

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Bone Fragility in Hemodialysis Patients

Shozo Yano

Additional information is available at the end of the chapter

<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 ( $Ccr$ )  $\leq 60$  mL/min and 24% (95%CI: 19-29%) were of  $Ccr < 35$  mL/min [1]. Another study demonstrated that  $Ccr \leq 60$  mL/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]. Fracture 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 women	7.45 13.63	4.44 (4.16-4.75) 4.40 (4.17-4.64)	[10]
Retrospective cohort study	1,272 dialysis patients in the US	hip	men women all	11.7 24.1 13.9	14.2 (9.3-28.6) 17.2 (7.1-19.4) 17.4 (12.4-34.0)	[11]
Prospective cohort study	12,782 HD patients in 320 HD facilities from 12 countries	hip  any	men, 15-54 men, 55-64 men, 65-74 men, 75- women, 15-54 women, 55-64 women, 65-74 women, 75- all men, 15-54 men, 55-64 men, 65-74 men, 75- women, 15-54 women, 55-64 women, 65-74 women, 75- all	        8.9 (8.4-9.4)        25.6 (24.4-27.0)	1.00 (Ref) 2.15 (1.06-4.57) 2.38 (1.07-5.26) 5.05 (2.36-10.82) 0.85 (0.30-2.35) 1.85 (0.75-4.59) 4.67 (2.22-9.83) 7.79 (3.69-16.43)  1.00 (Ref) 1.25 (0.84-1.85) 1.65 (1.10-2.48) 1.86 (1.24-2.77) 1.07 (0.67-1.69) 2.36 (1.56-3.54) 2.58 (1.79-3.63) 3.43 (2.33-5.06)  	[13]
Retrospective cohort study	128,141 HD patients in Japan	hip	men women	7.57 17.43	6.2 (5.7-6.8) 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 15-60 mL/min/1.73m<sup>2</sup> and eGFR >60 mL/min/1.73m<sup>2</sup>, 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 >100 mL/min/1.73m<sup>2</sup>. 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: 15-60 mL/min/1.73m<sup>2</sup>) 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<sup>2</sup> and 1.57 (95%CI: 0.89-2.76) in CCr 45-59 mL/min/1.73m<sup>2</sup>, compared to CCr ≥60 mL/min/1.73m<sup>2</sup>. 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 <sup>2</sup>	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 <sup>2</sup> 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 <sup>2</sup>	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].

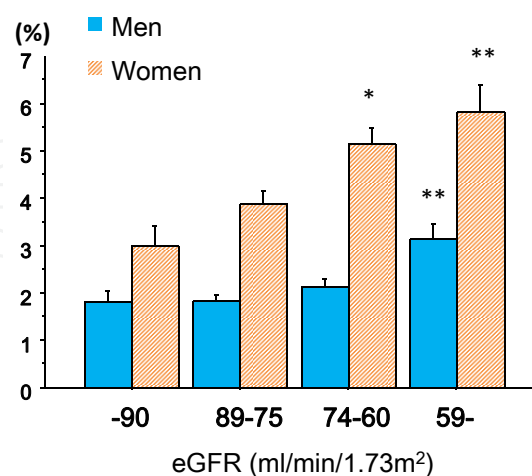
Since sarcopenia or protein-energy wasting (PEW) is commonly seen in CKD patients, eGFR derived from creatinine often underestimates actual kidney function. Cystatin C is more accurate estimate for kidney function than eGFR calculated from creatinine, especially in elderly people whose muscle mass is 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<sup>2</sup> 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<sup>2</sup> had prevalent vertebral fractures and the ratio was significantly higher than those with eGFR 60-89 mL/min/1.73m<sup>2</sup> (25.3%) and eGFR≥90 mL/min/1.73m<sup>2</sup> (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<sup>2</sup>).

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<sup>®</sup> (<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<sup>2</sup> and women with eGFR<75 mL/min/1.73m<sup>2</sup>. 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<sup>®</sup>, 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<sup>®</sup> in CKD patients [28].



**Figure 1.** Association between eGFR and 10 year-hip fracture incidence calculated by FRAX<sup>®</sup> 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<sup>®</sup> was shown. \*,  $p<0.001$  and \*\*,  $p<0.005$  (vs eGFR 90-ml/min/1.73m<sup>2</sup>), 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  $\geq 50$  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

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.

