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Chapter 5

Bone Fragility in Hemodialysis Patients

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http://dx.doi.org/10.5772/59408

1. Introduction

According to WHO technical report in 1994, osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and consequently increases the fracture risk. Since fracture does not solely depend on bone mass, osteoporosis was defined by NIH as a skeletal disorder, characterized by compromised bone strength predisposing to an increased risk of fracture. Although aging is a major risk for fracture, it is a strong risk for chronic kidney disease (CKD) as well. Thus, patients having comorbidity of CKD and osteoporosis are sometimes found. According to a study NHANES III (the Third National Health and Nutrition Examination Survey, 1988-1994) in the US, in women with osteoporosis, 85% (95%CI: 79-91%) showed Creatinine clearance (Ccr)≤60mL/min and 24% (95%CI: 19-29%) were of Ccr<35mL/min [1]. Another study demonstrated that Ccr≤60mL/min is an independent risk factor for fracture at vertebra, femur and radius [2].

In addition to aging, a female sex, low bone mineral density (BMD), prevalent fracture, family history of fracture and lower body weight, life style such as drinking, smoking and excise and common diseases would affect risk for fracture [3, 4]. Recent studies demonstrate that measurement of BMD by Dual-energy X-ray absorptiometry (DXA), which is a gold standard for diagnosis of osteoporosis, is less useful for the fracture prediction in the patients with diabetes mellitus and the patients under glucocorticoid therapy [5-8]. Among these population, BMD-independent bone fragility and falls may be involved in an elevation of the risk for fracture. Therefore, much interest is focused on the link between kidney dysfunction /CKD and fracture /osteoporosis [9].

2. Elevated risk for fracture in end-stage kidney disease

Compared with general population, the risk for fracture is reported to be much higher in end-stage kidney disease (ESKD) (Table 1) [10-14]. A multicenter cohort study in the US having more than 320,000 dialysis patients, 13.6 in women and 7.5 in men had an incident hip fracture among 1,000 person-years [10].The incidence ratio standardized with age was about 4.4 times higher than that of healthy subjects. Another study in a single institution in the US having 1,272 dialysis patients, 13.9 (24.1 in women and 11.7 in men) had an incident hip fracture among 1,000 person-years, which was 17.4 times higher than that of general population [11]. Increased risk of hip fracture was shown among Japanese hemodialysis (HD) patients, in which the risk was about 5 times higher than that of general population [12]. Facture risk of HD patients was increased in the west part of Japan, which showed similar results to the general population [12, 15]. A multicenter prospective study (DOPPS II) in 12,782 patients from 12 countries showed that 8.9/1,000 person-years had a hip fracture [13]. In addition, risk for fracture may even be higher for 3 years after kidney transplantation [16].

Study design	Subjects	Fracture type	Fracture incidence of 1,000 person-years and RR (95%CI) for general population	Reference
Retrospective cohort study	326,464 dialysis patients in the US	hip	men 7.45 4.44 (4.16-4.75) women 13.63 4.40 (4.17-4.64)	[10]
Retrospective cohort study	1,272 dialysis patients in the US	hip	men 11.7 14.2 (9.3-28.6) women 24.1 17.2 (7.1-19.4) all 13.9 17.4 (12.4-34.0)	[11]
Prospective cohort study	12,782 HD patients in 320 HD facilities from 12 countries	hip	men, 15-54 1.00 (Ref) men, 55-64 2.15 (1.06-4.57) men, 65-74 2.38 (1.07-5.26) men, 75- 5.05 (2.36-10.82) women, 15-54 0.85 (0.30-2.35) women, 55-64 1.85 (0.75-4.59) women, 65-74 4.67 (2.22-9.83) women, 75- 7.79 (3.69-16.43) all 8.9 (8.4-9.4)	[13]
		any	men, 15-54 1.00 (Ref) men, 55-64 1.25 (0.84-1.85) men, 65-74 1.65 (1.10-2.48) men, 75- 1.86 (1.24-2.77) women, 15-54 1.07 (0.67-1.69) women, 55-64 2.36 (1.56-3.54) women, 65-74 2.58 (1.79-3.63) women, 75- 3.43 (2.33-5.06) all 25.6 (24.4-27.0)	
Retrospective cohort study	128,141 HD patients in Japan	hip	men 7.57 6.2 (5.7-6.8) women 17.43 4.9 (4.6-5.3)	[12]

