P \geq .05$) (Table 2).

These findings indicate that, within this study population, the recorded type of PD solution was not significantly associated with the evaluated mineral metabolism parameters. However, the relatively small number of patients in some solution categories limits the interpretation of these comparisons.

Also, the one-way analysis of variance resulted in the mean serum level of calcium being different

Table 1. Descriptive Results of Variables

Variables	Categories	n (%)
Age (Mean)	-	55.91 (16.45)
Sex	Male	45 (52.9)
	Female	40 (47.1)
Causes	Congenital	2 (2.4)
	DM	19 (22.4)
	GN	3 (3.5)
	HTN	41 (48.23)
	Nephrolithiasis	1 (1.2)
	Neurogenic bladder	1 (1.2)
	PCKD	2 (2.4)
	Trauma	2 (2.4)
	Unknown	9 (10.6)
	VUR	5 (5.9)
KT/V	< 1.7	36 (42.4)
	≥ 1.7	49 (57.6)

Table 2. Comparison of Bone Mineral Metabolism Indexes by the Type of Peritoneal Dialysis Solution

Variables	PD solutions	Mean	SE	P
Ca	1.5% glucose	9.1944	.28588	.626
	1.5 and 2.5% glucose	9.1083	.22001	
	1.5 and 2.5% glucose & Extraneal	9.0857	.16421	
	1.5% glucose & Extraneal	8.9000	.13744	
	2.5% glucose	9.6000	0	
	2.5% glucose & Extraneal	9.0357	.11749	
	Extraneal	10.4000	.	
Ph	1.5% glucose	4.4294	.23837	.179
	1.5 and 2.5% glucose	4.6667	.35018	
	1.5 and 2.5% glucose & Extraneal	4.7819	.35517	
	1.5% glucose & Extraneal	5.0278	.24466	
	2.5% glucose	4.5000	0	
	2.5% glucose & Extraneal	5.7000	.30777	
	Extraneal	5.1000	0	
PTH	1.5% glucose	458.1222	106.15942	.961
	1.5 and 2.5% glucose	488.6017	120.28541	
	1.5 and 2.5% glucose & Extraneal	398.8414	125.82693	
	1.5% glucose & Extraneal	334.0072	63.07728	
	2.5% glucose	355.0000	0	
	2.5% glucose & Extraneal	412.2571	107.46337	
	Extraneal	167.0000	0	
ALP	1.5% glucose	275.9444	27.23961	.582
	1.5 and 2.5% glucose	291.5833	28.28948	
	1.5 and 2.5% glucose & Extraneal	313.2381	28.43170	
	1.5% glucose & Extraneal	303.1667	47.13850	
	2.5% glucose	529.0000	0	
	2.5% glucose & Extraneal	385.0714	79.61048	
	Extraneal	288.0000	0	
Vit D	1.5% glucose	26.3833	3.53330	.869
	1.5 and 2.5% glucose	32.4558	9.38076	
	1.5 and 2.5% glucose & Extraneal	31.7714	6.39555	
	1.5% glucose & Extraneal	27.4617	5.06375	
	2.5% glucose	18.3000	0	
	2.5% glucose & Extraneal	21.6286	2.93743	
	Extraneal	18.9000	0	

significantly depending on the number of daily peritoneal dialysis exchanges ($P = .034$) (Table 3), and the mean of phosphate, PTH, ALP, and vitamin D were not showed different significantly ($P \geq .05$) (Table 3). Tukey's post-test results indicated that the calcium-mean-difference between patients who were on dialysis twice a day and those with 3 times a day, was significant ($P = .048$), which was higher in patients who were on dialysis twice a day (Figure).

Pearson correlation coefficient was done to evaluate the relationship between variables of serum levels of calcium, phosphate, PTH, ALP, and Vit D and the dialysis adequacy (KT/V) and eGFR. The relationship between calcium and eGFR

was significantly a direct relationship ($r = 0.22$, $P = .039$) (Table 4).

