Research Article

Kidney Diseases

Kidney Dis 2019;5:118–125
DOI: 10.1159/000494924

Received: May 7, 2018
Accepted after revision: October 29, 2018
Published online: February 6, 2019

Factors and Outcome of Renal Osteodystrophy-Associated Initial Fragility Fracture in End-Stage Renal Disease Patients

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Keywords
Renal osteodystrophy · Fragility fracture · Metastatic calcification · Bone and mineral metabolism · End-stage renal disease

Abstract
Background: Renal osteodystrophy has caused increased risk of fragility fracture in end-stage renal disease (ESRD) patients. However, risk factors and outcome of ESRD patients with fragility fracture remain uncharacterized. We aimed to assess these parameters in ESRD patients. ***Summary:*** This retrospective case-control study analyzed 354 ESRD patients (initial fragility fracture [FF] group, $n = 59$; control group, $n = 295$). Pre-dialysis blood hemoglobin, serum albumin, lipid, calcium, phosphorus, alkaline phosphatase (ALP), and intact parathyroid hormone (iPTH) were collected. All procedures performed involving human participants were in accordance with the ethical standards of the institutional committee of The First Affiliated Hospital of Chongqing Medical University (IRB approval number 216-82), and informed consent was obtained from all participants. There were higher prevalence rates of primary hypertension and diabetes, higher serum ALP, corrected calcium, and lower serum total cholesterol, low-density lipoprotein, lipoprotein-α, and iPTH in the FF group. Fractures were more likely to occur in the higher level of corrected calcium as well as in the lower iPTH group. High corrected calcium ($p = 0.010$, OR = 11.308, 95% CI: 1.770–72.242) and serum ALP ($p = 0.000$, OR = 1.007, 95% CI: 1.004–1.011) were independent risk factors of fragility fracture. The incidence of all-cause mortality and cardiovascular (CV) events in ESRD patients with fragility fracture was higher than in those without fracture. ***Key Messages:*** Patients with hypertension, diabetes, excessive suppression of PTH, and poor nutritional status are more prone to fractures. Serum corrected calcium and ALP were independent risk factors of fragility fracture. Patients with initial fragility fracture had more CV events and higher mortality.

Introduction

Renal osteodystrophy (ROD) is a common complication of chronic kidney disease (CKD), which may lead to defective mineralization, altered bone morphology, and/or bone turnover [1–3]. Animal research found that bone

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changes occur even in the early stage of CKD [4], and with CKD progression, the patient may show symptoms such as bone pain, joint pain, bone deformation, and even spontaneous fractures.

CKD increases the risk of fractures [5], which are consequently associated with increased mortality, decreased quality of life, and higher economic burden. However, only few case reports [6, 7] and studies [8, 9] specifically focus on fractures in end-stage renal disease (ESRD) patients. In Chinese ESRD patients, fragility fractures remain uncharacterized, with the underlying mechanisms and risk factors undefined.

Recently, a preliminary epidemiologic investigation [8] showed that besides dialysis, old age, female gender, diabetes and liver cirrhosis, osteoporosis, and a prior history of hip fracture are also risk factors for hip fracture in patients with ESRD. Bone strength is mainly controlled by bone density, composition, and mineralization [10]. Alterations of bone turnover and defective mineralization are associated with increased risk of fracture. Recently, the organization of Kidney Disease: Improving Global Outcomes (KDIGO) proposed a new classification for ROD characterization, which encompasses changes in bone turnover, mineralization, and bone volume [11]. However, the exact associations of bone turnover and bone metabolism with fracture incidence in Chinese ROD patients remain unstudied.

In this study, we assessed the clinical characteristics and risk factors of Chinese ESRD patients with initial fragility fracture, in order to prevent ROD-associated fracture and provide evidence for therapy improvement.

