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ORIGINAL ARTICLE

Vertebral fracture is associated with myocardial infarction in incident hemodialysis patients: a Korean nationwide population-based study

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Abstract

Summary Chronic kidney disease (CKD)-mineral and bone disorder suggests that fragile bone and vascular disorder might be connected closely in CKD patients. In this study, fracture event was significantly associated with myocardial infarction (MI) in end-stage renal disease patients on hemodialysis (HD), especially for vertebral fractures.

Introduction CKD-mineral and bone disorder is characterized by biochemical abnormalities, bone disorders, and vascular calcification. We aimed to verify the association between fracture and MI in CKD patients.

Methods Records for incident CKD stage 3 to 5 patients and patients who initiated HD between July 2014 and June 2018 were retrieved from the Korean Health Insurance Review & Assessment Service Database. Fractures were defined using diagnostic codes and were classified into vertebral, femoral, and other site fractures. MI was defined using a combination of MI diagnostic codes and related procedure codes. Multiple logistic regressions and 1:1 propensity score matching analysis were conducted.

Results A total of 38,935 patients (HD, 11,379; pre-dialysis CKD, 27,556) were included in this study. A total of 5,057 (13.0%) patients experienced fracture, and 1,431 (3.7%) patients had MI. Multiple logistic regression analysis showed that fracture was significantly associated with MI in the HD group (odds ratio (OR) 1.34, $P = 0.024$), but not in the pre-dialysis CKD group (OR 1.04, $P = 0.701$). After propensity score matching for age, gender, and diabetes mellitus between patients with and without fracture, fracture still significantly correlated with MI in HD patients (OR 1.47, $P = 0.034$) but not in patients with pre-dialysis CKD (OR 1.04, $P = 0.751$). Subgroup analysis by fracture site found that vertebral fracture was associated with MI in HD patients (OR 2.11, $P = 0.024$), but femoral or other site fractures were not.

Conclusion In HD patients, fracture was significantly associated with MI, especially for vertebral fractures patients.

Keywords Fracture · Hemodialysis · Myocardial infarction · Vertebral

Abbreviations

CI	Confidence interval
CKD	Chronic kidney disease
ESRD	End-stage renal disease
FGF-23	Fibroblast growth factor-23
HD	Hemodialysis
HIRA	Health Insurance Review & Assessment Service
IRB	Institutional review board

D.-R. Ryu and Y.J. Kwon contributed equally to this work.

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KDIGO	Kidney Disease Improving Global Outcomes
MBD	Mineral and bone disorder
MI	Myocardial infarction
OR	Odds ratio

Introduction

Cardiovascular disease in chronic kidney disease (CKD) is associated with poor prognosis and remains a major cause of death. According to the 2018 annual data report from the US Renal Data System, the 2-year survival rate for adult end-stage renal disease (ESRD) patients with acute myocardial infarction (MI) was only 58.5%, compared with 78.4% for patients without acute MI [1]. Similarly, the 2018 Korean ESRD registry reported that cardiac disease was the most common cause of death in dialysis patients [2].

Mineral and bone disorder (MBD) is one of the major complications of CKD and is composed of three distinct components: biochemical abnormalities, bone abnormalities, and vascular calcification [3]. Hyperphosphatemia is one of the fundamental causes of biochemical abnormalities in these patients. It triggers an increase in fibroblast growth factor-23 (FGF-23) which leads to phosphaturia. With regard to bone abnormalities, CKD patients are vulnerable to fractures even with weak force. Fractures, especially femoral and vertebral fractures, are directly linked to devastating outcomes, such as functional disability and mortality. Vascular calcification, the third component of CKD-MBD, is closely associated with cardiovascular disease. Evaluation for vascular calcification was highlighted in the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for CKD-MBD [3, 4]. These guidelines emphasized that patients with vascular calcification should be considered at the highest risk for cardiovascular events.

As previously mentioned, the three components of CKD-MBD interact with each other. FGF-23 is involved in the regulation of vitamin D metabolism, and it was associated with increased fracture risks [5, 6], left ventricular hypertrophy [7–9], and cardiovascular mortality [10–12]. Vitamin D deficiency, increase or excessive suppression of parathyroid hormone, and bone GLa protein (osteocalcin) are connected with fractures and vascular calcifications in CKD patients [13–16]. Recently, the US Food and Drug Administration approved anti-sclerostin antibody (romosozumab) for osteoporosis treatment, and sclerostin began to emerge as a player to inhibit bone formation. It seems to be a powerful drug to treat osteoporosis, but cardiovascular adverse events have been reported, suggesting an important link between bone and cardiovascular system [17, 18].

As interest in CKD-MBD has increased, recent studies have evaluated the association between CKD-MBD parameters and poor outcomes, such as fracture and cardiovascular disease [19–22]. However, little is known about the interactions between the significant complications associated with CKD-MBD. The interrelationship between fracture risk and cardiovascular disease has been reported in other populations, such as rheumatoid arthritis patients [23], postmenopausal women [24], and in the general Taiwanese population [25]. The pathophysiology associated with CKD-MBD suggests that the association of fractures with cardiovascular disease is likely to be more significant in CKD patients. Therefore, the purpose of this study was to evaluate the association between fracture and MI, a major cardiovascular disease, in both pre-dialysis CKD and hemodialysis (HD) patients. We conducted a large-scale, nationwide study using the Korean Health Insurance Review & Assessment Service (HIRA) Database to investigate whether patients with fracture occurrence have a higher risk of MI after adjusting for confounding variables.

