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Serum calcium and phosphorus levels in patients undergoing maintenance hemodialysis: A multicentre study in Korea

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Abstract

Background: In many countries, nephrologists follow clinical practice guidelines for mineral bone disorders to control secondary hyperparathyroidism (SHPT) associated with abnormal serum calcium (Ca) and phosphorus (P) levels in patients undergoing maintenance hemodialysis (MHD). The Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines have long been used in Korea, and this study was undertaken to investigate the current status of serum Ca and P control in MHD patients.

Methods: Data were collected from a total of 1,018 patients undergoing MHD without intercurrent illness, in 17 hemodialysis centers throughout the country. Serum levels of Ca, P, and intact parathyroid hormone (iPTH) were measured over 1 year, and the average values were retrospectively analyzed.

Results: Serum levels of Ca, P, and the Ca × P product were 9.1 ± 0.7 mg/dL, 5.3 ± 1.4 mg/dL, and 48.0 ± 13.6 mg^2/dL^2, respectively. However, the percentages of patients with Ca, P, and Ca × P product levels within the KDOQI guideline ranges were 58.7%, 51.0%, and 70.7%, respectively. Of the 1,018 patients, 270 (26.5%) had iPTH > 300 pg/mL (uncontrolled SHPT), whereas 435 patients (42.7%) showed iPTH

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< 150 pg/mL. Patients with uncontrolled SHPT had significantly higher values of serum Ca, P, and Ca × P product than those with iPTH ≤ 300 pg/mL.
Conclusion: Despite the current clinical practice guidelines, SHPT seems to be inadequately controlled in many MHD patients. Uncontrolled SHPT was associated with higher levels of serum Ca, P, and Ca × P product, suggestive of the importance of SHPT management.

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Introduction

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD). In addition, hyperphosphatemia has emerged as an important clinical issue in dialysis patients over the past decade because higher levels of serum phosphorus (P) and calcium–phosphorus (Ca × P) product have now been associated with increased vascular calcification and cardiovascular mortality [1–6]. Similar to other countries, the number of patients with end-stage renal disease (ESRD) has been increasing in Korea. According to 2010 registry data from the Korean Society of Nephrology, hemodialysis was the most frequently used renal replacement therapy (in 39,509 patients) among the total 58,860 patients with ESRD. Diabetes mellitus was the leading cause of ESRD (45.2%), and cardiovascular disease was the major cause of death (45%) in patients undergoing dialysis [7].

To improve the quality of care in patients undergoing maintenance hemodialysis, clinical practice guidelines have been developed and used in many countries. Globally, including Korea, the Kidney Disease Outcome Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are popular [8,9]. In the Asia-Pacific area, Australia and Japan have their own guidelines for CKD-mineral bone disorder (MBD) management (Caring for Australasians with Renal Impairment [CARI] and Japanese Society for Dialysis Therapy [JSDT] guidelines, respectively) [10,11]. In these guidelines, target ranges for serum minerals have been recommended for the optimal management of patients undergoing MHD.

In Europe, America, and Japan, epidemiologic studies have been conducted in patients with MHD and demonstrated associations between abnormal mineral metabolism, based on patient serum mineral levels and patient outcomes [12–14]. We aimed to evaluate serum mineral levels in Korean patients undergoing MHD to determine their relationship with parathyroid hormone control. These results may provide insight into the status of current practice in the era of such guidelines.

Methods

Between January 1, 2009 and June 30, 2009, clinical data were collected from patients undergoing MHD in 17 centers (10 university hospitals and 7 secondary-care general hospitals) in Korea. Enrollment criteria included (1) patient age ≥ 18 years, (2) chronic hemodialysis for ≥ 6 months, and (3) multiple measurements of serum Ca, P, and intact parathyroid hormone (iPTH) during the preceding 12 months. Patients with intercurrent illnesses requiring hospitalization were excluded. As a result, 1,018 patients were found to be eligible among the 1,060 enrolled MHD patients. Patient consent was obtained, as required by the institutional review boards of the participating medical facilities.

