



Fracture risk in chronic kidney disease: A Korean population-based cohort study

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Background: Chronic kidney disease (CKD)-mineral and bone disorder (MBD) and fracture risk are both closely related to declining renal function. Controlling hyperphosphatemia with phosphate binders is a basic principle of CKD-MBD treatment. The aim of this study was to identify differences in fracture risk between pre-dialysis CKD patients and end-stage renal disease (ESRD) on dialysis, and to evaluate the effects of phosphate binders on fracture risk in ESRD patients.

Methods: Data from a total of 89,533 CKD patients comprising CKD diagnosis, dialysis, fracture history, and phosphate binder prescription history from 2012 to 2016 were retrieved from the Health Insurance Review and Assessment Service Database. Multivariate Cox regression analyses were performed to identify whether dialysis or phosphate binders were associated with an increased fracture risk.

Results: Overall, the rate of fractures in pre-dialysis CKD patients was 74 per 1,000 patient-years, while that in dialysis patients was 84 per 1,000 patient-years. The risk of fracture in ESRD patients was higher than pre-dialysis CKD patients (hazard ratio, 1.16; 95% confidence interval, 1.12–1.21; $P < 0.001$) after adjusting for confounding variables. In addition, the fracture risk in patients who were not taking phosphate binders was 20.0% higher compared to ESRD patients taking phosphate binders.

Conclusion: Fractures were more prevalent in ESRD patients on dialysis than pre-dialysis CKD patients. Use of phosphate binders was associated with a lower fracture risk in ESRD patients.

Keywords: Chronic renal insufficiency, Dialysis, Fracture, Phosphate binder

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Introduction

Chronic kidney disease (CKD) is a momentous issue both for individuals and society as a whole. The prevalence of CKD has been steadily increasing along with the size of the elderly population and the increasing prevalence of other chronic diseases such as diabetes mellitus and hypertension, and is associated with a tremendous increase in medical expenditures [1]. Individually, the various co-morbidities and complications associated with CKD significantly lower lifespan and quality of life.

CKD patients are susceptible to fractures, especially hip fractures that can lead to prolonged immobilization and subsequent fatal complications such as thromboembolism, pneumonia, and pressure sores [2,3]. Osteoporosis is the typical etiology of fractures in the general population. However, CKD-mineral and bone disorder (CKD-MBD), which refers to abnormalities of calcium and phosphorus metabolism, bone formation/turnover dysregulation, and vascular calcification is also associated with an increased risk of fracture. Importantly, patients with CKD-MBD can sustain fractures in cases with weak forces [4].

At the center of CKD-MBD is phosphorus, which has an important role as an essential mineral to control our body. Eighty to ninety percent of the body's phosphorus content is stored in the bones and teeth, while the remainder resides in cells, body fluids, and the blood to control cell metabolism and energy generation [5]. As renal function declines, phosphorus excretion through the kidneys decreases, resulting in hyperphosphatemia and hypocalcemia. This imbalance of phosphate and calcium stimulates excretion of parathyroid hormone, which acts to release calcium from bones into the blood, leading to weakening of bones. Phosphate binders are widely used to treat patients with hyperphosphatemia, as they promote excretion of phosphorus into the feces. However, previous research has focused primarily on the role of phosphate binders in improving vascular calcifications and reducing cardiovascular mortality [6–8].

Here, we studied the impact of renal function decline on fracture risk in non-dialysis and dialysis-dependent CKD patients. In addition, we investigated the difference in fracture risk according to use of phosphate binders in dialysis-dependent CKD patients using data obtained from the Health Insurance Review and Assessment Ser-

vice Database.

Methods

Ethics

Our study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Ewha Womans University College of Medicine (IRB number: EUMC 2017-08-028-001). Data was obtained from the Health Insurance Review and Assessment Service Database after anonymization. The IRB committee waived the requirement for informed consent due to the nature of the data and study design.