Methods and Materials

Study Subjects

We conducted a retrospective case-control study on hospitalized ESRD patients who received maintenance hemodialysis for at least 3 months at the First Affiliated Hospital of Chongqing Medical University from January 1, 2012 to September 30, 2016. Fifty-nine cases were hospitalized for bone pain that occurred spontaneously or sustained from a minor trauma (a fall from standing height, sitting position, horizontal positioning, from 1–3 steps) and confirmed initial fragility fracture according to history of present illness and X-ray or CT examination, assigned to the fragility fracture group (FF group). A total of 295 hemodialysis patients without fracture hospitalized in the same period were selected as control group, matched in a 5:1 ratio for age, sex, and dialysis duration. The exclusion criteria were: incomplete data, high energy trauma fractures (motor vehicle accident, high-velocity bicycle accident, fall from significant height, etc.), old fractures, malignancy, tuberculosis, Cushing syndrome, current or past history of treatment with selective estrogen receptor modulators, and accepted glucocorticosteroid treatment for more than 2 years. Etiologies of the 354 enrolled ESRD patients are shown intuitively by a pie chart, and the respective etiologies of the two groups are shown by a chart in the online supplementary material 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000494924). The 354 patients accepted the therapy of active vitamin D and calcic phosphorous binder from the stage of CKD3. A few of them may have changed the calcic agent to non-calcic phosphorous binder such as sevelamer or lanthanum carbonate. The usage of phosphorous binder within 3 months before enrollment is listed in the online supplementary material 2. There was no difference between the two groups. All dialysate Ca concentrations were not higher than 1.25–1.50 mmol/L.

Data Collection

Laboratory variables including blood hemoglobin, serum calcium, phosphorus, alkaline phosphatase (ALP), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), lipoprotein-α (LP-α), prealbumin, albumin, and intact parathyroid hormone (iPTH) were collected before one regular dialysis at the time of enrollment. Calcium was corrected for serum albumin levels <40 g/L as follows: corrected calcium (mmol/L) = measured calcium (mmol/L) + 0.2 × (4 – measured albumin [g/dL]) [12]. General information and body mass index (BMI) of the patients were recorded. Bone or cartilage structure fracture was defined as continuous bone interruption including epiphyseal separation, and evaluated by X-ray or CT. Radiological findings were analyzed by two observers blinded to clinical data, with an interobserver concordance of 95%. Vascular calcification was determined with a CT value of vessel of 130 or higher by CT scan [13]. All subjects underwent echocardiography on a Hewlett-Packard Sonos 100 device equipped with a 2.25-MHz probe to verify the presence of cardiac valvular calcification, if ≥1 mm strong echo occurred in aortic and mitral, tricuspid leaf, or disc ring as assessed by Doppler echocardiography [14].

Statistical Analysis

Statistical analysis was performed with the SPSS 22.0 statistical software. Numeric data were presented as mean ± SD or median (interquartile range) and analyzed by Student's *t* test or Wilcoxon test. Categorical variables were expressed as percentage and analyzed by χ^2 test. Logistic regression analyses were performed to assess possible relationships while controlling for relevant measured correlates. $p < 0.05$ was considered statistically significant.

Results

The Common Site of Initial Fragility Fracture

In this study, the most common fracture site was the hip (including 19 upper femur and 7 pubic bone fractures), followed by vertebrae (including 10 thoracic vertebral, 8 lumbar vertebral, and 1 case with both types). The other parts affected were radius, clavicle, patella, fibula, and scapula. Several fracture sites are shown in Figure 1.