Materials and methods

Study design and definition

This retrospective, population-based cohort study used claims data from the Korean HIRA Database from the period between July 2013 and June 2017. Public medical insurance registration in Korea is mandatory, and nearly all Koreans have public health insurance. HIRA is an organization that evaluates whether appropriate medical care has been provided or not. Therefore, our research analyzed all claims data covered by the Korean public health insurance during this period.

The patient selection process was illustrated with a flow chart in Supplemental Fig. 1. First, the diagnostic codes for CKD stage 3 to 5 (N18.3, N18.4, and N18.5) were used to find CKD and ESRD patients (whether they underwent dialysis or not). We set a 1-year wash-out period from July 2013 to June 2014 to select for incident patients and to exclude prevalent patients. Patients who underwent peritoneal dialysis and kidney transplantation were also excluded. Peritoneal dialysis patients were defined as patients with peritoneal dialysis solution prescription codes or peritoneal dialysis operation codes (O2016 and O2017), and kidney transplantation patients were defined as patients with a kidney allograft operation code (R3280) during the study period. Of the total participants ($n = 38{,}935$), patients who had HD procedure codes (O7020 and O9991) were classified into the HD group ($n = 11{,}379$), and the remaining patients were categorized into the pre-dialysis CKD group ($n = 27{,}556$).

The definition of a patient who experienced a fracture was limited to patients with the fracture diagnosis code as the major diagnostic code. Femoral fractures (S72) and vertebral fractures (S12.0 ~ 12.2, S12.7, S22.0, S22.1, S32.0 ~ S32.2,

S32.7, S32.83, T08), which are major osteoporotic fractures, were classified and analyzed separately.

The MI patient definition was restricted to patients with both an acute MI diagnosis code (I21, I22, or I23) and procedure codes for treating MI (M6561 ~ 2, M6561 ~ 4, M6571 ~ 2, O1641, O1642, O1647, OA641, OA642, OA647).

Patients who were prescribed anti-hypertensive, anti-diabetic medications, and/or hyperlipidemia treatment medications for more than 90 days were considered to have hypertension, diabetes mellitus, and/or hyperlipidemia histories. Fractures and MI diagnostic codes and medication prescriptions were searched for 4 years from July 2014 to June 2017.

Statistical analysis

We analyzed the pre-dialysis CKD group and the HD group separately. Categorical variables including gender, comorbidities, and the number of patients who experienced fracture or MI were expressed as frequencies (percentages). Continuous variables such as age were expressed as mean ± standard deviation.

Univariate logistic regression analysis was performed to find any factors associated with MI such as fracture history, gender, older age (≥ 65 years), hypertension, diabetes mellitus, and hyperlipidemia. Multivariate logistic regression analysis was also conducted, and two models (models 1 and 2) were created. Model 1 included variables for fracture history, gender, and older age (≥ 65 years). Model 2 included hypertension, diabetes mellitus, and hyperlipidemia history in addition to the variables analyzed in model 1.

Furthermore, 1:1 propensity score matching for age, gender, and diabetes mellitus was performed to account for these factors and to verify the effect of fracture on MI in both the HD group and in the pre-dialysis CKD group. The number of patients in the HD group and the pre-dialysis CKD group who experienced fracture was 1,315 and 3,742, respectively, after 1:1 propensity score matching. A P value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using SAS enterprise guide 6.1 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the study participants

The number of patients in the pre-dialysis CKD group and the HD group was 27,556 and 11,379, respectively. The mean age was 68.4 years in the pre-dialysis CKD group and 64.3 years in the HD group. The proportion of patients with hypertension or diabetes mellitus was higher in the HD group than in the pre-dialysis CKD group, but hyperlipidemia was more prevalent in the pre-dialysis CKD group. Overall, fractures occurred more frequently in the pre-dialysis CKD group than the in HD group, but the femoral fracture rate was the same in the two groups. In other words, vertebral fractures and other site fractures were more frequent in the pre-dialysis CKD than in the HD group (Table 1).

Association between fracture and MI in HD patients

In the HD group, fracture occurrence was associated with a higher risk of MI in univariate logistic regression analysis (Odds ratio (OR) 1.54, 95% confidence interval (CI) 1.20–1.97, $P < 0.001$). Male gender, older age (≥ 65 years), hypertension, diabetes, and hyperlipidemia history all showed higher ORs for MI in univariate logistic regression analyses. Model 1, which adjusted for demographic data such as gender and older age in multivariate logistic regression analysis, showed the same results as the univariate analysis (OR 1.54, 95% CI 1.20–1.97, $P < 0.001$). In model 2, which corrected for past medical history of hypertension, diabetes, and hyperlipidemia in addition to the variables in model 1, fracture occurrence was associated with a 34% higher risk for development of MI (OR 1.34, 95% CI 1.04–1.72, $P = 0.024$) (Table 2).