Table 1. Elevated fracture risk in ESKD

Mean age of incident fracture in dialysis patients is reported to be 61.4 in women and 64.4 in men, which are much younger than those of general population (74 and 80, respectively),

indicating that dialysis patients apt to suffer from bone fractures at younger age [11]. The incidence of hip fracture in dialysis patients of 60 and 70 years old is comparable to those of 75 and 80 years, respectively [13, 14].

CKD is not only at risk for fracture but also at mortality risk after fracture [11, 17, 18]. Coco et al. reported the mortality rate was 64% a year after hip fracture in HD patients, whereas it was about 20% in the healthy subjects [11]. Among HD patients, mortality rate was showed to be 2.7 times greater in patients with incident fracture, compared to those without fracture [17]. Moreover, significant elevation of fracture-associated mortality risk was found in patients even before the initiation of HD therapy [18].Although bisphosphonates may not be recommended in ESKD patients, they are useful in osteoporotic patients with great risk reduction for fracture [19]. PTH agent such as teriparatide, and selective estrogen receptor modulator (SERM) are also established therapies with 50% or more of relative risk reduction [20, 21].Thus, early starts of therapy for osteoporosis will prevent fracture. These findings suggest that clinicians need to evaluate bone status and initiate osteoporosis therapy in patients with CKD in early stages.

3. Elevated risk for fracture in early stages of CKD

Although considerably high risk for fracture has been shown in ESKD patients, recent epidemiological studies indicate that the risk for fracture is elevated in CKD patients, even in early stages (Table 2). Nickolas et al. reported that CKD was an independent predictor of prevalent hip fracture [22]. When categorized 6,270 participants by estimated glomerular filtration rate (eGFR) using MDRD formula, prevalent hip fracture was found in 5.2% and 2.0% of those with eGFR 15-60mL/min/1.73m^{2}and eGFR>60mL/min/1.73m^2, respectively. Odds ratio of prevalent hip fracture in those with CKD was 2.12 (95%CI: 1.18-3.80), compared with those with eGFR>100mL/min/1.73m^2. Multiple logistic analysis for prevalent hip fracture showed that osteoporosis (OR=2.52, 95%CI: 1.08-5.91), low activity (OR=2.10, 95%CI: 1.03-4.27) and CKD (OR=2.32, 95%CI: 1.13-4.74) were the risk factors independent of age, sex, body weight, race, BMD, history of hip fracture in mother, dietary calcium intake, and 25(OH)D blood level and propensity score to CKD. In ≥75 years subjects with and without prevalent fracture, the ratio of CKD suffered was 32.1% and 32.2%, respectively, whereas in < 75 years subjects, the ratio was 19.2% and 6.2%, respectively. This finding suggests that the younger patients with prevalent fractures suffer from CKD almost 3 times more frequently, compared to those without fractures. Thus, CKD (eGFR: 15-60mL/min/1.73m^2) is an independent risk of hip fracture, especially in subjects with <75 years old.

Ensrud et al. conducted a prospective study to examine risk for fracture in 9,704 women with >65 years, stratified by CCr (Cockcroft-Gault formula) corrected with body surface area [23]. During 6 years observational period, hazard ratios of hip fracture were 2.32 (95%CI: 1.15-4.68) in CCr<45 mL/min/1.73m^2 and 1.57 (95%CI: 0.89-2.76) in CCr45-59 mL/min/1.73m^2, compared to CCr≥60 mL/min/1.73m^2. These results suggest that decreased kidney function is a risk for incident hip fracture independent of age, body weight and calcaneal BMD. However, significant difference disappeared after adjustment by healthy status, smoking, walking excise,