Study design and population

We analyzed data from the Health Insurance Review & Assessment Service Database from 2012 to 2016. First, patients diagnosed with CKD or end-stage renal disease (ESRD) (coded as N18.1 to N18.5, and N18.9) were enrolled. Next, patients were classified into pre-dialysis CKD patient or dialysis patient groups. Specifically, if a patient's record included a hemodialysis treatment code (O7010 or O7020), peritoneal dialysis operation code (O7070), or peritoneal dialysate prescription code, they were classified into the dialysis patient group. Conversely, patients who did not fit the criteria for an ESRD patient on dialysis were classified into the pre-dialysis CKD group. To include incident pre-dialysis CKD or ESRD on dialysis patients only during the study period (2013–2016), we selected and excluded patients who already had CKD diagnosis codes or dialysis codes in 2012 (wash-out period). We were not focused on renal allograft patients in this study, so patients who underwent a renal allograft in 2012 were excluded.

Data on major and minor fracture diagnoses were obtained using fracture diagnosis codes for the spine (S32-), hip (S72-), upper extremities (S42-, S42.2, S42.4, S52-, S62-), lower extremities (S92-, S82-, S72.3, S72.4), skull (S02), thorax (S22), or other (S82-). Fracture data was collected from the time of CKD or ESRD diagnosis up to 2016 for all patients. We attempted to identify differences in fracture risk between age groups under 65 years and 65 years and over. We also performed analyses to identify the risk of fracture between the pre-dialysis CKD and ESRD patients on dialysis

groups. Lastly, we analyzed the association between fracture risk and use of phosphate binders in patients on dialysis.

Statistical analysis

Categorical variables including dialysis status, age, sex, and fracture occurrence were expressed as frequencies (percentages). The number of fractures were counted, and the person-years of the study population were calculated by multiplying the number of patients and the follow-up period (years) or the period until the time of fracture. The total number of fractures was first divided by total person-years in the respective CKD and ESRD groups, and logistic regression analysis was conducted to find the statistical significance of fracture risk. Kaplan–Meier plot analyses were performed to evaluate differences in fracture risk according to dialysis status, female sex, and age over 65 years. A multivariate Cox proportional hazard regression analysis was then conducted to identify the fracture risk of dialysis patients.

Lastly, Kaplan–Meier analysis was carried out to verify whether there was any difference in the time from dialysis initiation to fracture diagnosis between those who were and were not taking phosphate binders. In addition,

multivariate Cox proportional hazard regression analysis was performed to determine the effect of phosphate binders on fracture risk.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, USA).

Results

Baseline characteristics of the study population

Of the 89,533 CKD patients, 76,106 (85.0%) were pre-dialysis CKD patients. Among the 13,427 dialysis patients, 12,098 patients (90.1%) were receiving hemodialysis and 1,329 patients (9.9%) were undergoing peritoneal dialysis treatment. A total of 37,610 (42.0%) of the patients were female, and 51,723 (57.8%) of the study patients were over the age of 65 years. A total of 25,771 (28.8%) patients had between 0 and 5 points on the Charlson Comorbidity Index (CCI) scoring system, 35,840 (40.0%) had between 6 and 8 points, and 27,922 (31.2%) had between 9 and 27 points (Table 1).

Table 1. Baseline characteristics of the study population

Variable	Total (n = 89,533)	Pre-dialysis (n = 76,106)	Dialysis (n = 13,427)	P value
Age group (yr)				< 0.001
< 65	37,810 (42.2)	30,594 (40.2)	7,216 (53.7)	
≥ 65	51,723 (57.8)	45,512 (59.8)	6,211 (46.3)	
Sex, male	51,923 (58.0)	43,925 (57.7)	7,998 (59.6)	< 0.001
Charlson Comorbidity Index				< 0.001
0–5	25,771 (28.8)	23,140 (30.4)	2,631 (19.6)	
6–8	35,840 (40.0)	30,382 (39.9)	5,458 (40.6)	
9–27	27,922 (31.2)	22,584 (29.7)	5,338 (39.8)	
Phosphate binder use				
Calcium-based	NA	NA	7,456 (55.5)	
Non-calcium-based	NA	NA	2,462 (18.3)	

Data are presented as number (%).
NA, not available.