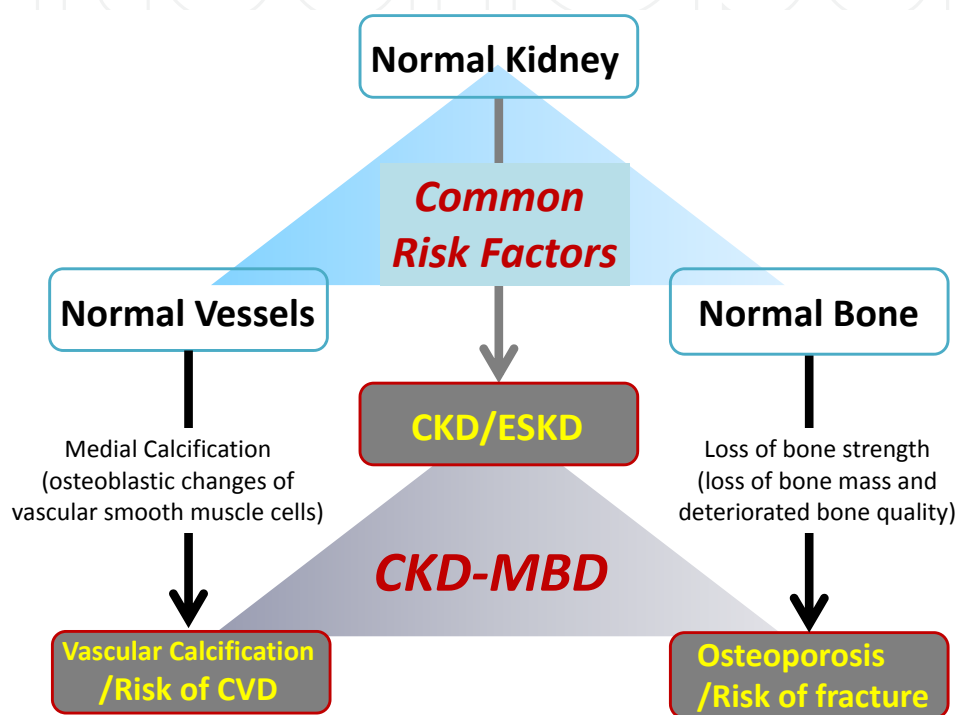
Many factors are known as a risk for fracture including low BMD, factors independent of BMD such as older age, female sex, prevalent fracture, smoking, drinking, steroid use, family history for fracture, excise, and factors dependent of BMD such as low body weight [3, 4]. On the other hand, in CKD patients, there may be additional factors including history of kidney transplant, decreased  $1,25(\text{OH})_2\text{D}$ , 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  $\text{GFR} < 45 \text{ mL/min}$ . 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  $1,25(\text{OH})_2\text{D}$  [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<sub>6</sub> [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).

## Author details

Shozo Yano\*

Address all correspondence to: [syano@med.shimane-u.ac.jp](mailto:syano@med.shimane-u.ac.jp)

Department of Laboratory Medicine, Shimane University Faculty of Medicine, Izumo city, Shimane, Japan

## References

- [1] Klawansky S, Komaroff E, Cavanaugh PF Jr, Mitchell DY, Gordon MJ, Connelly JE, Ross SD. Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int* 2003; 14: 570-576.
- [2] Dukas L, Schacht E, Stähelin HB: In elderly men and women treated for osteoporosis a low creatinine clearance of <65 ml/min is a risk factor for falls and fractures. *Osteoporos Int* 2005; 16: 1683–1690.
- [3] NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA* 2001; 285: 785-795.
- [4] Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; 19: 385-397.
- [5] Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton III LJ, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004; 19: 893-899.

- [6] Vestergaard P. Discrepancies in bone and mineral density and fracture risk in patients with type1 and type2 diabetes – a meta-analysis. *Osteoporos Int* 2007; 18: 427-444.
- [7] Janghorbani M, Van Dam RM, Willett WC, Hu FB: Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 2007; 166: 495-505.
- [8] Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. *J Bone Miner Res* 2009; 24: 702-709.
- [9] Nickolas TL, Leonard MB, Shane E: Chronic kidney disease and bone fracture: a growing concern. *Kidney Int* 2008; 74: 721-731.
- [10] Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 2000; 58: 396-399.
- [11] Coco M, Rush H: Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis* 2000; 36: 1115-1121.
- [12] Wakasugi M, Kazama JJ, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Narita I. Increased risk of hip fracture among Japanese hemodialysis patients. *J Bone Miner Metab* 2013; 31: 315-321.
- [13] Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, Mason N, Prutz KG, Young EW, Pisoni RL. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2006; 70: 1358-1366.
- [14] Sherrard DJ: Renal osteodystrophy and aging. *Semin Nephrol* 2009; 29: 636-642.
- [15] Wakasugi M, Kazama JJ, Wada A, Taniguchi M, Tsubakihara Y, Iseki K, Narita I. Regional variation in hip fracture incidence among Japanese hemodialysis patients. *Ther Apher Dial*. 2014; 18: 162-166.
- [16] Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C: Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 2002; 288(23):3014-3018.
- [17] Danese MD, Kim J, Doan QV, Dylan M, Griffiths R, Chertow GM: PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *Am J kidney Dis* 2006; 47: 149-156.
- [18] Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrol Dial Transplant* 2009; 24: 1539-1544.

