Can Calcium, Phosphate, Calcium Phosphate Product and Intact Parathyroid Hormone Levels Be Appropriately Controlled in Dialysis Patients?

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Key Words

Dialysis • Kidney Disease Outcome Quality Initiative • Vitamin D • Phosphate • Parathyroid hormone • Mineral metabolism

Abstract

Objective: To review the target levels of calcium (Ca), phosphate (P), calcium phosphate products ($\text{Ca} \times \text{P}$) and intact parathyroid hormone (iPTH) levels in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD) and compare them with the Kidney Disease Outcome Quality Initiative (K/DOQI) recommendations. **Subjects and Methods:** Three hundred and fifty-seven patients who had been undergoing dialysis for more than 3 months were included. Patients who had undergone a parathyroidectomy were excluded. The levels of Ca, P, iPTH and $\text{Ca} \times \text{P}$ were monitored for the last 3 months. The Ca and P levels were measured by standard techniques, and iPTH was assessed by the intact molecule assay. **Results:** Between HD and PD patients, there was no statistically significant difference for age, duration of dialysis or primary disease causing end-stage renal disease. The percentage of patients whose serum Ca, P, $\text{Ca} \times \text{P}$ product and iPTH were within K/DOQI recommended target ranges were

61.2, 66.4, 82.2 and 28.3% in HD patients, and 56.3, 60.6, 85.9 and 22.5% in PD patients, respectively. When all results for each group – HD and PD – were analyzed, 12.8% of patients had all 4 markers within the target range. **Conclusion:** Achieving target ranges of mineral markers is important in dialysis patients, but reaching K/DOQI target levels is difficult. Hence, physicians should be careful in using P binders and vitamin D analogs to achieve the normal ranges.

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Introduction

Abnormalities in mineral metabolism are common in chronic kidney disease (CKD). The changes in mineral abnormalities begin in the early stages of CKD (stage 3 CKD glomerular filtration rate $<60 \text{ ml/min/1.73 m}^2$). Common features of abnormalities include hypercalcemia, hyperphosphatemia, hyperparathyroidism or suppression of parathyroid hormone secretion and impaired

This work was presented at the 12th Congress of the International Society for Peritoneal Dialysis, Istanbul, Turkey, June 21–24, 2008.

production of calcitriol [1]. These changes may lead to bone and musculoskeletal diseases such as high-turnover bone disease, adynamic bone disease and mixed bone disease [2].

The increased risk of cardiovascular disease (CVD) is well established in patients with CKD. Several risk factors are responsible for the development of CVD such as age, gender, diabetes mellitus, smoking and albuminuria [3]. Disturbances in mineral metabolism not only affect the bone system, but are also associated with increased risk of all causes of cardiovascular hospitalization in CKD [4–6]. Due to these adverse outcomes of abnormal mineral metabolism, the Kidney Disease Outcome Quality Initiative (K/DOQI) published clinical practice guidelines for bone metabolism in 2003 [2]. This guideline recommended strict target ranges for calcium (Ca) of 8.4–9.5 mg/dl, phosphate (P) of 3.5–5.5 mg/dl, calcium $\times$ phosphate product (Ca $\times$ P) of <55 and intact parathyroid hormone (iPTH) of 150–300 pg/ml in patients receiving dialysis [2]. As previous studies have reported, achieving the Ca, P, iPTH and Ca $\times$ P product target levels mentioned in this guideline is very difficult for both dialysis and early-stage CKD patients. The authors of these studies have determined that many patients have suboptimal control of minerals and iPTH [7–11].

In the present study, we aimed to analyze our patients' dialysis (hemodialysis, HD, and peritoneal dialysis, PD) measurements and compare them with the K/DOQI recommendations.

Subjects and Methods

This retrospective study included 286 HD patients who received regular hemodialysis lasting from 3.5 to 4 h, thrice weekly from Gazi University Hemodialysis Center and RFM Dialysis Center (males/females: 186/100) with the mean age of 50.55 ± 16.63 years and 71 PD patients who were followed up in our center (males/females: 38/33) with the mean age of 46.04 ± 14.31 years. All participants had been undergoing dialysis for more than 3 months. The duration of dialysis was 47.51 ± 43.11 months for HD and 47.29 ± 43.96 months for PD patients. Both HD and PD patients were prescribed dialyzate containing 1.5 mmol/l (3 mEq/l) Ca. The following data were recorded: the duration of dialysis, primary disease causing end-stage renal disease, albumin-corrected serum Ca using the formula recommended by the K/DOQI, i.e. corrected Ca + $0.8 \times (4 - \text{albumin})$ [2], and P, iPTH, Ca $\times$ P products from the usage of phosphorus-binding agents and vitamin D analogs and dosages. We examined the last 3 months' values between September and November 2008. Mid-month blood samples were taken from HD patients prior to hemodialysis. We excluded patients who had undergone a parathyroidectomy. Ca and P levels were measured