Table 2. Fracture risks in the dialysis group according to the fracture site

	Total			Spine			Hip			Others		
	OR	95% CI	P value									
Pre-dialysis	Reference			Reference			Reference			Reference		
Dialysis	1.10	1.05–1.16	< 0.001	0.98	0.90–1.08	0.694	1.66	1.54–1.82	< 0.001	1.04	0.99–1.10	0.133

Odds ratio (OR) and 95% confidence interval (CI) were attained by multivariate logistic regression analysis adjusted for age group and sex.

Fractures in patients with CKD according to dialysis, sex, and age

In Supplementary Table 1 (available online), we present the number of fractures per total patient-years in CKD patients divided into dialysis and pre-dialysis groups. Overall, the rate of fractures in pre-dialysis CKD patients was 74 per 1,000 patient-years, while that of dialysis-dependent CKD patients was 84 per 1,000 patient-years. Based on multivariate logistic regression analysis (Table 2), the odds ratio (OR) for total fracture events in dialysis patients was 1.10 (95% confidence interval [CI] 1.05–1.16, $P < 0.001$) compared to pre-dialysis patients.

We next compared the risk of fractures using Kaplan–Meier curves depending on dialysis status, gender, and

age (cutoff 65 years). Fig. 1 shows that the incidence of fracture was significantly higher in dialysis patients than in pre-dialysis patients. Furthermore, when pre-dialysis CKD and dialysis-dependent ESRD patients were analyzed by gender and age group, the incidence of fractures was significantly higher among females compared to males, and individuals 65 years and older compared to those less than 65 (Fig. 2).

Cox proportional hazard regression analysis was performed to determine the risk of fracture in dialysis patients compared to pre-dialysis patients after adjusting for confounding variables. Univariate analysis showed the hazard ratio (HR) for fracture risk in dialysis patients was 1.11 (95% CI 1.07–1.16, $P < 0.001$). After adjusting for age, gender, and CCI, the fracture risk in dialysis patients was higher than in pre-dialysis dependent CKD patients (HR 1.16, 95% CI 1.12–1.21, $P < 0.001$) (Table 3 and Fig. 3).

Fracture risk in dialysis patients according to the use of phosphate binders

We next investigated the incidence of fracture according to the use of phosphate binders in dialysis patients. Of the 13,427 dialysis patients, 9,918 were taking phosphate binders. Among those taking phosphate binders, 1,935 patients (19.5%) experienced fractures. Among the patients who were not taking phosphate binders ($n = 3,509$), 671 (19.1%) experienced a fracture (Table 4).

We also investigated fracture risk according to the use of phosphate binders in dialysis patients using Cox pro-

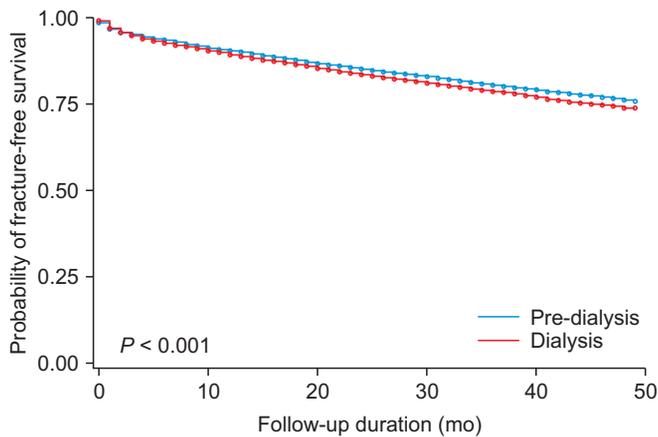


Figure 1. Kaplan–Meier plot of fracture incidence in pre-dialysis chronic kidney disease and end-stage renal disease patients.