In the pre-dialysis CKD group, however, fracture occurrence was not associated with MI in either the univariate or the multivariate logistic regression analyses (univariate, OR 1.07, 95% CI 0.89–1.29, $P = 0.459$; model 1, OR 1.08, 95% CI 0.90–1.31, $P = 0.404$; model 2, OR 1.04, 95% CI 0.86–1.25, $P = 0.701$) (Table 3).

Association between fracture and MI after propensity score matching

Gender, older age, and diabetes were clinically significant factors in relation to both fracture occurrence and MI. We performed 1:1 propensity score matching using these three variables. The number of selected patients in the HD group and in the pre-dialysis CKD group after propensity score matching was 2,630 and 7,484, respectively. The patients in each group were divided equally into two subgroups (1:1 ratio) according to fracture occurrence or no fracture, and logistic regression analyses were conducted separately. Both univariate and multivariate logistic regression analyses showed that fracture occurrence was significantly associated with MI in the HD group (univariate, OR 1.54, 95% CI 1.08–2.20, $P = 0.017$; multivariate, OR 1.47, 95% CI 1.03–2.11, $P = 0.034$). There was no corresponding significant association in the pre-dialysis CKD group (univariate, OR 1.07, 95% CI 0.84–1.74, $P = 0.572$; multivariate, OR 1.04, 95% CI 0.81–1.33, $P = 0.751$) (Table 4).

Table 1 Characteristics of the study population

	Pre-dialysis CKD (n=27,556)	Hemodialysis (n=11,379)	P
Age, year	68.4±13.7	64.3±14.5	<0.001
Male, n(%)	17,097 (62.0)	6,802 (59.8)	<0.001
Hypertension, n(%)	24,521 (89.0)	10,913 (95.9)	<0.001
Diabetes mellitus, n(%)	13,092 (47.5)	6,025 (52.9)	<0.001
Hyperlipidemia, n(%)	18,010 (65.4)	7,220 (63.5)	<0.001
Patients who experienced fracture event, n(%)	3,742 (13.6)	1,315 (11.6)	<0.001
Femoral fracture	898 (3.3)	372 (3.3)	0.958
Vertebral fracture	532 (1.9)	109 (1.0)	<0.001
Others	2,629 (9.5)	925 (8.1)	<0.001
Coronary artery disease, n(%)	945 (3.4)	486 (4.3)	<0.001

Abbreviation: CKD, chronic kidney disease

Categorical variables are presented as number (%), and continuous variable is presented as mean±standard deviation.

Different relationship between fracture and MI according to fracture site

We performed additional logistic regression analyses by major fracture site, including vertebral fracture, femoral fracture, and other site fractures. First, we performed both univariate and multivariate logistic regression analyses in HD patients, using the same variables listed in Tables 2 (Table 5). Vertebral fractures were strongly associated with MI (univariate, OR 2.55, 95% CI 1.36–4.79, $P = 0.004$; model 1, OR 2.28, 95% CI 1.21–4.31, $P = 0.011$; model 2, OR 2.11, 95% CI 1.10–4.02, $P = 0.024$). Univariate analysis showed that femoral fracture was significantly associated with MI (OR 1.57, 95% CI 1.03–2.41, $P = 0.036$), but multivariate analyses did not demonstrate the same significance (model 1, OR 1.41, 95% CI 0.92–2.17, $P = 0.113$; model 2 OR 1.36, 95% CI 0.88–2.10, $P = 0.165$). Univariate analysis of other site fractures showed an increased association with MI, but the association did not reach significance level (OR 1.35, 95% CI 1.00–1.81, $P = 0.052$). On the other hand, multivariate analyses showed different results for model 1 compared with model 2. In model 1, fracture occurrence was associated with MI after adjusting for gender and older age (OR 1.41, 95% CI 1.05–1.91, $P = 0.024$). However, fracture occurrence was not associated with MI in model 2 (OR 1.18, 95% CI 0.87–1.59, $P = 0.298$). Next, we repeated the identical analyses in the pre-dialysis CKD

Table 2 Association between coronary artery disease and fracture in hemodialysis patients using univariate and multivariate logistic regression analysis

Variables	Univariate			Multivariate					
				Model 1			Model 2		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Fracture	1.54	1.20–1.97	<0.001	1.54	1.20–1.97	<0.001	1.34	1.04–1.72	0.024
Male	1.24	1.03–1.50	0.027	1.35	1.11–1.63	0.002	1.44	1.18–1.75	<0.001
Age≥65	1.80	1.49–2.19	<0.001	1.82	1.50–2.21	<0.001	1.97	1.62–2.40	<0.001
HTN	4.25	1.75–10.31	0.001				1.61	0.65–3.96	0.303
DM	2.44	1.99–2.99	<0.001				1.82	1.48–2.24	<0.001
Hyperlipidemia	5.05	3.78–6.75	<0.001				4.44	3.30–5.97	<0.001