Serum phosphate showed significant inverse correlations with urea Kt/V ($r = -0.242$, $P = .026$) and eGFR ($r = -0.586$, $P < .001$) (Table 5).

The Independent t-test was done to compare the mean serum levels of calcium and phosphate depending on the total KT/V < 1.7 and ≥ 1.7 ($P = .458$). Similarly, the difference in mean serum phosphate between the two Kt/V groups did not reach statistical significance ($P = .062$) (Table 5).

Although serum phosphate was inversely correlated with Kt/V when Kt/V was analyzed as a continuous variable, categorization of Kt/V into < 1.7 and ≥ 1.7 did not demonstrate a statistically

Table 3. Comparison of Bone Mineral Metabolism Indexes by the Number of Peritoneal Dialysis Exchanges per Day

Variables	PD exchanges	Mean	SE	P
Ca	2	10.0333	.59255	.034
	3	9.0333	.13978	
	4	8.9731	.10342	
	5	9.2000	.14720	
	6	9.5000	.10000	
Ph	2	4.5717	.40481	.854
	3	4.7057	.21691	
	4	4.9808	.19765	
	5	5.0250	.61424	
	6	5.3500	.85000	
PTH	2	329.2000	89.91744	.841
	3	351.4976	51.01384	
	4	434.9071	68.92623	
	5	563.7500	341.05483	
	6	282.0000	73.00000	
ALP	2	367.3333	30.13267	.172
	3	260.3714	38.30322	
	4	313.3308	19.34578	
	5	466.0000	258.84390	
	6	440.0000	89.00000	
Vit D	2	23.1667	5.61199	.719
	3	22.5952	2.84599	
	4	30.4169	3.74717	
	5	30.4500	7.07124	
	6	24.4500	6.15000	

Table 4. The Relationship Between Bone Mineral Metabolism Indexes with Dialysis Adequacy and Residual Renal Function

Variables	eGFR	KT/V
Ca		
Pearson correlation	.224*	-.145
P	.039	.184
Ph		
Pearson correlation	-.586*	-.242*
P	.000	.026
PTH		
Pearson correlation	-.097	.125
P	.376	.255
ALP		
Pearson correlation	.126	-.154
P	.251	.160
Vit D		
Pearson correlation	-.140	-.016
P	.202	.885

significant difference in mean phosphate levels.

DISCUSSION

The present study evaluated selected biochemical parameters of mineral metabolism in patients undergoing PD and examined their associations with dialysis adequacy and estimated kidney function. The main findings were that serum calcium differed