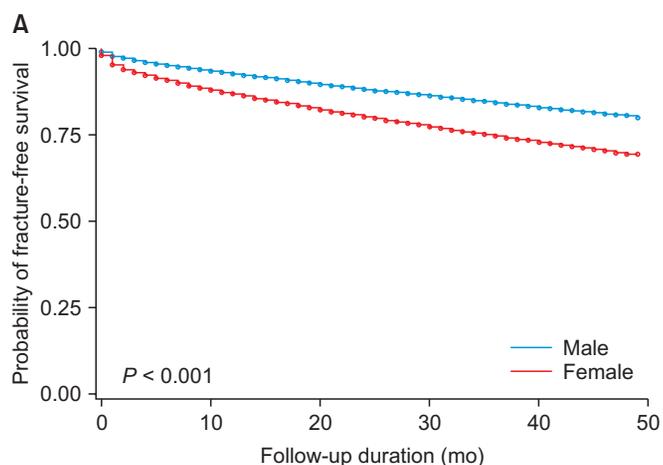


Figure 2. Kaplan–Meier plot of fracture incidence in patients with pre-dialysis and dialysis chronic kidney disease according to (A) sex and (B) age group.

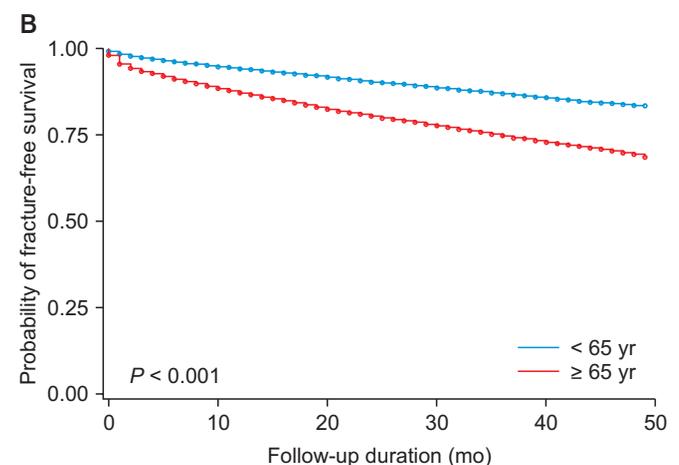


Table 3. Cox regression analysis for fracture risk of ESRD patients compared to pre-dialysis CKD patients

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Dialysis						
Pre-dialysis CKD		Reference			Reference	
ESRD	1.11	1.07–1.16	< 0.001	1.16	1.12–1.21	< 0.001
Age (yr)						
< 65		Reference			Reference	
≥ 65	2.07	2.01–2.14	< 0.001	1.80	1.74–1.86	< 0.001
Sex						
Male		Reference			Reference	
Female	1.71	1.66–1.76	< 0.001	1.69	1.64–1.74	< 0.001
Charlson Comorbidity Index						
0–5		Reference			Reference	
6–8	1.61	1.55–1.68	< 0.001	1.41	1.35–1.47	< 0.001
9–27	2.35	2.25–2.45	< 0.001	1.92	1.84–2.01	< 0.001

CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio.

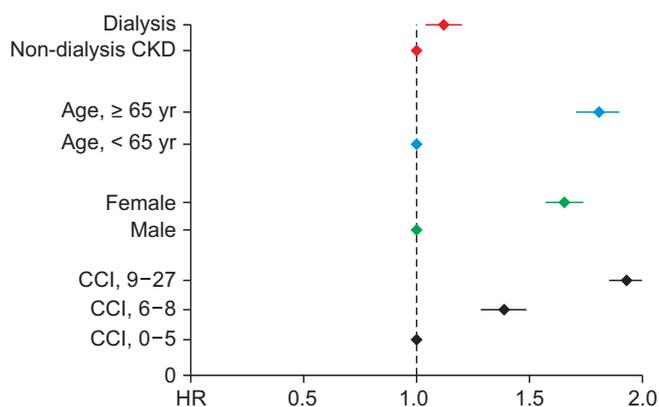


Figure 3. Fracture risk of end-stage renal disease patients compared to pre-dialysis chronic kidney disease (CKD) patients. CCI, Charlson Comorbidity Index; HR, hazard ratio.