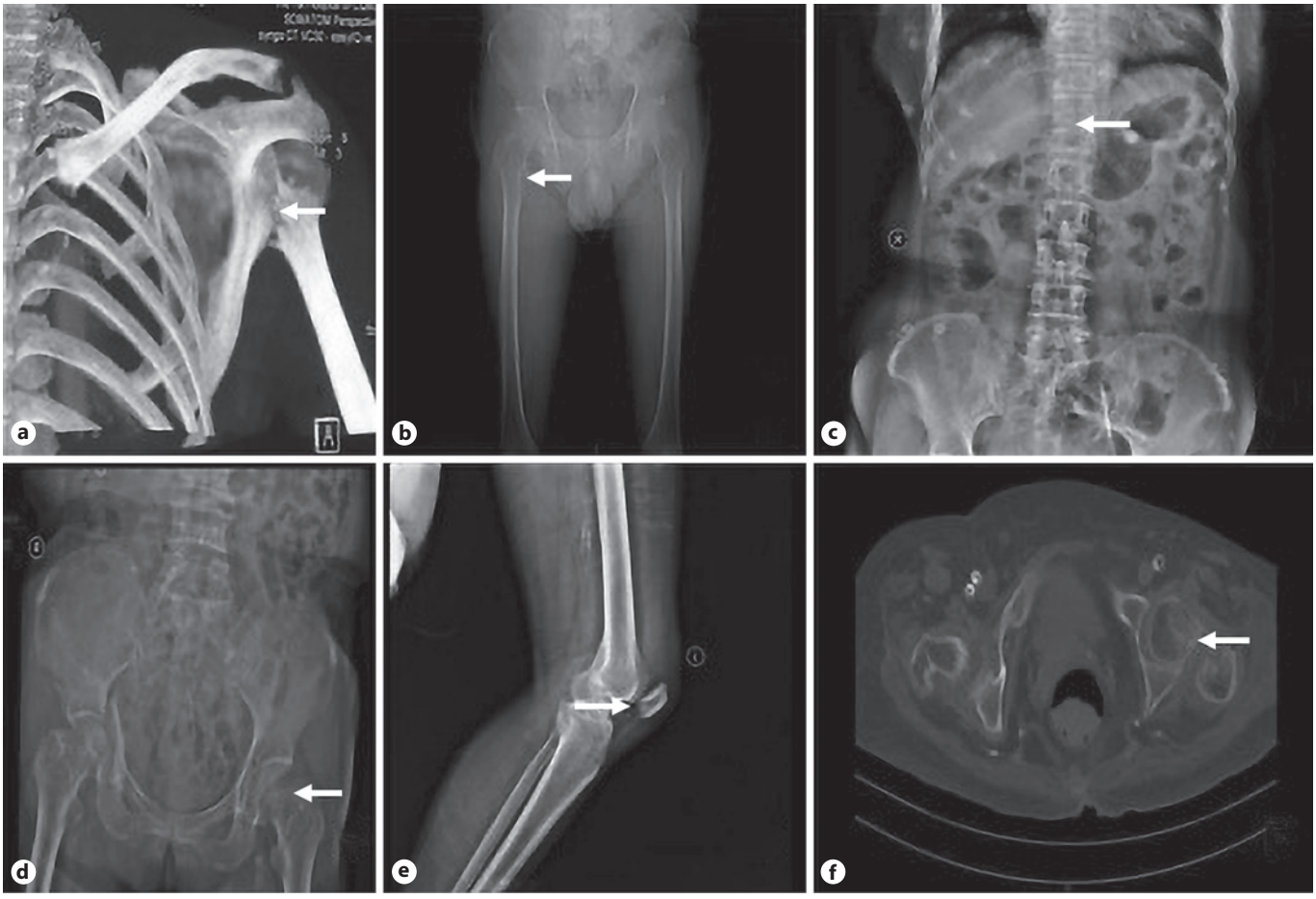

Fig. 1. Different fracture sites (arrows) revealed by X-ray or CT. **a** Fracture of left humerus head and surgical neck. **b** Avulsion fracture of right lesser trochanter. **c** Compression fracture of the twelfth thoracic spinal. **d** Left acetabular fracture. **e** Left patella fracture. **f** Left collum femoris fracture.