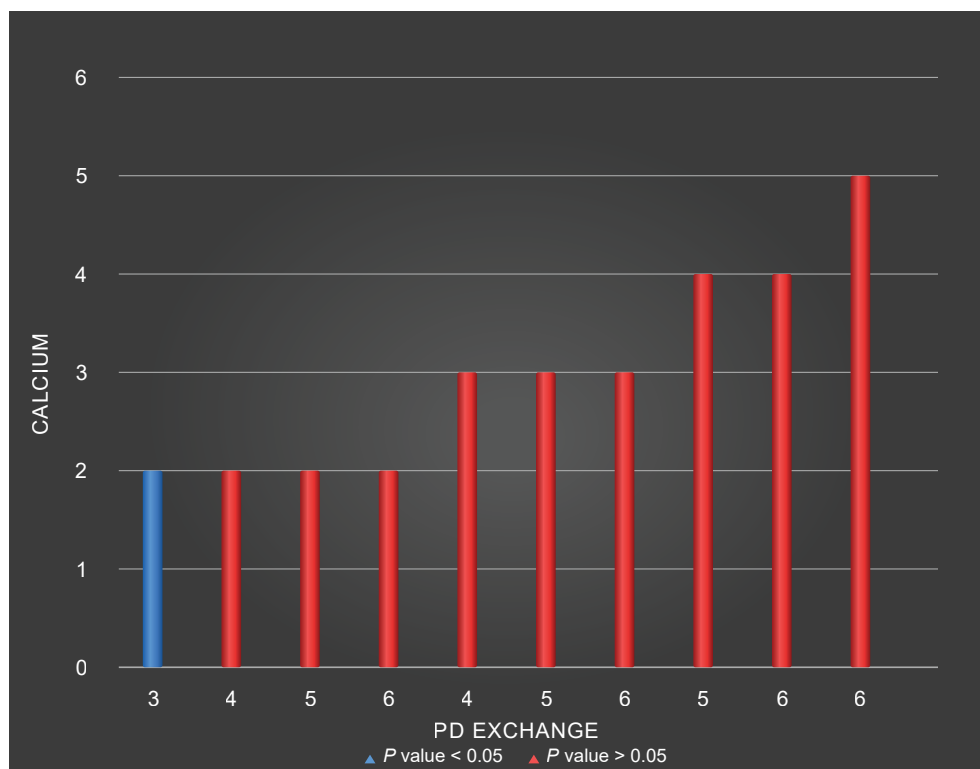
**Figure 1.**

Table 5. The Comparison of the Mean Serum Levels of Calcium and Phosphate, Depending on the Total KT/V < 1.7 and ≥ 1.7

KT/V	Mean	STD	P (independent t-test)
Ca			
< 1.7	9.1639	.88387	.458
≥ 1.7	9.0286	.73824	
Ph			
< 1.7	5.1953	1.42292	.062
≥ 1.7	4.6739	1.11793	

according to the number of daily PD exchanges, serum calcium was positively correlated with eGFR, and serum phosphate was inversely correlated with both eGFR and urea Kt/V. The results revealed that the mean of serum Ca level was different depend on the number of dialysis sessions.

However, this finding should be interpreted cautiously. Although the overall ANOVA was statistically significant, the only significant pairwise comparison was between the groups receiving two and three exchanges per day. PD prescriptions are individualized according to several clinical factors, including volume status, solute clearance, residual kidney function, and patient characteristics. Therefore, confounding by treatment indication cannot be excluded.

Although it is not clear whether low levels of Ca are detrimental, high levels are known to be associated with a poor prognosis.^{16,17} Vascular calcification due to a high level of Ca is an important pathological condition that affects survival prognosis. Also, the prevalence of aortic and cardiac valve calcification is much higher in patients with higher serum adjusted-calcium levels.¹⁸ In the present study, however, clinical outcomes such as vascular calcification, bone density, fractures, or cardiovascular events were not directly evaluated. Therefore, our findings should be interpreted as associations involving biochemical mineral metabolism parameters rather than a comprehensive assessment of CKD-MBD.

Chen Z *et al.* have come to this conclusion that the combination of low serum PTH and high serum ALP levels was independently associated with higher cardiovascular mortality in peritoneal dialysis patients.¹⁹ Doi *et al.* documented that a serum calcium level > 8.5 mg/dL at hemodialysis initiation was associated with poor outcomes one

year after dialysis initiation,²⁰ but only a few other reports have described similar findings. Thus, managing of Ca level is more important in the dialysis process.

The finding of the present cross-sectional study suggests a direct relationship between eGFR and serum Ca in men and women selected from a population sample, but this relationship does not indicate a cause-and-effect one. Because this study was cross-sectional, the observed association does not establish a causal relationship. It cannot be determined whether lower calcium levels contribute to declining kidney function or whether reduced kidney function contributes to alterations in calcium metabolism.