Patient demographic and laboratory data were obtained by reviewing medical records from 2008 to 2009. The laboratory values were averaged because most centers measured serum Ca and P monthly, and measured iPTH quarterly. Albumin-corrected calcium (mg/dL) was calculated as [4 – albumin (g/dL)] × 0.8 + total serum calcium (mg/dL) when the serum albumin level was less than 4.0 g/dL. The iPTH concentration was measured by second-generation PTH assays using four different assay kits: Elecsys PTH (Roche Diagnostics; Meylan, France), Immulite 2000 intact PTH (DPC; Los Angeles, USA), ELISA-PTH (Schering-Cis Bio; Gif-sur-Yvette, France), and Architect intact PTH (Abbott; Wiesbaden, Germany). Among different second-generation PTH assays, our methods had a relatively small interassay variability [15]. After data collection, the distributions of serum mineral levels were examined, based on the KDOQI guidelines.

Continuous data are presented as means ± standard deviation, and categorical variables are expressed as frequency counts and percentages. Box plots are used for a visual presentation of continuous variables; median, 75th, and 25th percentiles, and ranges between the 10th to 90th percentile are shown. The Kruskal-Wallis test was used to compare continuous variables among three or more groups, and the Mann-Whitney *U* test was used for comparisons between two groups. The chi-square test and Pearson correlation efficiency test were used to evaluate associations between categorical and continuous variables, respectively. Statistical significance was defined as $P < 0.05$.

Results

General patient characteristics

Table 1 shows the general characteristics of the 1,018 patients. The mean age was 54 years, with an equal distribution by sex. In most patients, hemodialysis was performed three times a week, in 4-hour sessions. Interestingly, 87.2% of patients reported adherence to dietary phosphorus restrictions. Phosphorus binders were used by 72.3% of the study participants and vitamin D receptor agonists were used by 45.9% of the participants. The former covered both calcium-based and calcium-free phosphate binders (Table 2), and the latter included calcitriol, paricalcitol, and alfacalcidol, in order of the frequency of their use. Nevertheless, 270 patients (26.5%) had iPTH > 300 pg/mL. Most of the patients used a dialysate calcium concentration of 3.0 mEq/L. Fig. 1 illustrates the distribution of dialysate calcium concentrations.

Serum levels of Ca, P, and Ca × P product

The mean values of serum Ca, P, and Ca × P product were 9.1 ± 0.7 mg/dL, 5.3 ± 1.4 mg/dL, and 48.0 ± 13.6 mg^2/dL^2, respectively. The mean iPTH level was 262.1 ± 298.8 pg/mL. Fig. 2 illustrates the distributions of serum Ca, P, Ca × P product, and iPTH levels, based on the recommended KDOQI guideline ranges. Only approximately half of the patients were considered within the guideline range for serum Ca (8.4–9.5 mg/dL) and P (3.5–5.5 mg/dL). Uncontrolled hyperphosphatemia and elevated Ca × P product levels (≥ 55 mg^2/dL^2) were observed in 40.7% and 29.3% of the patients, respectively. Only a third of the patients were within the guideline range for iPTH (150–300 pg/mL). Among patients outside the guideline range for iPTH, more patients were considered to be in the low (< 150 pg/mL, 42.7%) than the high (> 300 pg/mL, 26.5%) range.

Serum levels of Ca, P, and Ca × P product by iPTH levels

Serum Ca, P, and Ca × P product levels were compared by iPTH levels (< 150, 150–300, and > 300 pg/mL). As shown in Fig. 3, serum Ca, P, and Ca × P product levels were significantly increased in patients with iPTH > 300 pg/mL, compared with the other two groups. Patients with iPTH < 150 pg/mL had significantly lower P and Ca × P product values than those with iPTH levels in the 150–300 pg/mL range, although serum Ca was not significantly different between the two groups.