Basic Clinical Characteristics of the Patients

A total of 354 ESRD patients aged 20–90 years were enrolled in this study, including 182 males and 172 females. There were 59 initial fragility fracture patients aged 65.3 ± 14.3 years in the FF group, including 26 males and 33 females, and 295 patients aged 61.7 ± 14.2 years in the control group, including 156 males and 139 females. Then, the primary causes of ESRD with or without fragility fracture were assessed, and higher prevalence rates of primary hypertension and diabetes mellitus were obtained in ESRD patients with initial fragility fracture compared with the control group ($p < 0.05$). No significant differences in BMI and glucocorticosteroid treatment were found between the two groups (Table 1).

Nutritional State of ESRD Patients with Initial Fragility Fracture

Nutritional state is often an important influential factor for fracture occurrence; therefore, we explored the correlation between the nutritional index and initial fragility fracture in ESRD patients. As shown in Table 1, there were lower serum TC, LDL, LP-α while higher hemoglobin levels ($p < 0.05$) in the FF group compared with control group values. No significant differences were obtained in serum albumin, prealbumin, TG, and HDL levels between the two groups.

Mineral-Bone Metabolism Associated Parameters of ESRD Patients with Initial Fragility Fracture

Alterations of mineral-bone metabolism are associated with increased risk of fracture. In this study, we ana-

Table 1. Clinical data, biochemical data, metastatic calcification, and outcomes in the two groups

	FF group (n = 59)	Control group (n = 295)	p value
BMI	22.89 (19.48, 25.08)	22.66 (20.18, 24.71)	0.984
Glucocorticosteroid treatment, n (%)	14 (3.7)	108 (36.6)	0.08
Primary hypertension, n (%)	28 (47.5)[a]	89 (30.2)	0.042
Diabetes, n (%)	27 (45.8)[a]	95 (32.2)	0.045
Hemoglobin, g/L	102.0±24.14[a]	93±25.0	0.012
Prealbumin, mg/L	126.15±20.15	129.14±20.06	0.298
Albumin, g/L	36.3±5.90	36.3±5.91	0.968
TC, mmol/L	3.55 (3.06, 4.16)[a]	4.02 (3.34, 4.75)	0.019
TG, mmol/L	1.29 (1.01, 1.70)	1.26 (0.92, 1.86)	0.846
LDL, mmol/L	1.87 (1.45, 2.46)[b]	2.21 (1.70, 2.96)	0.007
HDL, mmol/L	1.13±0.35	1.23±0.38	0.084
LP-α, mg/L	234 (106.0, 445.0)[a]	405 (184.8, 561.8)	0.015
ALP, U/L	99.0 (70.0, 173.0)[a]	86.0 (67.0, 114.0)	0.014
Calcium, mmol/L	2.19 (2.03, 2.32)[c]	2.10 (1.87, 2.20)	0.000
Corrected calcium, mmol/L	2.27 (2.15, 2.42)[b]	2.18 (2.00, 2.30)	0.000
Phosphorus, mmol/L	1.60 (1.24, 1.81)	1.76 (1.37, 1.98)	0.060
iPTH, pg/mL	207.9 (134.0, 448.7)[b]	362.5 (222.4, 503.5)	0.002
Calcium-phosphorus product, $mmol^2/L^2$	3.63 (2.71, 4.25)	3.60 (2.91, 4.27)	0.594
Aortic calcification, n (%)	32 (54.2)[b]	94 (31.9)	0.002
Cardiac valve calcification, n (%)	17 (28.8)[a]	43 (14.6)	0.013
All-cause death, n (%)	34 (57.6)[c]	51 (17.3)	0.000
CV events, n (%)	26 (44.1)[a]	85 (28.8)	0.017

CV events include stable or unstable angina, myocardial infarction, heart failure, transient ischemic attack, cerebral ischemic stroke and subarachnoid hemorrhage, cerebral hemorrhage, peripheral arterial diseases, abdominal aortic aneurysm, arrhythmia, and sudden cardiac death. [a] $p < 0.05$ versus control group; [b] $p < 0.01$ versus control group; [c] $p < 0.001$ versus control group.