Therefore, it not simply means that lower serum Ca levels impair kidney function, or, conversely, that lower serum Ca levels are a consequence of a rapid decrease in GFR. A 1-year follow-up study of a general non-CKD Japanese population, documented that lower serum Ca levels, even when they were within a normal physiological range, were a significant risk factor for a rapid decrease in GFR, independent of metabolic risk factors for kidney dysfunction such as blood pressure, diabetes and dyslipidemia. In the above-mentioned study, multivariable correlation analysis revealed serum Ca levels as the best correlated with GFR variation after adjustment with multiple factors ($\beta = 0.184$, $P < .001$). It means that serum Ca level is related to several factors such as serum level of Vit D and PTH; lower serum Ca level appears not to be simply a reflection of existing or current kidney dysfunction but is a reflection of a steady or rapid decrease in GFR.²¹ Also, we found an inverse relationship between serum Ph and eGFR and peritoneal dialysis adequacy, KT/V.

The inverse association between serum phosphate and eGFR is biologically plausible because declining kidney function reduces renal phosphate excretion and may lead to phosphate retention.²² The inverse association between serum phosphate and Kt/V may reflect the contribution of adequate dialysis to phosphate removal. Previous studies have reported associations between phosphate clearance and urea clearance in patients undergoing PD.²³ However, Kt/V is primarily a measure of small-solute clearance and does not directly quantify phosphate

clearance. Serum phosphate is also influenced by dietary phosphate intake, phosphate binder therapy, residual kidney function, bone turnover, and other factors.²² Therefore, the observed association should not be interpreted as evidence of a causal effect of increasing Kt/V on serum phosphate. Serum phosphate is used to monitor Ph retention that is a consequence of low glomerular filtration rate and a determinant of severe metabolic bone disease and the cardiovascular system of patients with kidney failure.²⁴ In agree with our findings, John GB *et al.* in a prospective cohort analysis including 1492 patients indicated when the glomerular filtration rate decreases, serum phosphate level increases, and becomes especially significant in CKD stage G4.²⁵ Selamat U *et al.* showed in patients with GFR of less than 30 mL/min/ 1.73 m² serum phosphate concentration increased because renal function decreased.²⁶ An inverse relationship between kidney function and serum Ph could be explained by changes in the level of parathyroid hormone.^{27,28} Phosphatonins²⁹ and active vitamin D^{30,31} secondary to GFR reduction.

To investigate whether dialysate calcium concentrations were significantly associated with cardiac function, in a study conducted by Wang Z *et al.*, a total of 60 PD patients were registered, with a calcium content of the PD solution of 1.25 mmol/L in 30 patients (low-calcium group) and 1.75 mmol/L in 30 patients (standard-calcium group). They showed that no significant difference in calcium, phosphorus, parathyroid hormone (PTH), blood pressure, etc., have been found between the two groups after 12-month follow-up. The same study also showed that residual renal function, which is associated with left ventricular diastolic function, was significantly decreased in the standard-calcium group in comparison with the low-calcium group (5.64 ± 3.23 vs. 9.38 ± 3.17 ; $P = .001$). The data collected by the above-mentioned researchers suggested that low calcium dialysate treatment is significantly associated with better left ventricular diastolic function.³²

Hence, the limited information on dietary factors should have played a minor role, if any. Another possible limitation was the collection of data on a single ethnic group residing in one town. An inverse relationship between KT/V and serum Ph

level in this study could be explained by the higher phosphate clearance that was associated with lower serum phosphorus. Joana Santos *et al.* evaluated if peritoneal phosphate clearance correlates to urea clearance in patients with peritoneal dialysis, and regression analysis in this study showed that phosphate clearance was associated with creatinine clearance ($r = 0.87$, $P < 0.001$) and with urea KT/V ($r = 0.74$, $P < .001$), also a negative correlation between peritoneal phosphate clearance and serum phosphate ($r = -5.19$, $P < .001$) but no correlation was found to PTH.³³ Also similar to the present study, Malgorzata Debowska *et al.* found that in automated peritoneal dialysis patients, the peritoneal and total phosphate clearances correlated positively with peritoneal and total urea KT/V, respectively. Also higher phosphate clearance was associated with lower serum phosphorus,³⁴ but in another study no correlations were found between KT/V and biochemical outcomes such as hemoglobin ($P = .4922$), calcium ($P = .650$), phosphate ($P = .508$), and phosphatase ($P = .091$) in hemodialysis patients.³⁵

These findings are consistent with our observation that phosphate was inversely correlated with Kt/V. Nevertheless, differences in study populations, dialysis prescriptions, residual kidney function, dietary intake, and medication use should be considered when comparing these findings.