using standard biochemical techniques (colorimetric method) whereas iPTH levels were determined with the immunochemiluminometric assay (Roche Switzerland for both PD and HD patients). Patients using vitamin D analogs received oral or intravenous calcitriol, and Ca acetate, Ca carbonate, sevelamer, aluminum hydroxide and the combination drugs were used as P binders.

Data were analyzed using SPSS for Windows (version 11.0) and expressed as means $\pm$ standard deviation. To compare the mean of quantitative variables between groups, Student's *t* test was used. The χ^2 test was used to compare the differences in categorical variables. A *p* value less than 0.05 was considered statistically significant.

Results

Demographic characteristics are summarized in table 1. Sixteen PD patients used continuous cyclic peritoneal dialysis, 5 used nocturnal intermittent PD and 50 used the continuous ambulatory PD type. Between HD and PD patients, there was no statistically significant difference for age or duration of dialysis. The mean Kt/V was 1.27 ± 0.15 and 1.40 ± 0.74 in HD and PD patients, respectively. The mean mineral metabolism data are presented in table 1. The respective percentages of HD and PD patients within the range of K/DOQI target recommendations were 61.2 and 56.3% for Ca, and 66.4 and 60.6% for P. There was no difference between the two groups ($p > 0.05$). The average of Ca $\times$ P products was 4.65 ± 12.11 mg²/dl² in HD patients and 40.87 ± 11.4 mg²/dl² in PD patients although the Ca $\times$ P value for PD patients was lower than that of HD patients. Both groups had favorable percentages for target values: 82.2% in HD and 85.9% in PD patients. The mean iPTH levels were significantly lower in HD patients than in PD patients ($p = 0.005$). At the same time, 48.6% of HD patients had serum iPTH levels below the recommended range, whereas 50.7% of PD patients had levels over it ($p < 0.0001$). Only 28.3% of HD and 22.5% of PD patients reached the target range for iPTH. Medication results are presented in table 1. Although the vitamin D analog nonuser average was higher in the HD than PD group ($p < 0.0001$), the mean calcitriol dosage was higher in HD patients (0.4 ± 0.12 μ g/week in HD, 0.20 ± 0.22 μ g/week in PD patients; $p < 0.0001$).

In both groups, 12.8% of patients had all 4 markers within the target range. Seven of the HD patients and 2 of the PD patients had all 4 markers within the target range. The results of all patients are summarized in table 2.

Table 1. Characteristics of patients

	HD (n = 286)	PD (n = 71)	p
Age, years	50.55 ± 16.63	46.04 ± 14.31	n.s.
Gender (M/F)	186/100	38/33	0.03
Duration of dialysis, months	32 ± 48.11	37 ± 46.96	n.s.
Primary disease, %			
Glomerulonephritis	13.3	14.1	
Diabetes mellitus	14.7	14.1	
Hypertension	20.6	29.6	
Amyloidosis	4.2	8.5	
Nephrolithiasis	9.1	11.3	–
Unknown	34.3	14.1	
Others	3	7	
Ca, mg/dl	9.13 ± 0.81	8.89 ± 0.94	n.s.
P, mg/dl	4.9 ± 1.3	4.6 ± 1.17	n.s.
iPTH, pg/ml	275.80 ± 367.91	432.52 ± 414.52	0.005
Ca × P, mg ² /dl ²	44.65 ± 12.11	40.87 ± 11.4	0.01
Kt/V	1.26 ± 0.15	1.59 ± 0.74	
Ca-containing phosphate binders, mg/day	1,075 ± 437	965 ± 375	<0.001
Vitamin D analog use, %			
Nonuser	80.1	48.5	
User	19.9	51.5	<0.001
Phosphate binder usage, %			
Nonuser	9.1	32.4	
Ca carbonate	4.9	4.2	
Ca acetate	71.3	53.5	
Sevelamer	13.6	2.8	
Aluminum hydroxide	–	1.4	–
Sevelamer + Ca acetate	1	1.4	
Calcitriol dosage, µg/week	0.4 ± 0.12	0.20 ± 0.22	<0.001
Means ± standard deviation. M = Male; F = female; n.s. = nonsignificant.			