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio

Reference group of each variables: fracture (reference: non-fracture), male (reference: female). age≥65 (reference: age group <65 years), HTN (reference: no HTN history), DM (reference: no DM history), hyperlipidemia (reference: no hyperlipidemia history)

Model 1: Adjusted for gender and age over 65 years old

Model 2: Model 1 + comorbidities (hypertension, DM, and hyperlipidemia)

Table 3 Association between coronary artery disease and fracture in pre-dialysis chronic kidney disease patients using univariate and multivariate logistic regression analysis

Variables	Univariate			Multivariate					
				Model 1			Model 2		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Fracture	1.07	0.89–1.29	0.459	1.08	0.90–1.31	0.404	1.04	0.86–1.25	0.701
Male	1.24	1.08–1.42	0.002	1.30	1.13–1.49	<0.001	1.36	1.19–1.57	<0.001
Age≥65	1.53	1.32–1.78	<0.001	1.57	1.35–1.82	<0.001	1.56	1.34–1.81	<0.001
HTN	3.82	2.20–6.62	<0.001				3.53	2.03–6.13	<0.001
DM	1.69	1.48–1.94	<0.001				1.40	1.22–1.60	<0.001
Hyperlipidemia	3.71	3.01–4.57	<0.001				3.56	2.89–4.40	<0.001

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio

Reference group of each variables: fracture (reference: non-fracture), male (reference: female). age≥65 (reference: age group <65 years), HTN (reference: no HTN history), DM (reference: no DM history), hyperlipidemia (reference: no hyperlipidemia history)

Model 1: Adjusted for gender and age over 65 years old

Model 2: Model 1 + comorbidities (HTN, DM, and hyperlipidemia)

patient group and found no association between fracture occurrence and MI (Table 6).

Discussion

This study analyzed the relationship between fracture and MI using a large-scale, nationwide, claims database in Korea. Fracture occurrence was significantly associated with MI in HD patients when analyzed by univariate and multivariate logistic regression. In addition, propensity score matching analysis showed a similar association between fracture and MI in HD patients. When further analyzed by fracture site, vertebral fracture was significantly associated with increased MI risk in HD patients. However, this relationship between fracture occurrence and MI was not reproduced in the pre-dialysis CKD group. To the best of our knowledge, this is the first large-scale clinical research study to verify the direct association between fracture occurrence and MI in ESRD patients who underwent HD.

CKD patients have fragile bones and are prone to fractures. CKD-MBD is not the only major cause of bone fragility; the number of CKD patients with coexisting osteoporosis increases as the number of elderly CKD patients increases. Femoral fractures and vertebral fractures can have serious impacts including prolonged rehabilitation, long-term sequelae,

Table 4 Association between coronary artery disease and fracture using univariate and multivariate logistic regression analysis after propensity score matching

Variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Hemodialysis (n=2,630)						
Fracture	1.54	1.08–2.20	0.017	1.47	1.03–2.11	0.034
HTN	3.75	0.52–27.22	0.191	1.90	0.26–14.06	0.531
Hyperlipidemia	3.98	2.27–6.97	<0.001	3.80	2.16–6.67	<0.001
Pre-dialysis CKD (n=7,484)						
Fracture	1.07	0.84–1.74	0.572	1.04	0.81–1.33	0.751
HTN	6.94	2.58–18.68	<0.001	4.44	1.64–12.06	0.003
Hyperlipidemia	3.90	2.66–5.72	<0.001	3.40	2.31–5.00	<0.001

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HTN, hypertension; OR, odds ratio

Note: 1:1 propensity score matching

Variables entered into derive propensity scores were age, gender, and diabetes mellitus.

Table 5 Association between coronary artery disease and fractures according to the fracture sites in hemodialysis patients using univariate and multivariate logistic regression analysis

Variables	Univariate			Multivariate					
				Model 1			Model 2		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Vertebral fracture									
Fracture	2.55	1.36–4.79	0.004	2.28	1.21–4.31	0.011	2.11	1.10–4.02	0.024
Male	1.24	1.03–1.50	0.027	1.32	1.09–1.60	0.004	1.42	1.17–1.73	<0.001
Age≥65	1.80	1.49–2.19	<0.001	1.82	1.50–2.21	<0.001	1.96	1.61–2.39	<0.001
HTN	4.25	1.75–10.31	0.001				1.63	0.66–4.01	0.291
DM	2.44	1.99–2.99	<0.001				1.84	1.50–2.27	<0.001
Hyperlipidemia	5.05	3.78–6.75	<0.001				4.45	3.31–6.00	<0.001
Femoral fracture									
Fracture	1.57	1.03–2.41	0.036	1.41	0.92–2.17	0.113	1.36	0.88–2.10	0.165
Male	1.24	1.03–1.50	0.027	1.32	1.09–1.60	0.005	1.42	1.17–1.72	<0.001
Age≥65	1.80	1.49–2.19	<0.001	1.82	1.50–2.21	<0.001	1.97	1.61–2.39	<0.001
HTN	4.25	1.75–10.31	0.001				1.62	0.66–3.99	0.295
DM	2.44	1.99–2.99	<0.001				1.84	1.50–2.27	<0.001
Hyperlipidemia	5.05	3.78–6.75	<0.001				4.47	3.32–6.01	<0.001
Other fractures									
Fracture	1.35	1.00–1.81	0.052	1.41	1.05–1.91	0.024	1.18	0.87–1.59	0.298
Male	1.24	1.03–1.50	0.027	1.32	1.09–1.60	0.004	1.42	1.17–1.72	<0.001
Age≥65	1.80	1.49–2.19	<0.001	1.86	1.53–2.25	<0.001	1.99	1.64–2.42	<0.001
HTN	4.25	1.75–10.31	0.001				1.63	0.66–4.00	0.291
DM	2.44	1.99–2.99	<0.001				1.83	1.49–2.25	<0.001
Hyperlipidemia	5.05	3.78–6.75	<0.001				4.45	3.31–6.00	<0.001