An important point is that the continuous correlation between phosphate and Kt/V should be distinguished from the categorical comparison according to $Kt/V < 1.7$ versus ≥ 1.7 . In our study, the continuous correlation was statistically significant ($r = -0.242$, $P = .026$), whereas the difference in mean phosphate between the two Kt/V categories was not statistically significant ($P = .062$). Categorization of a continuous variable can reduce statistical information and statistical power and may therefore result in different findings.

Regarding PD solution type, dialysate composition may influence mineral metabolism. Dialysate calcium concentration can affect calcium balance and PTH regulation, whereas glucose concentration influences ultrafiltration and volume management. Icodextrin-containing solutions may provide sustained ultrafiltration during long dwell periods.¹¹

In our study, no significant differences in calcium, phosphate, PTH, ALP, or vitamin D were observed according to PD solution type.

This finding should be interpreted cautiously because some solution categories contained relatively few patients. In addition, the selection of PD solution is individualized and may depend on clinical factors such as fluid status and dialysis requirements. Therefore, confounding by indication cannot be excluded.

The underlying cause of kidney disease may also influence mineral metabolism through differences in disease duration, comorbidities, nutritional status, inflammation, residual kidney function, and treatment patterns. Although the underlying kidney disease was recorded in our study, the relatively small sample size and the small number of patients in several individual disease categories prevented reliable subgroup analyses. Therefore, we cannot determine whether the underlying cause of CKD independently influenced mineral metabolism parameters.

Limitations

This study has several limitations. First, its cross-sectional design prevents assessment of temporal relationships and causal inference. Therefore, the observed associations between mineral metabolism parameters, eGFR, and Kt/V should not be interpreted as causal relationships.

Second, the study was conducted at a single center and included a relatively small number of patients. This limits the generalizability of the findings and reduced the ability to perform reliable subgroup analyses according to underlying kidney disease or specific PD prescriptions.

Third, detailed information regarding medications that may affect mineral metabolism, including vitamin D analogues, calcium supplements, phosphate binders, and calcimimetics, was not systematically available in the dataset. Consequently, treatment-related confounding could not be assessed or adjusted for.

Fourth, detailed information regarding dietary phosphate intake, nutritional status, inflammatory markers, and other factors that may affect serum phosphate and calcium was not comprehensively available.

Finally, some categories of PD solution type and exchange frequency included relatively few patients, which may have limited statistical power and increased uncertainty in subgroup comparisons.

CONCLUSION

Among patients undergoing peritoneal dialysis, serum phosphate was inversely associated with both urea Kt/V and eGFR, while serum calcium showed a modest positive association with eGFR. Serum calcium also differed according to the number of daily PD exchanges.

However, categorization of patients according to Kt/V < 1.7 versus ≥ 1.7 did not demonstrate significant differences in serum calcium or phosphate.

These findings suggest that dialysis adequacy and estimated kidney function may be associated with selected biochemical parameters of mineral metabolism in patients undergoing PD. However, the cross-sectional design, limited sample size, and lack of detailed information on medications and directly measured residual kidney function limit causal interpretation. Further prospective studies incorporating residual renal clearance, daily urine output, medication use, dietary factors, and longitudinal mineral metabolism measurements are warrant.

DECLARATIONS

Disclosure

Nothing to disclose.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Author's Contributions

Mojgan Mortazavi carried out the presented idea and supervised the findings of this work. Romina Rahimifar helped for data collection and analytic

calculation. Shiva Seirafian helped supervise the project and analytic calculation. Pantea Miralaei wrote the manuscript with support from other authors. All authors discussed the results and contributed to the final manuscript.

Conflict of Interest Statement

there is no conflict of interest in our study.

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