portional hazard regression analysis. The crude HR for sustaining a fracture in the group not taking phosphate binders was 1.33 (95% CI 1.22–1.45, $P < 0.001$) compared to the group taking phosphate binders. Multivariate analyses to adjust for confounding factors were performed using two models. Model 1 adjusted for age and sex, while model 2 adjusted for the factors used in model 1 as well as CCI. In both models, no use of phosphate binders was significantly associated with increased fracture risk (model 1: HR 1.19, 95% CI 1.09–1.30, $P < 0.001$; model 2: HR 1.20, 95% CI 1.09–1.31, $P < 0.001$). The HRs for each factor (dialysis, age, gender, and CCI scores) are described in Fig. 3. In dialysis patients, the risk of fracture in

Table 4. Baseline demographic and fracture incidence data according to phosphate binder prescription in end-stage renal disease patients

Variable	Taking phosphate binders (n = 9,918)	Not taking phosphate binders (n = 3,509)
Fracture		
Yes	1,935 (19.5)	671 (19.1)
No	7,983 (80.5)	2,838 (80.9)
Age (yr)		
< 65	5,878 (59.3)	1,338 (38.1)
≥ 65	4,040 (40.7)	2,171 (61.9)
Sex		
Male	5,945 (59.9)	2,053 (58.5)
Female	3,973 (40.1)	1,456 (41.5)
Charlson Comorbidity Index		
0–5	1,972 (19.9)	659 (18.8)
6–8	4,090 (41.2)	1,368 (39.0)
9–27	3,856 (38.9)	1,482 (42.2)

Data are presented as number (%).

dialysis patients not taking phosphate binders was 20.0% higher compared to patients taking phosphate binders (Table 5 and Fig. 4).

Discussion

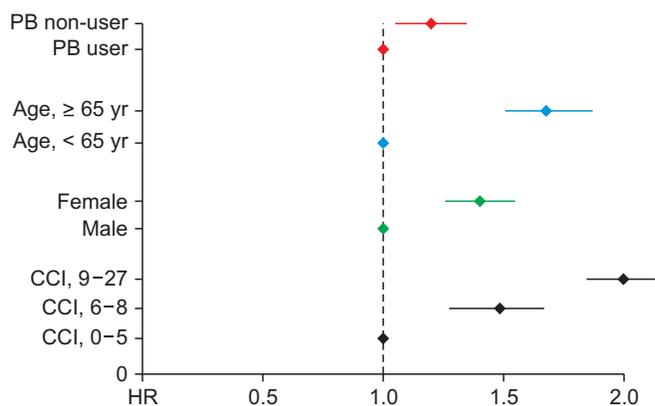
This large-scaled, nationwide, observational study showed that the fracture risk of dialysis patients was 16.0% higher than that of pre-dialysis CKD patients. In addition, dialy-

Table 5. Cox regression analysis for fracture risk in patients who did and did not take phosphate binders in end-stage renal disease

Variable	Univariate			Multivariate					
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Phosphate binders									
Users		Reference			Reference			Reference	
Non-users	1.33	1.22–1.45	< 0.001	1.19	1.09–1.30	< 0.001	1.20	1.09–1.31	< 0.001
Age (yr)									
< 65		Reference			Reference			Reference	
≥ 65	2.04	1.89–2.21	< 0.001	1.95	1.80–2.11	< 0.001	1.70	1.57–1.84	< 0.001
Sex									
Male		Reference			Reference			Reference	
Female	1.47	1.36–1.59	< 0.001	1.39	1.29–1.50	< 0.001	1.45	1.34–1.56	< 0.001
Charlson Comorbidity Index									
0–5		Reference						Reference	
6–8	1.63	1.43–1.85	< 0.001				1.51	1.33–1.72	< 0.001
9–27	2.43	2.15–2.75	< 0.001				2.05	1.81–2.33	< 0.001

Model 1: phosphate binder prescription, age, sex; model 2: model 1 + Charlson Comorbidity Index.