- [19] Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008; CD001155.
- [20] Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporos Int* 2006; 17: 313-316.
- [21] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344: 1434-1441.
- [22] Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 2006; 17: 3223-3232.
- [23] Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antonucci DM, Cummings SR; Osteoporotic Fractures Research Group. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 2007; 167: 133-139.
- [24] Shlipak MG, Stehman-Breen C, Fried LF, Song X, Siscovick D, Fried LP, Psaty BM, Newman AB. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis* 2004; 43: 861-867.
- [25] Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J. Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol* 2007; 18: 282-286.
- [26] Kaji H, Yamauchi M, Yamaguchi T, Shigematsu T, Sugimoto T. Mild renal dysfunction is a risk factor for a decrease in bone mineral density and vertebral fractures in Japanese postmenopausal women. *J Clin Endocrinol Metab* 2010; 95: 4635-4642.
- [27] Yano S, Nabika T, Shiwaku K, Yamaguchi S, Sugimoto T. Relationship between fracture risk and kidney function in the community-dwelling population: a cross-sectional study using FRAX® (Shimane CoHRE study). *Osteoporosis Japan (in Japanese)* 2012; 20: 98-101.
- [28] Jamal SA, West SL, Nickolas TL. The clinical utility of FRAX to discriminate fracture status in men and women with chronic kidney disease. *Osteoporos Int* 2014; 25: 71-76.
- [29] Jassal SK, von Muhlen D, Barrett-Connor E. Measures of Renal Function, BMD, Bone Loss, and Osteoporotic Fracture in Older Adults: The Rancho Bernardo Study. *J Bone Miner Res* 2007; 22: 203-210.

- [30] Fried L, Shlipak M, Stehman-Breen C, Mittalhenkle A, Seliger S, Sarnak M, Robbins R, Siscovick D, Harris T, Newman A, Cauley J: Cystatin C as a predictor of loss of bone mineral density. *J Gerontol Med Sci* 2006;61: 743-748.
- [31] Ishani A, Paudel M, Taylor BC, Barrett-Connor E, Jamal S, Canales M, Steffes M, Fink HA, Orwoll E, Cummings SR, Ensrud KE; Osteoporotic Fractures in Men (MrOS) Study Group. Renal function and rate of hip bone loss in older men: the Osteoporotic Fractures in Men Study. *Osteoporos Int* 2008; 19: 1549-1556.
- [32] Iimori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, Kuwahara M, Sasaki S, Tsukamoto Y. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients — a single-center cohort study. *Nephrol Dial Transplant* 2012; 27: 345-351.
- [33] Leonard MB: A structural approach to skeletal fragility in chronic kidney disease. *Semin Nephrol* 2009; 29: 133-143.
- [34] Cejka D, Patsch JM, Weber M, Diarra D, Riegersperger M, Kikic Z, Krestan C, Schuelter-Weidekamm C, Kainberger F, Haas M. Bone microarchitecture in hemodialysis patients assessed by HR-pQCT. *Clin J Am Soc Nephrol* 2011; 6: 2264-2271.
- [35] Bacchetta J, Boutroy S, Vilayphiou N, Juillard L, Guebre-Egziabher F, Rognant N, Sornay-Rendu E, Szulc P, Laville M, Delmas PD, Fouque D, Chapurlat R: Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II-IV chronic kidney disease. *J Bone Miner Res* 2010; 25:849-857.
- [36] Nickolas TL, Stein EM, Dworakowski E, Nishiyama KK, Komandah-Kosseih M, Zhang CA, McMahon DJ, Liu XS, Boutroy S, Cremers S, Shane E. Rapid cortical bone loss in patients with chronic kidney disease. *J Bone Miner Res* 2013; 28: 1811-1820.
- [37] Tomiyama C, Carvalho AB, Higa A, Jorgetti V, Draibe SA, Canziani ME. Coronary calcification is associated with lower bone formation rate in CKD patients not yet in dialysis treatment. *J Bone Miner Res* 2010; 25: 499-504.
- [38] Inaba M, Okuno S, Kumeda T, Yamakawa T, Ishimura E, Nishizawa Y. Increased incidence of vertebral fracture in older female hemodialyzed patients with type2 diabetes mellitus. *Calcif Tissue Int* 2005; 76: 256-260.
- [39] Schwartz AV, Sellmeyer DE, Strotmeyer ES, Tylavsky FA, Feingold KR, Resnick HE, Shorr RI, Nevitt MC, Black DM, Cauley JA, Cummings SR, Harris TB; Health ABC Study. Diabetes and bone loss at the hip in older black and white adults. *J Bone Miner Res* 2005; 20: 596-603.
- [40] Desmet C, Beguin C, Swine C, Jadoul M; Université Catholique de Louvain Collaborative Group. Falls in hemodialysis patients: prospective study of incidence, risk factors, and complications. *Am J Kidney Dis* 2005; 45: 148-153.