Table 2. Comparison with K/DOQI target values (% patients)

		HD (n = 286)	PD (n = 71)	p
Ca	<8.4 mg/dl	13.3	21.1	
	8.4–9.5 mg/dl	61.2	56.3	
	>9.5 mg/dl	25.5	22.5	n.s.
P	<3.5 mg/dl	10.8	16.9	
	3.5–5.5 mg/dl	66.4	60.6	
	>5.5 mg/dl	22.7	22.5	n.s.
Ca × P	<55 mg ² /dl ²	82.2	85.9	n.s.
	>55 mg ² /dl ²	17.8	14.1	
iPTH	<150 pg/ml	48.6	25.4	
	150–300 pg/ml	28.3	22.5	
	>300 pg/ml	23.1	50.7	<0.0001
n.s. = Nonsignificant.				

Discussion

In this study, we observed that we could achieve target serum Ca, P and Ca × P product values in both HD and PD patients. However, success levels were low in both groups in reaching target iPTH values. Only 28.3% of HD patients and 22.5% of PD patients reached the recommended percentages of iPTH. Among HD patients, most (48.6%) individuals had lower values than the recommended range (<150 pg/ml), and 23.1% had values above the recommended levels, whereas in PD patients 25.4% of patients are below the target range and half (50.7%) of the patients are above 300 pg/ml. The observed difference in iPTH values between HD and PD patients could be due to the fact that a higher dose of calcitriol was used in the HD group. When we analyzed all of the Ca, P, Ca × P

products and iPTH results, only 12% of patients achieved recommended ranges for all. Our iPTH values were not consistent with those reported in the 2007 Turkish registry [12]; our values were too high in PD and too low in HD patients. Comparing these results with the large multicenter Dialysis Outcome and Practice Pattern Study which only included patients receiving HD [6], our results were more favorable for Ca, P, Ca $\times$ P products, whereas iPTH levels were similar with those of the Dialysis Outcome and Practice Pattern Study. Our findings are not unique as several previous studies have all suggested that it is difficult to gain and maintain the target values of mineral metabolism recommended by the K/DOQI [6, 8, 9, 11].

CKD is an independent risk factor for CVD. Therefore, appropriate prevention and treatment strategies must be used to reduce the morbidity and mortality from CVD [13]. There is also a strong association between mineral metabolism disturbance and CVD in CKD [4–6]. As previous studies have reported, as nontraditional risk factors, hyperphosphatemia, elevated Ca $\times$ P products and hyperparathyroidism appear to increase the risk of cardiovascular mortality and morbidity [4–6]. A recent meta-analysis emphasized this important association [14].

In 2003, the K/DOQI published guidelines to manage mineral metabolism. They recommended the following target levels for Ca, P, Ca $\times$ P products and iPTH, respectively: 8.4–9.5 mg/dl, 3.5–5.5 mg/dl, $<55 \text{ mg}^2/\text{dl}^2$ and 150–300 pg/ml [2]. The treatment of abnormal mineral metabolism includes nonpharmacological treatment such as restriction of dietary P and Ca intake. Its pharmacological treatment includes P binders (Ca-based P binders or non-Ca-, non-aluminum-, non-magnesium-containing P binders like sevelamer hydrochloride and lanthanum carbonate), and vitamin D analogs and calci-

mimetics (cinacalcet hydrochloride) [2]. To protect patients with end-stage renal disease from cardiovascular events, target levels should be attained. However, as previous studies have reported, it is difficult to reach these targets in CKD [6–11]. In a recent publication of Kidney Disease Improving Global Outcomes recommendations, the PTH ranges were widened and diverged from the K/DOQI guidelines [15]. The Canadian Society of Nephrology Mineral Metabolism Guidelines recommend giving priority to P and Ca targets over the management of PTH [11]. Our study results are favorable according to both of these guidelines. In recent years, Ca and P management have been considered more important than PTH management. Nevertheless, it is important to remember that PTH has important effects on bone metabolism and the cardiovascular system.

Our study has several limitations. First, we did not determine the dialysis dose and frequency of our patients. Most of our patients underwent HD 3 times per week, but some patients were treated twice weekly. Second, we did not collect the data of the patient-dietitian session, which significantly reduces PO₄ management [11]. Third, because of the nonaccess to cinacalcet in our country, we were not able to determine the effects of cinacalcet on PTH.

Conclusion

Achieving target ranges of mineral markers is important in dialysis patients, but reaching K/DOQI target levels is difficult. Hence, physicians should be careful in using P binders and vitamin D analogs to achieve the normal ranges.

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