CI, confidence interval; HR, hazard ratio.

**Figure 4.** Fracture risk of patients with end-stage renal disease according to use of phosphate binders (PB).

CCI, Charlson Comorbidity Index; HR, hazard ratio.

sis patients who were not taking phosphate binders had a 20.0% higher risk of fracture compared to those who were taking phosphate binders.

Fractures can be a fatal complication in patients with CKD, and these patients have a higher fracture risk for a number of reasons. First, bones of CKD patients are fragile. Increasing age over 65 years as well as increased steroid exposure, alterations in vitamin D metabolism, and parathyroid hormone abnormalities all have an impact on bone quantity and strength in CKD patients. To date, most of the therapeutic modalities aimed at reducing

fracture risk have targeted the general population, and not CKD patients. Bisphosphonates, which are representative osteoporosis medications, cannot be prescribed to advanced CKD patients with a creatinine clearance under 30 mL/min/1.73 m². Therefore, despite a higher prevalence of osteoporosis in patients with advanced CKD and ESRD, they cannot be treated appropriately. Next, ESRD patients are more likely to experience dizziness, and thus have a higher risk of falling. Multiple other factors including anemia, intradialytic hypotension, and autonomic neuropathy due to diabetes, all common manifestations in ESRD patients, can also influence dizziness and falls [9]. Hip fracture, which frequently occurs after a falling accident, is strongly associated with poor clinical outcomes. According to the additional analysis based on fracture site, the dialysis group hip fracture risk was 66% higher than that of the pre-dialysis group (OR 1.66, 95% CI 1.54–1.82, $P < 0.001$) (Table 2). Therefore, nephrologists need to recognize the higher risk for critical fractures, including hip fracture, among dialysis patients.

Controversy persists as to whether decreased renal function is associated with osteoporosis and increased fracture risk, and the statistical significance of the relationship between renal function and fracture risk varies according to fracture site and study population, especially in patients with mild to moderate renal dysfunc-

tion [10–12]. However, the majority of studies that have studied ESRD populations have identified a higher risk of fracture compared to the general population [3,13–15]. The significance of this study was the delineation of a higher risk of fracture in patients with ESRD compared to those with pre-dialysis CKD. This study is also significant for presenting statistics regarding the risk of fracture in a Korean population.

In this study, dialysis patients who were not taking phosphate binders had a higher risk of fracture compared to patients taking phosphate binders. There are several explanations for this finding. First, control of secondary hyperparathyroidism by treating hyperphosphatemia using phosphate binders may, at least in part, contribute to a decreased fracture risk. A reduction in fracture risk in patients taking phosphate binders has not been identified in randomized controlled trials; however, phosphate binders may nevertheless impact fracture risk. For example, one study showed that treatment of secondary hyperparathyroidism with cinacalcet was associated with a reduced risk of fracture (relative risk 0.46, 95% CI 0.22–0.95) [16].

A second explanation for the difference in fracture risk according to phosphate binder treatment is that calcium-based phosphate binders may specifically lead to reduced fracture risk. One study showed a clear association between use of calcium-based phosphate binders and reduced fracture risk in child patients (HR 0.37, 95% CI 0.15–0.91, $P = 0.03$) [17], which the authors attributed to calcium supplementation by the binding agent. Importantly, calcium is the most deficient nutrient in the Korean diet, with only 78% of males and 67% of females meeting the recommended daily dietary allowance [18]. According to the 2017 Korean ESRD registry report, 60% of hemodialysis patients and 53% of peritoneal dialysis patients are being treated with calcium-based phosphate binders [19]. In this way, calcium supplementation secondary to the use of calcium-based phosphate binders may also contribute to the reduced fracture risk seen in these patients.