Table 1. General patient characteristics (n = 1,018)

Characteristics	Values
Demographics	
Age (y)	54.0 ± 13.3
Female, *n* (%)	507 (49.8)
Height (cm)	162.2 ± 8.9
Weight (kg)	57.7 ± 10.6
BMI (kg/m^2)	21.9 ± 3.2
Hemodialysis	
Vintage (y)	5.4 ± 5.2
Frequency (times/wk)	3.0 ± 0.2
Session length (h/wk)	11.9 ± 0.6
Comorbidity	
Diabetes mellitus, *n* (%)	378 (37.1)
Hypertension, *n* (%)	618 (60.7)
Management for SHPT	
Dietary phosphorus restriction, *n* (%)	888 (87.2)
Phosphate binders, *n* (%)	736 (72.3)
Vitamin D receptor agonists, *n* (%)	429 (42.1)

Continuous variables are expressed as means ± standard deviation.
BMI, body mass index; SHPT, secondary hyperparathyroidism.

Among the 270 patients with iPTH levels > 300 pg/mL, 122 patients (45.2%) had serum Ca levels > 9.5 mg/dL, whereas only 35 patients (13.0%) had serum Ca levels < 8.4 mg/dL. In contrast, of the 435 patients with iPTH levels < 150 pg/mL, 90 patients (20.7%) had serum Ca levels > 9.5 mg/dL. Most of the patients with iPTH levels > 300 pg/mL also had serum P (> 5.5 mg/dL, 63.0%) and Ca × P product (≥ 55 mg^2/dL^2, 53.7%) levels above the guideline ranges. Consistent with these observations, the Pearson correlation efficiency analysis revealed that the iPTH levels were positively correlated with serum Ca (r^2 = 0.05, P < 0.0001), P (r^2 = 0.08, P < 0.0001), and Ca × P product (r^2 = 0.11, P < 0.0001) levels. The iPTH level was also significantly associated with the vintage of hemodialysis (r^2 = 0.04, P < 0.0001).

Use of phosphate binders and vitamin D receptor agonists

Table 2 shows that serum Ca, P, and iPTH levels were different according to the current use of phosphate binders. As expected, there was a tendency to use calcium-based binders and calcium-free agents in patients with rather low and high serum calcium, respectively. Calcium-free phosphate binders were used for the patients with a higher iPTH level.

The current use of vitamin D receptor agonists was significantly associated with iPTH levels (Table 3). Calcitriol and paricalcitol were the major agents used for the patients with iPTH levels > 300 pg/mL. Table 4 shows serum mineral levels

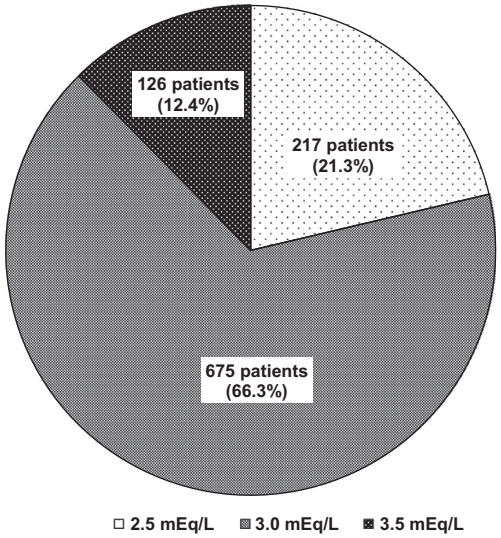

Figure 1. Distribution of dialysate calcium concentrations used in patients.

Table 2. Serum mineral levels according to the current use of phosphate binders

Serum parameters	Phosphate binders				P
	Combined use (n = 306)	Calcium-based agents (n = 329)	Calcium-free agents (n = 101)	No use (n = 282)	
Calcium (mg/dL)	9.0 ± 0.6	9.0 ± 0.6	9.6 ± 0.9	9.2 ± 0.9	< 0.0001*
Phosphorus (mg/dL)	5.9 ± 1.1	4.7 ± 1.1	6.2 ± 1.2	5.0 ± 1.5	< 0.0001*
Calcium-phosphorus product (mg^2/dL^2)	52.9 ± 10.4	41.7 ± 10.3	59.5 ± 12.7	45.8 ± 15.7	< 0.0001*
iPTH (pg/mL)	262.6 ± 247.9	203.0 ± 226.6	370.9 ± 315.5	291.3 ± 389.7	< 0.0001†

Data are described as mean ± standard deviation.
Combined use, calcium-based phosphate binders + calcium-free phosphate binders; iPTH, intact-parathyroid hormone.
* Comparisons were made using analysis of variance.
† Comparisons were made using the Kruskal-Wallis test.