Study design	Subjects	Kidney function	Odds ratio of fracture risk (95%CI)		Reference
Cross-sectional study	5313 osteoporotic patients aged >65 in Germany	CCr ＜65mL/min	hip radius vertebra	1.57 (1.18–2.09) 1.79 (1.39–2.31) 1.31 (1.19–1.55)	[2]
Cross-sectional study	6270 subjects aged >50 in the US	eGFR ＜60mL/min/1.73m^2	hip	2.32 (1.13–4.74)	[22]
Cohort study	9704 women aged >65 in the US	CCr 45～59mL/min CCr ＜45mL/min CCr 45～59mL/min CCr ＜45mL/min CCr 45～59mL/min CCr ＜45mL/min	femoral neck femoral neck trochanter trochanter vertebra vertebra	1.24 (0.60–2.56) 1.41(0.59–3.36) 3.69(1.21–11.24) 5.04(1.38–18.45) 1.08(0.61–1.92) 1.33(0.63–2.80)	[23]
Case-control study	6458 postmenopausal osteoporotic women in Canada	CCr ＜45mL/min	all vertebra	1.3(1.0–1.6) 2.5(1.6–3.9)	[66]
Cohort study	4699 subjects aged >65 in the US	eGFR＜60mL/min/1.73m^2 Cystatin C 1SD above	hip hip	1.38(0.99–1.94) 1.16(1.01–1.33)	[25]
Case-control study	397 incident hip fracture cases and 397 matched controls in the US	eGFR＜60mL/min/1.73m^2	hip	2.50(1.32–4.72)	[67]
Case-control study	659 postmenopausal women in Japan	CCr 60～89mL/min	vertebra	2.79(1.31–5.95)	[26]

Table 2. Elevated fracture risk in CKD

diabetes mellitus (DM), and history of fracture occurred after 50 years old. On the other hand, only a tendency was observed using eGFR by MDRD formula instead of CCr. Moreover, the analysis of fracture sites shows that the risk for fracture was elevated at the trochanter not at the femoral neck, indicating that hip fracture in CKD patients could be associated with the frailty [24].

Since sarcopenia or protein-energy wasting (PEW) is commonly seen in CKD patients, eGFR derived from creatinine often underestimates actual kidney function. Cystatin C is more accurate estimate for kidney function than eGFR calculated from creatinine, especially in elderly people whose muscle mass is reduced. Fried et al. demonstrated a significant association between cystatin C blood level and hip fracture risk in 4,699 subjects in their prospective study. Women with eGFR<60 mL/min/1.73m^2 have an increased risk for fracture even after adjusting the covariates [25].

So far, few studies are performed to evaluate the relationship between kidney function and vertebral fractures. In a case-control study of 659 postmenopausal osteoporotic women with an average age of 64.5 years, 45.3% of those with eGFR<60 mL/min/1.73m^2 had prevalent vertebral fractures and the ratio was significantly higher than those with eGFR 60-89 mL/min/1.73m^2 (25.3%) and eGFR≥90 mL/min/1.73m^2 (23.8%) [26]. Multiple logistic regression analysis showed that CCr was selected as a significant predictor of prevalent vertebral fracture after

adjustment for years after menopause, smoking, drinking, and BMD at vertebrae (OR=0.359, 95%CI: 0.168-0.765, p=0.01). There were significant positive correlations between eGFR and BMD at the femoral neck and the radius. These findings suggest that the reduction of BMD and the elevation of risk for fracture may start during early CKD (eGFR<90 mL/min/1.73m^2).

However, Ensrud et al. could not find a significant association of incident vertebral fractures with kidney function calculated by C-G as well as MDRD formulas [23]. The discrepancies of these two reports could be derived from the differences of participants' background such as race, age, and kidney function, and the methodology. In the latter study, 150 patients, who had incident vertebral fractures, were relatively older (mean age: 73.1 years) than those of the former study. In addition, the second X-ray was not performed in 22% of women possibly due to bed rest or death. Thus, such limitation should be taken into account when the results of prospective study are assessed.