Lastly, protein-energy wasting (PEW) in dialysis patients might be associated with differences in fracture risk. PEW refers to decreased protein and energy in the body and is common among ESRD patients [20]. Inadequate intake as well as nonspecific inflammation is a widely known component of PEW, which leads to muscle wasting in advanced cases. Patients who take small amounts of protein and energy because of PEW may not necessarily take

phosphate binders. In other words, patients who do not take phosphate binders because of PEW may have existing fragile bone and muscle, leading to increased risk of fracture.

There were some limitations to our study. First, we did not have data regarding the specific diagnosis of osteoporosis and CKD stages among study patients. In particular, we could not verify the estimated glomerular filtration rate for individual patients because we only used CKD diagnostic codes to extract CKD patients from the Health Insurance Review and Assessment Service Database. As a result, we tended to recruit advanced CKD patients rather than early stage CKD patients. This bias may have underestimated the incidence of CKD and caused sampling error. In addition, the proportion of patients over 65 years was statistically higher in the pre-dialysis CKD patient group than in the dialysis-dependent ESRD patient group (Table 1). However, the elderly generally tend to experience more fractures than the young. This sampling bias may slightly influence our main results inversely, that is, by underestimating fracture risks in ESRD patients. Next, we did not have information about the nutritional status of patients due to the nature of the dataset. However, as discussed above, PEW may be associated with use of phosphate binders. Thus, further research will be necessary to determine whether use of phosphate binders is associated with reduced nutritional status. Fourthly, a phosphate binder user was defined only as a patient prescribed phosphate binders for over 30 days. However, phosphate binders are prescribed off and on based on current phosphate levels. A more detailed definition of phosphate binder user is needed to investigate the accurate impact of phosphate binders on fracture risks, but we did not use such a definition. Lastly, we could not obtain data on phosphate binder type, such as calcium-based phosphate binders versus non-calcium-based phosphate binders. This might have a different impact on bone and fracture risks, but we could not verify the effect according to the type of phosphate binders in this study.

Taken together, the results of this study demonstrated that fracture was more prevalent in dialysis patients compared to pre-dialysis CKD patients, and ESRD patients on dialysis taking phosphate binders experienced less fractures compared to patients not taking phosphate binders. This study confirmed that decreased renal function might be associated with a higher fracture risk, and suggests the

possibility of an association between phosphate binders and fracture risk. Additional studies, including randomized controlled trials, will be needed to verify our results.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

Young Eun Kwon wrote the manuscript. Hyung Yun Choi participated in the study design and performed the statistical analysis. Sol Kim helped to draft the manuscript and provided technical support. Dong-Ryeol Ryu provided intellectual content of critical importance to the work. Hyung Jung Oh participated in the conception, analysis, and interpretation of data. All authors read and approved the final manuscript.

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Supplementary Table 1. Number of fractures per 1,000 person-years for patients with CKD according to age/sex groups

Age (yr)	Sex	Pre-dialysis CKD		Hemodialysis		Peritoneal dialysis	
		Number of fracture (n)	Total (person-years)	Number of Fracture (n)	Total (person-years)	Number of fractures (n)	Total (person-years)
< 65	Male	2,358	55,452	653	11,046	68	1,655
	Female	1,735	35,854	405	6,051	49	1,175
≥ 65	Male	4,255	62,097	586	5,874	34	438
	Female	6,306	44,745	762	4,552	49	340
Total		14,654	198,148	2,406	27,523	200	3,608
Fracture number per 1,000 person-years			74		87		55

CKD, chronic kidney disease.