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio

higher cost, and increased mortality. The incidence of hip fracture in HD patients was reported as 7.45 per 1000 person-years for males and 13.63 per 1000 person-years for females [26]. A previous study of CKD patients found that the incidence of hip fracture increased gradually as renal function worsened, and the rate of fracture in CKD stage 5 or chronic dialysis patients was 3 to 5 times higher than in patients whose estimated glomerular filtration rate was 60 ml/min/1.73 m^2 or higher [27]. In contrast, data about vertebral fracture incidence was scarce. According to a small cross-sectional, observational study, the prevalence of vertebral fracture assessed by quantitative vertebral morphometry was similar in HD patients and patients with normal renal function (55.3% in HD patients and 51.0% in controls), but vertebral fractures were found to be highly associated with vascular calcification [28].

Furthermore, evaluation of fracture risk and prophylactic management are both limited in advanced CKD patients. Although the 2017 KDIGO CKD-MBD guidelines added the recommendation to assess fracture risk using bone mineral density [4], bone mineral density testing was not recommended in the 2009 KDIGO CKD-MBD guidelines. Bone biopsy is the most effective method for evaluating CKD-MBD but is difficult in clinical practice because of invasiveness [3]. Prescribing drugs for osteoporosis treatment is also contraindicated in advanced CKD, and drugs to control biochemical abnormalities related to CKD-MBD did not show consistent results or clear fracture prevention [29–31]. As a new drug, denosumab, is now available for treating osteoporosis in CKD patients, fracture risk in advanced CKD patients may change soon. Furthermore, romosozumab, an anti-sclerostin monoclonal antibody, was approved in the USA and Korea in 2019, and its clinical application is on the verge. Miller et al. [32] reported post hoc analysis of FRAME study [33] and suggested similar efficacy and adverse events in mild to moderate renal insufficiency patients. However, advanced CKD and ESRD patients' data has not been available, and further research for these patients' group is needed with consideration about the cardiovascular side effects.

The "calcification paradox," in which demineralizing bone disease and vascular calcification co-exist, may explain the core pathophysiology of fracture and MI [34]. Vascular calcification is a significant complication in CKD patients,

Table 6 Association between coronary artery disease and fractures according to the fracture sites in pre-dialysis chronic kidney disease patients using univariate and multivariate logistic regression analysis

Variables	Univariate			Multivariate					
				Model 1			Model 2		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Vertebral fracture									
Fracture	0.99	0.61–1.59	0.953	0.96	0.60–1.55	0.869	1.00	0.62–1.62	0.987
Male	1.24	1.08–1.42	0.002	1.29	1.12–1.48	<0.001	1.36	1.18–1.56	<0.001
Age≥65	1.53	1.32–1.78	<0.001	1.57	1.35–1.83	<0.001	1.58	1.36–1.84	<0.001
HTN	3.82	2.20–6.62	<0.001				3.28	2.09–5.14	<0.001
DM	1.69	1.48–1.94	<0.001				1.40	1.22–1.60	<0.001
Hyperlipidemia	3.71	3.01–4.57	<0.001				3.54	2.88–4.35	<0.001
Femoral fracture									
Fracture	1.08	0.76–1.53	0.681	1.04	0.73–1.48	0.850	1.08	0.75–1.55	0.715
Male	1.24	1.08–1.42	0.002	1.29	1.12–1.48	<0.001	1.36	1.19–1.57	<0.001
Age≥65	1.53	1.32–1.78	<0.001	1.57	1.35–1.82	<0.001	1.58	1.36–1.84	<0.001
HTN	3.82	2.20–6.62	<0.001				3.28	2.09–5.14	<0.001
DM	1.69	1.48–1.94	<0.001				1.39	1.22–1.60	<0.001
Hyperlipidemia	3.71	3.01–4.57	<0.001				3.54	2.88–4.35	<0.001
Other fractures									
Fracture	1.05	0.84–1.30	0.665	1.08	0.87–1.35	0.480	0.99	0.80–1.23	0.936
Male	1.24	1.08–1.42	0.002	1.29	1.13–1.48	<0.001	1.36	1.18–1.56	<0.001
Age≥65	1.53	1.32–1.78	<0.001	1.57	1.35–1.83	<0.001	1.58	1.36–1.84	<0.001
HTN	3.82	2.20–6.62	<0.001				3.28	2.09–5.15	<0.001
DM	1.69	1.48–1.94	<0.001				1.40	1.22–1.60	<0.001
Hyperlipidemia	3.71	3.01–4.57	<0.001				3.54	2.88–4.35	<0.001