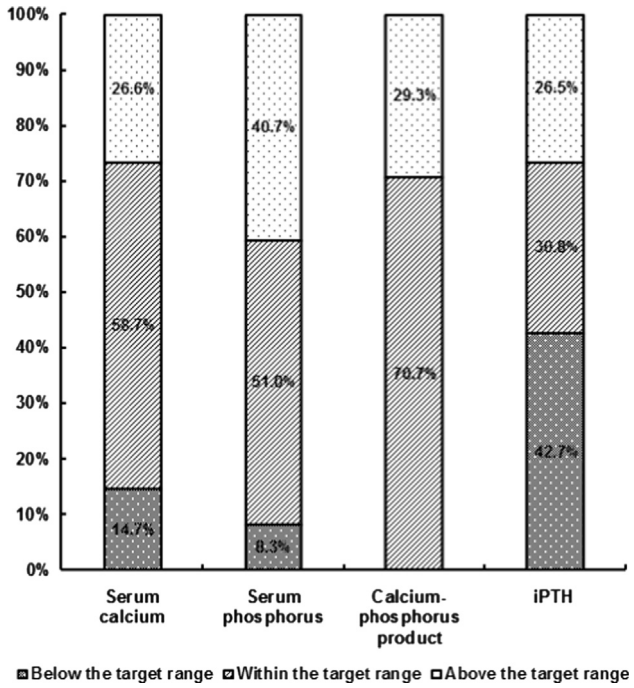

Figure 2. Distribution of serum calcium, phosphorus, calcium-phosphorus product, and intact parathyroid hormone (iPTH) levels, classified by the ranges recommended in the KDOQI guidelines.

among patients taking the different vitamin D receptor agonists. Although the serum P level did not differ among the groups, serum Ca, Ca × P product, and iPTH levels showed significant differences, according to the use of the different vitamin D receptor agonists. Paricalcitol was prescribed in the patients with higher Ca and iPTH levels.

Discussion

The current study showed that relatively large percentages of patients undergoing MHD were outside of the KDOQI guideline target ranges for serum Ca, P, Ca × P product, and iPTH levels. Thus, the percentages of our patients who were within the KDOQI guideline ranges were relatively modest: Ca, 58.7%; P, 51.0%; Ca × P product, 70.7%, and iPTH, 30.8%. These data may represent the current status of serum mineral control in Korea because our patients had demographic characteristics comparable to the overall Korean patient population undergoing MHD [7].

In this study, the percentage of patients who were within the guideline ranges was a little larger than that observed in the Dialysis Outcomes and Practice Patterns Studies (DOPPS I) that was performed between 1996 and 2001, before the KDOQI guidelines were published [8]. In DOPPS I, the percentages of patients within the KDOQI guideline ranges were 40.5% for Ca, 40.8% for P, 56.6% for Ca × P product, and 21.4% for iPTH [12]. The percentages of patients within the KDOQI guideline ranges in DOPPS II (2002–2004) were 42.5% for Ca, 44.4% for P, 61.4% for the Ca × P product, and 26.2% for iPTH [12]. Further improvements in these data were also reported in DOPPS III (2005–2007) [13], which was performed after the KDOQI Guidelines were published in 2003. Thus, a time factor may be responsible for the differences between the DOPPS data and the current findings. Whether or not the data were influenced by differences in dietary phosphorus intake, medication use, such as phosphate binders and vitamin D receptor agonists, and dialysate calcium between the studies is unclear.