Table 2. Risk factors of initial fragility fracture in ESRD patients analyzed by logistic regression

Variables at baseline	Wald z value	p value	OR (95% CI)
Hemoglobin (g/L)	7.891	0.005	1.024 (1.007–1.041)
ALP (U/L)	15.131	0.000	1.007 (1.004–1.011)
Corrected calcium (mmol/L)	6.572	0.010	11.308 (1.770–72.242)
iPTH (pg/mL)	4.722	0.030	0.999 (0.998–1.000)

lyzed the changes of mineral-bone metabolism-associated parameters in ESRD patients with initial fragility fracture. As shown in Table 1, higher serum ALP, corrected calcium, and lower serum iPTH levels were found in the FF group compared with the control group ($p < 0.05$). No significant differences in phosphorus and calcium-phosphorus product were found between the two groups.

We further assessed the incidence of initial fragility fracture in patients with different levels of serum corrected calcium, phosphorus, and iPTH. According to the KDIGO recommendations regarding target corrected calcium (2.1–2.5 mmol/L) and phosphorus (1.13–1.78 mmol/L) or K/DOQI guideline recommendations about target iPTH (150–300 pg/mL) in CKD5 patients, the 354 patients were divided into three subgroups: lower, target, and higher level subgroups, respectively. As shown in Figure 2, fractures were more likely to occur in the higher level subgroups by corrected calcium levels as well as in the lower iPTH group ($p < 0.05$). However, no differences were found among the various serum phosphorus subgroups ($p > 0.05$).

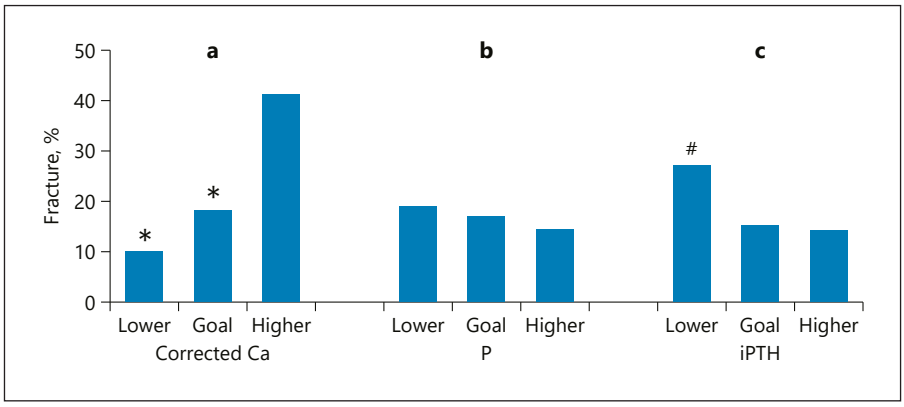

Fig. 2. Initial fragility fracture incidence in the three subgroups of serum corrected calcium (Ca) (**a**), phosphorus (P) (**b**), and iPTH (**c**). Corrected Ca subgroups, total comparison: $\chi^2 = 8.99$, $p < 0.05$, * $p < 0.05$ versus higher corrected Ca group. P subgroups, total comparison: $\chi^2 = 0.56$, $p > 0.05$. iPTH subgroups, total comparison: $\chi^2 = 5.33$, $p < 0.05$, # $p < 0.05$ versus higher iPTH group.

Risk Factors Associated with Initial Fragility Fracture Analyzed by Logistic Regression

All factors with $p < 0.10$ in univariate analysis were included in a binary logistic regression model with backward selection. As shown in Table 2, higher serum corrected calcium and ALP were significant independent risk factors for initial fragility fracture in ESRD patients.

Outcome Analyses

We continued to follow-up all the investigated subjects till April 31, 2017, to collect the metastatic calcification (arterial and cardiac valve calcification), cardiovascular (CV) events, and all-cause death during the follow-up period. 1.7% patients were lost to follow-up halfway. 85 all-cause deaths were observed; 34 and 51 cases were in the FF and control groups, respectively. In the FF group, the ratios of aortic and cardiac valve calcification, CV events, and all-cause death were higher in the FF group compared with control group values (Table 1).