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio

especially arterial medial calcification [35]. Osteogenic differentiation of vascular smooth muscle cells; upregulation of osteochondrogenic markers such as Runx2, osteopontin, and alkaline phosphatase; and elastin degradation have all been identified as factors in the pathophysiology of vascular calcification [34]. Laboratory abnormalities such as hypercalcemia, hyperphosphatemia, parathyroid hormone level, and increased FGF-23 have an influence on vascular calcification. In addition, failures in anti-calcific mechanisms like changes in matrix Gla protein and fetuin-A levels can also lead to vascular calcification [34, 35]. The association between vascular calcification and fracture risk in CKD patients has been reported in previous studies [36–38], and the link between fracture and MI in this study can be considered an extension of these findings.

The association between fracture and MI was statistically significant in HD patients and not in pre-dialysis CKD patients. There are several explanations for this. First, the factors that influence both vascular calcification and bone strength, such as hyperphosphatemia, increased FGF-23 levels, and abnormalities in vitamin D activation and parathyroid hormone levels, have a greater effect as renal function worsens. This may explain why the link between fracture occurrence and MI may have been stronger in HD patients than in pre-dialysis CKD patients. Moreover, osteoporosis treatment can be a confounding factor, as it may cause negative outcomes in pre-dialysis CKD patients. Bisphosphonate, a representative therapeutic drug for osteoporosis, is not recommended for dialysis patients. However, CKD stage 3 patients may have been treated for osteoporosis, which might have influenced the results in pre-dialysis CKD patients. In addition, dialysis-related factors, such as intradialytic hypotension and ischemic damage, may have intensified the prominent association between fracture and MI in HD patients. Also, our study found that vertebral fracture was associated with MI, but that femoral fracture was not. The reason for this difference, and the pathogenesis involved, is unclear. Further research is needed to clarify the pathophysiology.

One limitation of this study is the unclear cause and effect relationship between fracture and MI. We also could not define whether fracture or MI was the preceding factor. There were cases in which the fracture occurred before MI and vice

versa. Because the study period was limited to 5 years, there was not enough time to clarify the causal link between fractures and MI. In addition, it might be helpful to adjust prior fracture history to clarify the temporal relationship between fracture and MI, but we could not obtain this data due to the essential limitations of HIRA Database. It may be possible to determine the cause and effect relationship with further research if data from a longer period are available. Second, we could not analyze laboratory data and other risk factors such as cigarette smoking, menopause, body mass index, and family history of fracture and MI due to the nature of claims data from the HIRA. Third, other co-morbid diseases except hypertension, hyperlipidemia, and diabetes mellitus were not investigated because we focused on these three major comorbidities to associate with MI. Fourth, the patients' past medical histories (hypertension, diabetes mellitus, and hyperlipidemia) may have been overestimated because we defined past history using drug prescription codes. For example, if a patient was prescribed an angiotensin II receptor blocker to reduce proteinuria, the patient may have been misidentified as having a history of hypertension. Lastly, MI was defined only in patients who underwent coronary angiography or cardiac surgery to exclude patients who may or may not have had heart disease. Therefore, we could have underestimated the number of MI patients in our study, which is a known limitation of the claims data-based study design.

In summary, we demonstrated an association between fracture occurrence and MI in incident HD patients. Our findings persisted after adjusting for age, gender, and major comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia. It is necessary to monitor for the occurrence of MI in HD patients with fracture. Further research using long-term follow-up data and more studies to clarify the pathophysiological mechanisms behind our findings are needed.

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Authors' contributions Study design: D-RR and YJK.
Study conduct: YEK.
Data acquisition: HJO and SYA.
Data analysis: HYC.
Data interpretation: YEK, D-RR and YJK.
Drafting manuscript: YEK.
All authors reviewed and approved the paper. D-RR and YJK take responsibility for the integrity of the data analysis.

Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical approval This study was carried out according to the Declaration of Helsinki Principles. Patient information was anonymized using a non-identifying code; thus, the Institutional Review Board (IRB) of Myongji Hospital, Hanyang University College of Medicine (IRB number: MJH 2019-02-010), waived the requirement for informed consent.