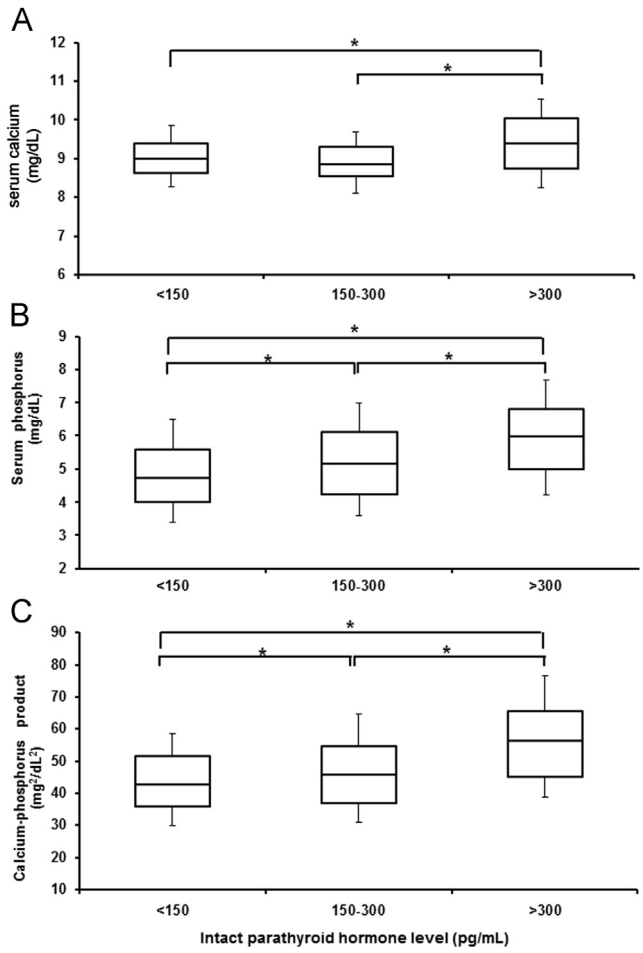

Figure 3. Comparisons of (A) serum calcium, (B) phosphorus, and (C) calcium-phosphorus product, according to the different levels of intact parathyroid hormone. Boxes are median and interquartile ranges. Vertical lines represent the 10th to 90th percentile. *$P < 0.05$ using the Mann-Whitney *U test*.

Table 3. The current use of vitamin D receptor agonists by different levels of intact parathyroid hormone*

Vitamin D receptor agonists	iPTH (pg/mL)		
	< 150 (n = 435)	150~300 (n = 313)	> 300 (n = 270)
Alfacalcidol	19 (1.9)	28 (2.8)	10 (1.0)
Calcitriol	55 (5.4)	138 (13.6)	99 (9.7)
Paricalcitol	1 (0.1)	7 (0.7)	30 (3.0)
Alfacalcidol+calcitriol	0 (0.0)	5 (0.5)	6 (0.6)
Paricalcitol+others	0 (0.0)	13 (1.3)	56 (5.5)
No treatment	360 (35.4)	122 (12.0)	69 (6.8)

iPTH, intact parathyroid hormone.

* Value are presented as n (%). The association between the iPTH levels and vitamin D receptor agonist types were significant ($P < 0.0001$ by chi-square test).

In a similar context, the patients in the current study showed better serum mineral profiles compared with individuals in other DOPPS countries. A multicenter study from Italy reported that serum P was > 5.5 mg/dL in 51.6% and the Ca × P product was > 55 mg^2/dL^2 in 35.5% of the patients [14]. In a cohort study in Japan (J-DOPPS), the mean values of serum Ca, P, Ca × P

Table 4. Serum mineral levels according to different vitamin D receptor agonists in patients with intact parathyroid hormone > 300 pg/mL (*n* = 270)

Serum parameters	Alfacalcidol ($n = 10$)	Calcitriol ($n = 99$)	Paricalcitol ($n = 30$)	Alfacalcidol+ Calcitriol ($n = 6$)	Paricalcitol+ Others ($n = 56$)	P^*
Serum calcium (mg/dL)	8.7 ± 0.5[†]	9.0 ± 0.7[†]	10.1 ± 0.7	9.3 ± 0.8	9.7 ± 0.7[†,‡,§]	< 0.0001
Serum phosphorous (mg/dL)	5.8 ± 1.0	5.7 ± 1.4	6.0 ± 0.8	5.8 ± 1.2	6.2 ± 1.5	0.5450
Ca × P product (mg^2/dL^2)	49.9 ± 7.7[†]	51.4 ± 13.6[†]	60.5 ± 9.3	54.1 ± 12.0	59.5 ± 15.4[‡]	0.0004
iPTH (pg/mL)	496.0 ± 189.0	537.0 ± 331.0[†]	703.0 ± 373.0	496.0 ± 408.0	490.0 ± 260.0[*]	0.0112