Discussion

Hip Fractures Were the Most Common, Followed by Vertebrae Fractures

In this study, the hip (including femoral neck, greater trochanter, and pubic bone) was the most frequent fracture site, accounting for 44.1%, followed by vertebrae fractures, which accounted for 32.2%. Many studies [9, 11] showed that ESRD patients have significantly increased risk of fractures, with fragility fracture being a common complication of uremia. Based on US Renal Data System (USRDS) datasets, Wagner et al. [15] found that the incidence of vertebral and hip fractures in ESRD patients increased significantly, from 12.5‰ patient-years in 1992 to 25.3‰ patient-years in 2004. Alem et al. [11] reported an annual incidence of hip fracture of 7.45‰ in male and 13.63‰ in female ESRD patients, respectively, i.e., 4.16 and 4.4 times higher than in normal gender-matched individuals. Lin et al. [8] reported an overall incidence rate of hip fracture of 89.21‰ patient-years for ESRD patients.

Risk Factors of Fragility Fracture

Fragility fracture is a common complication in patients with ESRD; however, the risk factors for fragility fracture remain undetermined. Firstly, we assessed the relationship between fragility fracture and the underlying primary disease of ESRD and found an increased risk of fragility fracture in ESRD patients with hypertension and diabetes; indeed, hypertension was independently associated with initial fragility fracture, corroborating previous reports [16–20]. A 10-year prospective study of 3,676 women in the United States showed that mineral (including urinary calcium) loss is increased in hypertension patients, which may constitute an important mechanism for fracture occurrence in hypertension patients with ESRD. Some scholars proposed that hypertension patients treated with calcium channel blockers show reduced bone absorption of calcium [21]. In addition, high blood pressure and blood pressure fluctuations increase the risk of falls and fracture [17]. Diabetes mellitus was found associated with increased fracture risk [22–25]. Blood sugar fluctuations may lead to increased risk of falls [26], and diabetic patients have bone fragility regardless of bone mineral density; the underlying mechanisms may include osteoblastic dysfunction, advanced glycation end products collagen cross-links, and micro-architectural abnormalities such as cortical porosity and deterioration of trabecular bone structure [27].

Poor nutritional status is a conditional risk factor for fracture. As shown above, serum TC, LDL, and LP-α levels were significantly lower in ESRD patients with initial fragility fracture. Sivas et al. [28] found that increasing TC by 1 mg/dL results in a 2.2% risk decrease for vertebral fractures. In agreement, Yamaguchi et al. [29] demonstrated that low TG levels are associated with vertebral fracture occurrence in postmenopausal women. Indeed, studies reported that osteoblasts and adipocytes originate from the same progenitor cells. It was demonstrated that the LDL receptor-related protein 5 (LRP5) gene plays an important role in bone mass loss and the risk of fractures [30]. In addition, drugs, such as statins and bisphosphonates, may affect bone and lipid metabolism [31, 32]. Besides, from clinical and nutritional standpoints, good nutritional status often means a good exercise of skeletal muscles, which prevents fracture in these patients. Unexpectedly, we found that higher hemoglobin levels in the FF group may be explained in this way: hyperhemoglobinemia often means increased blood viscosity, which results in endotheliocyte damage and micro-inflammatory state, thus affecting bone metabolism [33]. In fact, it was reported that hypohemoglobinemia and hyperhemoglobinemia are both associated with increased risk of fracture.