References

1. United States Renal Data System (2018) 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD
2. ESRD Registry Committee, Korean Society of Nephrology (2019) Current Renal Replacement therapy in Korea - Insan Memorial Dialysis Registry, 2018
3. Kidney Disease: Improving Global Outcomes CKDMBDWG (2009) KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl S1–130
4. Kidney Disease: Improving global outcomes CKDMBDUWG (2017) KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011) 7:1–59
5. Desbiens LC, Sidibe A, Ung RV, Fortier C, Munger M, Wang YP, Bisson SK, Marquis K, Agharazii M, Mac-Way F (2018) FGF23-klotho axis, bone fractures, and arterial stiffness in dialysis: a case-control study. Osteoporos Int 29:2345–2353
6. Mirza MA, Karlsson MK, Mellstrom D, Orwoll E, Ohlsson C, Ljunggren O, Larsson TE (2011) Serum fibroblast growth factor-23 (FGF-23) and fracture risk in elderly men. J Bone Miner Res 26: 857–864
7. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St. John Sutton M, Ojo A, Gadegbeku C, di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-o M, Kusek JW, Keane MG, Wolf M (2011) FGF23 induces left ventricular hypertrophy. J Clin Invest 121:4393–4408
8. Mitsnefes MM, Betoko A, Schneider MF, Salusky IB, Wolf MS, Juppner H, Warady BA, Furth SL, Portale AA (2018) FGF23 and left ventricular hypertrophy in children with CKD. Clin J Am Soc Nephrol 13:45–52
9. Leifheit-Nestler M, Grosse Siemer R, Flasbart K et al (2016) Induction of cardiac FGF23/FGFR4 expression is associated with left ventricular hypertrophy in patients with chronic kidney disease. Nephrol Dial Transplant 31:1088–1099
10. Souma N, Isakova T, Lipiszko D, Sacco RL, Elkind MSV, DeRosa JT, Silverberg SJ, Mendez AJ, Dong C, Wright CB, Wolf M (2016) Fibroblast growth factor 23 and cause-specific mortality in the general population: the northern Manhattan study. J Clin Endocrinol Metab 101:3779–3786
11. Isakova T, Cai X, Lee J, Xie D, Wang X, Mehta R, Allen NB, Scialla JJ, Pencina MJ, Anderson AH, Talierco J, Chen J, Fischer MJ, Steigerwalt SP, Leonard MB, Hsu CY, de Boer IH, Kusek JW, Feldman HI, Wolf M, Chronic Renal Insufficiency Cohort (CRIC) Study Investigators (2018) Longitudinal FGF23 trajectories and mortality in patients with CKD. J Am Soc Nephrol 29:579–590
12. Qin Z, Liu X, Song M, Zhou Q, Yu J, Zhou B, Wu Y, He Y, Huang L (2017) Fibroblast growth factor 23 as a predictor of cardiovascular and all-cause mortality in prospective studies. Atherosclerosis 261:1–11
13. Sakuma M, Endo N, Oinuma T, Hayami T, Endo E, Yazawa T, Watanabe K, Watanabe S (2006) Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int 17:1608–1614