Previous studies suggest that the risk for fracture is elevated in parallel with a decrease in kidney function. We estimated the risk for fracture with the assessment tool FRAX® (http://www.shef.ac.uk/FRAX/) in 1,935 community-dwelling healthy Japanese people (1,123 women and 812 men, mean age: 68.9) [27]. Estimated risk of hip fracture for 10 years was 2.1% in men and 4.6% in women, respectively (Figure 1), and the risk was inversely proportionate to eGFR. Significant increase of the risk for fracture was observed in men with eGFR<60 ml/min/1.73m^2 and women with eGFR<75 ml/min/1.73m^2. Major risk of osteoporotic fracture (vertebrae, hip, radius and humerus) for 10 years was estimated as 6.8% in men and 14.0% in women, which was also elevated as a loss of kidney function. As we have shown the elevated risk for fracture in CKD population using FRAX®, this tool has originally been developed for the screening of patients with high risk for fracture. Indeed, Jamal et al. have recently reported the utility of FRAX® in CKD patients [28].

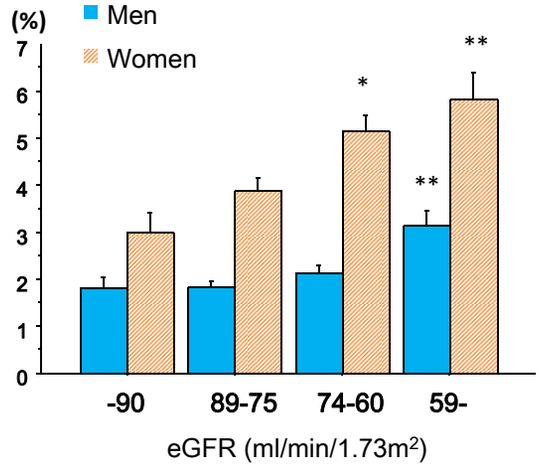

Figure 1. Association between eGFR and 10 year-hip fracture incidence calculated by FRAX® In 1,935 community-dwelling healthy Japanese people (1,123 women and 812 men, mean age: 68.9), association between eGFR (MDRD formula) and 10 year-hip fracture incidence calculated by FRAX® was shown. *; p<0.001and **; p<0.005 (vs eGFR 90-ml/min/1.73m^2), Post-hoc test (Fisher's PLSD) (modified by ref. [27])

In this part, terms such as eGFR and CCr were used followed by the original reports. Moreover, CCr was corrected with body surface in some reports and not in others. Kidney function is prone to be underestimated in C-G formula and overestimated in MDRD, which may lead confusion and the discrepancy among study results as described by Ensrud et al. [23].

4. Pathophysiology of elevated risk for fracture in CKD

Low BMD is a risk for fracture in the general population, and this is also true for CKD patients [29-32]. Recent longitudinal studies using high resolution peripheral quantitative computed tomography (HR-pQCT) have demonstrated that loss of kidney function is associated with a decrease in BMD, independent of age and body mass [29-32]. HR-pQCT is developed to measure volumetric bone mass, and to discriminate between cortical bone and trabecular bone. Volumetric BMD measured by HR-pQCT is more accurate than areal BMD by DXA, because areal BMD depends on body size and cannot exclude aortic calcification [33]. Cejka et al. reported the characteristics of bone microarchitecture of 74 HD patients, where cortical and trabecular microarchitecture was significantly impaired in patients with fracture [34]. Trabecular BMD at the tibia was the strongest determinant of fracture in these patients. In 70 patients aged ≥50 with CKD stage 2-4, trabecular BMD at the tibia and radius, trabecular number and cortical thickness were significantly decreased and trabecular separation was increased [35]. Another study by Nickolas demonstrated a significant loss of cortical BMD at the distal radius, and marked increase in cortical porosity without any changes in trabecular indices in CKD patients [36]. There was a significant association between kidney dysfunction and cortical bone loss as well as increased porosity [35]. Although DXA has a lower discriminatory power than HR-pQCT measured volumetric density, a recent report suggests a benefit of BMD measurement even with DXA to identify HD patients with high risk of fracture [32].

Although bone histological analysis is the most accurate method, a few studies have been reported because of its invasiveness and difficulty. Tomiyama et al. conducted bone biopsy at the iliac crest of 50 CKD patients after tetracycline labelling [37]. Interestingly, histomorphometry showed low turnover of bone in most patients; 100% in stage 2, 88% in stage 3, and 78% in stage 4. This finding suggests that the bone formation rate is markedly depressed in CKD at early stages.