Data are described as means ± standard deviation.
Ca × P product, calcium-phosphorous product; iPTH, intact parathyroid hormone.
[*] Comparisons were made using the Kruskal-Wallis test.
[†] Comparison made using the Mann-Whitney *U* test with Bonferroni adjustment ($P < 0.05$) versus the paricalcitol group.
[‡] Comparison made using the Mann-Whitney *U* test with Bonferroni adjustment ($P < 0.05$) versus the calcitriol group.
[§] Comparison made using the Mann-Whitney *U* test with Bonferroni adjustment ($P < 0.05$) versus the alfacalcidol group.

product, and iPTH were 9.4 ± 1.0 mg/dL, 5.7 ± 1.6 mg/dL, 52.8 ± 15.9 mg^2/dL^2, and 194 ± 263 pg/mL, respectively [16]. The percentages of patients with laboratory values within the KDOQI guideline ranges were 44.2% for Ca, 43.1% for P, 58.9% for Ca × P product, and 24.4% for iPTH in the J-DOPPS report.

Interestingly, in the current study, more patients had low iPTH levels (< 150 pg/mL, 42.7%) than high iPTH levels (> 300 pg/mL, 26.5%). This finding appears to be similar to those from Western countries [12–14] and to correlate with changes in the histological spectrum of uremic bone disease over the past decades [17,18]; adynamic bone disease is emerging as a major mineral disorder in patients undergoing MHD [19]. Because oversuppression of PTH and excessive calcium intake can induce adynamic bone disease [8], careful use of vitamin D receptor agonists is required. Notably, the new standard target range for iPTH in JSDT is between 60 and 240 pg/mL [11].

A high iPTH level was also found to be significant because it was associated with increased serum mineral levels. Serum Ca, P, and the Ca × P product values correlated with iPTH and significantly increased in patients with iPTH levels > 300 pg/mL. The positive correlation between serum P and iPTH may be linked to increased mortality [19], emphasizing the importance of SHPT control.

Management of SHPT includes dietary phosphorus restriction, use of phosphate binders, and adequate dialysis. The use of vitamin D receptor agonists is another important tool for suppressing PTH secretion. Consistent with this finding, the current cross-sectional data showed that patients taking vitamin D receptor agonists had lower serum P and Ca × P product values. Serum mineral values were also compared among patients taking three different vitamin D receptor agonists. The observation that serum Ca and Ca × P product values were lower in calcitriol users than in paricalcitol users was unexpected because hypercalcemia and hyperphosphatemia—side effects associated with these types of drugs—have been more common in those taking calcitriol, according to previous studies [20–22]. This paradoxical finding may result from the cross-sectional design of the current study. Hypercalcemia may have been more frequent in patients medicated with paricalcitol because paricalcitol is a second-line treatment that is only allowed after calcitriol has been attempted, according to the Korean National Health Insurance Service guidelines.

In summary, this study demonstrated the current status of serum Ca, P, Ca × P product, and parathyroid hormone control in MHD patients. As international practice guidelines were introduced, serum mineral profiles appeared to improve. However, relatively modest percentages of the patients remain outside of the guideline's target ranges. Because uncontrolled secondary hyperparathyroidism (SHPT) was associated with higher serum Ca, P, and Ca × P product levels, adequate treatment of SHPT may lead to reduced cardiovascular mortality and improved patient outcomes.

Conflicts of interest

GH Kim has received speaker fees from and has been a consultant for AbbVie. GH Kim, BS Choi, DR Cha, EA Hwang, HW Kim, JH Chang, JK Kim, JW Noh, KW Joo, SC Lee, SW Han, SW Kim, SK Shin, WD Park, W Kim, WS Huh, and YJ Kwon have received research funding from AbbVie. DH Chee is an employee of AbbVie, and owns AbbVie Stocks. SJ Kim and YS Kang have nothing to disclose.

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