14. Jansz TT, Goto NA, van Ballegooijen AJ, Willems HC, Verhaar MC, van Jaarsveld BC (2019) The prevalence and incidence of vertebral fractures in end-stage renal disease and the role of parathyroid hormone. Osteoporos Int 32:635–643
15. Fusaro M, Gallieni M, Aghi A, Rizzo MA, Iervasi G, Nickolas TL, Fabris F, Mereu MC, Giannini S, Sella S, Giusti A, Pitino A, D'Arrigo G, Rossini M, Gatti D, Ravera M, di Lullo L, Bellasi A, Brunori G, Piccoli A, Tripepi G, Plebani M (2019) Osteocalcin (bone GLA protein) levels, vascular calcifications, vertebral fractures and mortality in hemodialysis patients with diabetes mellitus. J Nephrol 32:635–643
16. Fusaro M, Crepaldi G, Maggi S, Galli F, D'Angelo A, Calo L, Giannini S, Miozzo D, Gallieni M (2011) Vitamin K, bone fractures, and vascular calcifications in chronic kidney disease: an important but poorly studied relationship. J Endocrinol Investig 34: 317–323
17. Lau EMC, Dinavahi R, Woo YC, Wu CH, Guan J, Maddox J, Tolman C, Yang W, Shin CS (2020) Romosozumab or alendronate for fracture prevention in east Asian patients: a subanalysis of the phase III, randomized ARCH study. Osteoporos Int 31:677–685
18. Lv F, Cai X, Yang W, Gao L, Chen L, Wu J, Ji L (2020) Denosumab or romosozumab therapy and risk of cardiovascular events in patients with primary osteoporosis: systematic review and meta- analysis. Bone 130:115121
19. Rodriguez-Garcia M, Gomez-Alonso C, Naves-Diaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andia JB, Asturias Study G (2009) Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant 24:239–246
20. Torres A, Torregrosa V, Marcen R, Campistol JM, Arias M, Hernández D, Fernández C, Esforzado N, Paschoalin R, Pérez N, García AI, del Amo M, Pomés J, González Rinne A, Marrero D, Pérez E, Henríquez F, Díaz JM, Silva I, López V, Perello M, Ramos D, Beneyto I, Cruzado JM, Martínez Castelao A, Bravo J, Rodríguez M, Díaz C, Crespo J, Anaya F, Rodríguez ML, Cubero JJ, Pascual P, Romero R, Andrés Belmonte A, Checa MD, Jiménez C, Escuin F, Crespo M, Mir M, Gómez G, Bayes B, González MJ, Gutiérrez A, Cuberes M, Rodríguez Benoit A, García T, Llamas F, Ortega A, Conde JL, Gómez Alamillo C (2016) Mineral metabolism disorders, vertebral fractures and aortic calcifications in stable kidney transplant recipients: the role of gender (EMITRAL study). Nefrologia 36:255–267
21. Magnus JH, Broussard DL (2005) Relationship between bone mineral density and myocardial infarction in US adults. Osteoporos Int 16:2053–2062
22. Farhat GN, Newman AB, Sutton-Tyrrell K, Matthews KA, Boudreau R, Schwartz AV, Harris T, Tylavsky F, Visser M, Cauley JA, for the Health ABC study (2007) The association of bone mineral density measures with incident cardiovascular disease in older adults. Osteoporos Int 18:999–1008
23. Hong WJ, Chen W, Yeo KJ, Huang PH, Chen DY, Lan JL (2019) Increased risk of osteoporotic vertebral fracture in rheumatoid arthritis patients with new-onset cardiovascular diseases: a retrospective nationwide cohort study in Taiwan. Osteoporos Int 30:1617–1625
24. Makovey J, Macara M, Chen JS, Hayward CS, March L, Sambrook PN (2013) High osteoporotic fracture risk and CVD risk co-exist in postmenopausal women. Bone 52:120–125
25. Chen YC, Wu JC, Liu L, Huang WC, Cheng H, Chen TJ, Thien PF, Lo SS (2013) Hospitalized osteoporotic vertebral fracture increases the risk of stroke: a population-based cohort study. J Bone Miner Res 28:516–523
26. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C (2000) Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int 58:396–399
27. Naylor KL, McArthur E, Leslie WD, Fraser LA, Jamal SA, Cadarette SM, Pouget JG, Lok CE, Hodsman AB, Adachi JD, Garg AX (2014) The three-year incidence of fracture in chronic kidney disease. Kidney Int 86:810–818
28. Fusaro M, Tripepi G, Noale M, Vajente N, Plebani M, Zaninotto M, Guglielmi G, Miotto D, Carbonare LD, D'Angelo A, Ciurlino D, Puggia R, Miozzo D, Giannini S, Gallieni M (2013) High prevalence of vertebral fractures assessed by quantitative morphometry in hemodialysis patients, strongly associated with vascular calcifications. Calcif Tissue Int 93:39–47
29. Raggi P, Vukicevic S, Moyses RM, Wesseling K, Spiegel DM (2010) Ten-year experience with sevelamer and calcium salts as phosphate binders. Clin J Am Soc Nephrol 5(Suppl 1):S31–S40
30. Moe SM, Abdalla S, Chertow GM, Parfrey PS, Block GA, Correa-Rotter R, Floege J, Herzog CA, London GM, Mahaffey KW, Wheeler DC, Dehmel B, Goodman WG, Drüeke TB, Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators (2015) Effects of cinacalcet on fracture events in patients receiving hemodialysis: the EVOLVE trial. J Am Soc Nephrol 26:1466–1475
31. Evans M, Methven S, Gasparini A, Barany P, Birnie K, MacNeill S, May MT, Caskey FJ, Carrero JJ (2018) Cinacalcet use and the risk of cardiovascular events, fractures and mortality in chronic kidney disease patients with secondary hyperparathyroidism. Sci Rep 8: 2103
32. Miller P, Chines A, Albergaria B-H, Gielen E, Langdahl B, Miyauchi A, Vanderkelen M, Milmont CE, Maddox J, Adachi J (2019) Efficacy and safety of romosozumab vs placebo among patients with mild-to-moderate chronic kidney disease. J Bone Miner Res 32 (Suppl 1) Abvailable at https://www.asbmr.org/education/2019-abstracts. Access April 12, 2020
33. Cosman F, Crittenden DB, Ferrari S, Lewiecki EM, Jaller-Raad J, Zerbini C, Milmont CE, Meisner PD, Libanati C, Grauer A (2018) Romosozumab FRAME study: a post hoc analysis of the role of regional background fracture risk on nonvertebral fracture outcome. J Bone Miner Res 33:1407–1416
34. Paloian NJ, Giachelli CM (2014) A current understanding of vascular calcification in CKD. Am J Physiol Renal Physiol 307:F891–F900
35. Reiss AB, Miyawaki N, Moon J, Kasselman LJ, Voloshyna I, D'Avino R Jr, De Leon J (2018) CKD, arterial calcification, atherosclerosis and bone health: inter-relationships and controversies. Atherosclerosis 278:49–59
36. Szulc P, Samelson EJ, Sornay-Rendu E, Chapurlat R, Kiel DP (2013) Severity of aortic calcification is positively associated with vertebral fracture in older men–a densitometry study in the STRAMBO cohort. Osteoporos Int 24:1177–1184
37. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V (2004) Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 89:4246–4253
38. El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Dehhaoui M, Ghozlani I (2013) Vertebral fractures and abdominal aortic calcification in postmenopausal women. A cohort study Bone 56:213–219