Bone strength depends not only on BMD but also on the other factors, which have been called as a bone quality. In primary osteoporosis, bone strength is explained about 70% by BMD and the rest by bone quality. Since the risk for fracture is dissociated with BMD especially in patients with DM and with glucocorticoid-induced osteoporosis, areal BMD cannot effectively predict fracture [5-8]. This might be the case in CKD, and the factors other than BMD, such as bone quality would play a part in bone fragility, especially in later stages of CKD. Especially in patients with type 2 DM, bone strength is significantly decreased, while BMD tends to be increased due to obesity. Because DM is a leading cause of ESKD, at least to some extent DM affects risk for fracture in CKD population. Actually, previous reports demonstrated the significant elevation of risk for fracture in ESKD patients with DM, compared to those without

http://dx.doi.org/10.5772/59408

DM [38]. Pathogenesis of elevated risk for fracture in DM is explained by deteriorated bone quality as well as increased incidence of falls. DM patients treated by insulin have 2.78 times higher risk for falls than non-DM subjects [39]. In addition, DM is an independent risk for falls in HD patients with OR of 2.75 [40]. Increased risk of falls in DM may be caused by impaired neuromuscular function, increased instability, loss of vision, hypoglycemia, arthritis, cardiovascular disorders, depression and medication such as hypnotics or tranquilizers. Thus, these factors including DM should be the risks for falls and fracture in CKD patients.

Many factors are known as a risk for fracture including low BMD, factors independent of BMD such as older age, female sex, prevalent fracture, smoking, drinking, steroid use, family history for fracture, excise, and factors dependent of BMD such as low body weight [3, 4]. On the other hand, in CKD patients, there may be additional factors including history of kidney transplant, decreased $1,25(OH)_2D$, increased parathyroid hormone (PTH), other hormonal changes, metabolic acidosis, uremic toxins, inflammatory cytokines, and homocysteine play a role [41-48]. Although each occurs at different stages of CKD, all can affect the bone at the end-stage. Bone changes can be associated with PTH and bone metabolic markers. However, increase in serum PTH level generally starts at GFR <45mL/min. Actually, recent studies using cystatin C demonstrated that PTH, inflammation, and bone turnover did not affect the risk for fracture at least in early CKD [49, 50]. On the contrary, increasing evidences suggest that fibroblast growth factor 23 (FGF23) level is elevated to suppress bone formation at CKD stage 2, which occurs at an earlier time than the increase in PTH or decrease in $1,25(OH)_2D$ [51-53]. In addition, FGF23 may be an independent risk of vertebral fracture [54].

Bone quality is classified by material and structural properties, both of which are considered to be altered in CKD. As for structural properties, cortical thinning, porosity, and irregular thickness and loss of connectivity in trabecular bone have been reported [36]. On the other hand, material properties are not well understood. Animal study shows the changes in chemical composition of cortical bone and the deterioration in the quality of bone matrix proteins, such as type I collagen and collagen crosslinking [55], although there is a controversy [56]. These changes are thought to be resulted from an increase in advanced glycation end products (AGEs) including pentosidine that causes loss of normal crosslinking; which are mediated by high glucose, homocysteine, reactive oxygen species and low vitamin B_6 [57, 58]. Therefore, both loss of bone volume and deterioration of bone quality (altered material and structural properties at micro and macro levels) may be involved in the progression of bone fragility in CKD. Future study is needed to elucidate the deteriorated bone quality in CKD including functional changes in osteocytes and involvement of sclerostin, which regulates osteoblastic activity.

At present, however, most conceivable reason for increased risk for fracture in CKD patients is that CKD and osteoporosis have a lot of common risk factors for the pathogenesis and disease progression (Figure 2). This fact is supported by clinical findings [20, 46]. The factors including aging, inflammation, renin-angiotensin axis, oxidative stress, insulin resistance, hyperglycemia, AGEs, smoking, menopause, lack of exercise, homocysteine, uremic toxins, ADMA, and FGF23 are possible common candidates. At the same time, these factors are thought to be involved in the development of vascular calcification [46, 59-63]. In addition to the relationship

between vascular calcification/ atherosclerosis and osteoporosis, so called bone-vascular relationship, hypertension and chronic obstructive pulmonary disease (COPD) also become aware of fracture risks. On the other hand, cortical bone thickness measured by HR-pQCT was reported to be the best predictor for hip fracture in CKD patients [64]. Since bone turnover markers such as P1NP and TRACP5b are risk factors for fracture independent of BMD in CKD patients, combination of BMD and bone turnover markers makes it possible to discriminate subjects with bone fragility [64]. Further studies are necessary to identify noninvasive assessment tools for fracture risk.