The pathogenesis of renal osteopathy is associated with an insufficient synthesis of $1,25(OH)_2D$, hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism after renal failure [34, 35]. Interestingly, we found that serum corrected calcium levels were significantly higher in the FF group, and serum iPTH levels were lower compared with control group values; in addition, patients in the higher corrected calcium and lower PTH subgroups were more prone to fragility fracture, as shown by Figure 2, in agreement with previous findings [36]. Logistic regression analysis showed that fragility fracture was indeed associated with high corrected calcium levels. Similar studies have reported that hip fractures [9, 37, 38] and vertebral body fractures [26] are starkly associated with low iPTH. In recent years, with a wide clinical use of calcium carbonate and vitamin D analogues, alongside improved dialysis techniques in ESRD, occurrence of high-bone turnover ROD has decreased, whereas hypercalcemia, excessive suppression of PTH, and secondary low-bone turnover ROD are increasingly prevalent and acknowledged [37, 39]. Although hyperphosphatemia, another important complication in ESRD, plays an important role in vascular calcification and affects prognosis of patients with ESRD [40], we found that hyperphosphatemia was not a risk factor for fracture in our study.

As a representative of osteoblast activity, ALP plays an important role in bone calcification or tissue calcification. Maruyama et al. [41] demonstrated that elevated ALP is associated with reduced bone mineral density and may increase the risk of fracture in ESRD patients [42]. In this study, serum calcium and ALP levels in initial fragility fracture patients were significantly higher, but iPTH amounts were significantly reduced, with more severe arterial and cardiac valve calcification (Table 1). These findings suggested that elevated serum calcium cannot increase calcium deposits in the bone; on the contrary, it causes significantly increased metastatic calcification in soft tissues. An epidemiological study found that high serum ALP level may be associated with metastatic soft tissue calcification in ESRD patients [43]. Studies [44, 45] showed that elevated ALP amounts increase the hydrolysis of pyrophosphate, an inhibiting factor of vascular calcification, hence increasing the risk of metastatic calcification. Therefore, high serum ALP levels may also constitute a risk factor of initial fragility fracture and metastatic calcification in patients with ESRD.

Outcome and Metastatic Calcification in ESRD Patients

ROD may influence the prognosis of ESRD patients. Mittalhenkle et al. [46] firstly focused on hip fracture and found that hip fracture was significantly correlated with high all-cause mortality in dialysis patients. In this study, we found that the CV events and all-cause death in the FF group were all higher than those in the control group.

To the best of our knowledge, this retrospective case-control study may be the first population-based investigation assessing the risk factors of fragility fracture in ESRD patients in China. Multiple reports showed that presence and seriousness of vascular calcification are associated with CV and all-cause mortality independently [39]. In this study, we found that ESRD patients with initial fragility fracture had more overt vascular calcification, heart valve calcification, and CV events, compared with the control group. Previous findings indicated that CKD-mineral and bone disorder, including metastatic calcification, in addition to causing significantly increased risk of fracture, is associated with higher CV mortality and morbidity. Indeed, in CKD, the bone may detrimentally impact vascular calcification through many ways, including altered secretion of PTH, abnormal bone remodeling, calcium-phosphate disorders, and excessive vitamin D supplementation [47]. The present study revealed that Chinese ESRD patients with initial fragility fracture had higher incidence of metastatic calcification

as well as increased risk of CV events and all-cause death compared with those without fracture.

This was a single-center study, with a sample size not large enough in the analysis, which may constitute a sampling error. The bone mineral density data were not taken into consideration in the analysis. A bone biopsy may offer a guide for fragility fracture prevention and treatment, but it was not carried out. The follow-up period was not long enough since some patients entered the study late, especially those enrolled in 2015–2016, which may introduce a bias into mineral-bone metabolism and outcome analyses, and if possible, we need to conduct a further survival analysis of ESRD patients.

In summary, this retrospective case-control study showed that hip fractures were the most common fracture site, serum corrected calcium and ALP were found to be independent risk factors for initial fragility fracture in patients with ESRD, and excessive suppression of PTH and poor nutritional status are unfavorable for ESRD patients. In addition, our findings demonstrated that ESRD patients with initial fragility fracture had more CV events and a poor outcome.

Statement of Ethics

The research was ethically conducted in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors declare no conflicts of interest.

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