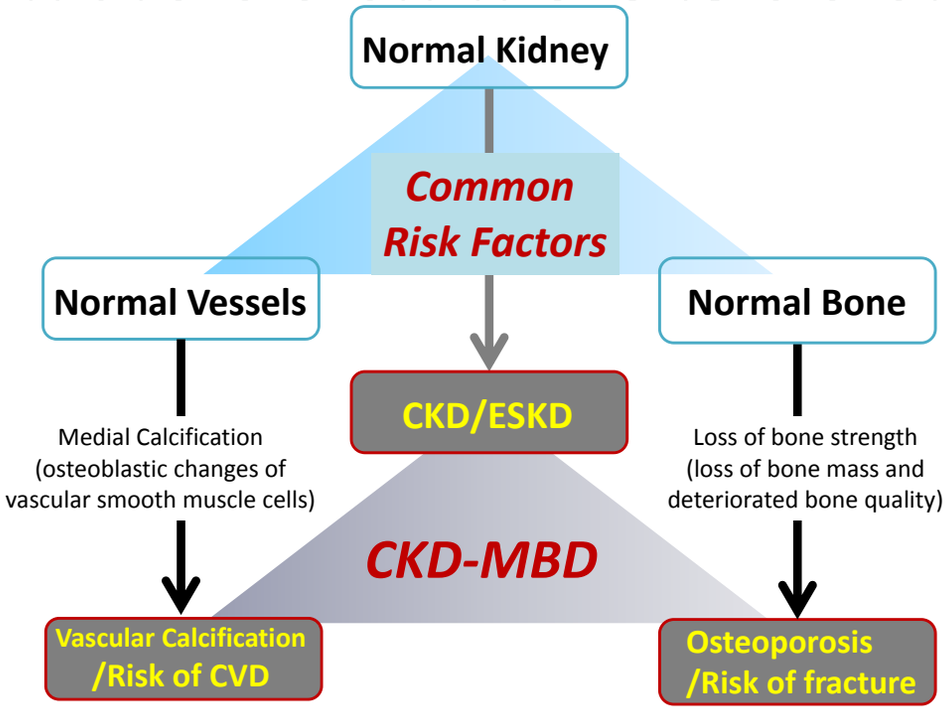

Figure 2. Mechanisms of elevated risk for fracture in CKD patients. Although precise mechanisms remain uncertain, CKD and osteoporosis have many common risk factors, and in addition, CKD progression is associated with increased risk for fracture probably due to bone loss as well as deterioration of bone quality. Aging, inflammation, renin-angiotensin axis, oxidative stress, insulin resistance, hyperglycemia, AGEs, smoking, menopause, lack of exercise, homocysteine, uremic toxins, ADMA, and FGF23 are possible candidates for the common factors, and at the same time, these are thought to be involved in the development of vascular calcification.

5. Conclusion

CKD is not a single disease but a kind of syndrome. Thus, hypertension, obesity, atherosclerosis, gout, nephrolithiasis and life style are highly linked to the pathogenesis and the development of CKD. Diabetic nephropathy and hypertensive nephropathy are commonly observed in CKD, and these are probably at high risk for fracture. Because prevalence of CKD and osteoporosis increases in parallel with age, aged people often suffer from both disorders. Nowadays, CKD has been established as a risk factor for fragility fracture independent of age

and BMD. Not only CKD progression but also bone loss is associated with mortality [61-63]. Thus, bone should be cared in early stages of CKD, at least followed by guidelines [42, 65]. Since bisphosphonates are not recommended in ESKD patients, future work is necessary to establish treatment of osteoporosis or osteopenia complicated with ESKD.

Acknowledgements

This work is partly supported by Grant-In-Aids for Scientific research, Kakenhi (C) (24591230).

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