- [41] Pitts TO, Piraino BH, Mitro R, Chen TC, Segre GV, Greenberg A, Puschett JB. Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab* 1988; 67: 876-881.
- [42] National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism, disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1-201.
- [43] van Meurs JBJ, Dhonukshe-Rutten RAM, Pluijm SMF, van der Klift M, de Jonge R, Lindemans J, de Groot LCPGM, Hofman A, Witteman JCM, van Leeuwen JPTM, Breteler MMB, Lips P, Pols HAP, Uitterlinden AG: Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; 350: 2033-2041.
- [44] McLean RR, Jaques PF, Selhub J, Tucker KL, Samelson EJ, Broe KE, Hannah MT, Cupples LA, Kiel DP: Homocysteine as a predictive factor for hip fractures in older persons. *N Engl J Med* 2004; 350: 2042-2049.
- [45] Keller CR, Odden MC, Fried LF, Newman AB, Angleman S, Green CA, Cummings SR, Harris TB, Shlipak MG. Kidney function and markers of inflammation in elderly persons without chronic kidney disease: the health, aging, and body composition study. *Kidney Int* 2007; 71: 239-244.
- [46] Jamal SA, Leiter RE, Bauer DC. Hyperhomocysteinaemia and aortic calcification are associated with fractures in patients on haemodialysis. *QJM* 98: 575-579, 2005
- [47] Nii-Kono T, Iwasaki Y, Uchida M, Fujieda A, Hosokawa A, Motojima M, Yamato H, Kurokawa K, Fukagawa M. Indoxyl sulfate induces skeletal resistance to parathyroid hormone in cultured osteoblastic cells. *Kidney Int* 2007; 71: 738-743.
- [48] Yano S, Yamaguchi T, Kanazawa I, Ogawa N, Hayashi K, Yamauchi M, Sugimoto T. Uraemic toxin, phenylacetic acid, inhibits osteoblastic proliferation and differentiation: an implication for the pathogenesis of low turnover bone in chronic renal failure. *Nephrol Dial Transplant* 2007; 22: 3160-3165.
- [49] Ensrud KE, Parimi N, Fink HA, Ishani A, Taylor BC, Steffes M, Cauley JA, Lewis CE, Orwoll ES; Osteoporotic Fractures in Men Study Group. Estimated GFR and risk of hip fracture in older men: comparison of associations using cystatin C and creatinine. *Am J Kidney Dis* 2014; 63: 31-39.
- [50] Fujita Y, Iki M, Tamaki J, Kouda K, Yura A, Kadowaki E, Sato Y, Moon JS, Tomioka K, Okamoto N, Kurumatani N. Renal function and bone mineral density in community-dwelling elderly Japanese men: the Fujiwara-kyo Osteoporosis Risk in Men (FOR-MEN) Study. *Bone*. 2013; 56: 61-66.
- [51] Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, Rits E, Kronenberg F, Kuen E, König P, Kraatz G, Mann JF, Müller GA, Köhler H, Riegler P, the MMKD Study Group. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the mild to moderate kidney disease (MMKD) study. *J Am Soc Nephrol* 2007; 18: 2600-2608.

- [52] Manghat P, Fraser WD, Wierzbicki AS, Fogelman I, Goldsmith DJ, Hampson G. Fibroblast growth factor-23 is associated with C-reactive protein, serum phosphate and bone mineral density in chronic kidney disease. *Osteoporos Int* 2010; 21: 1853-1861.
- [53] Ix JH, Shlipak MG, Wassel CL, Whooley MA: Fibroblast growth factor-23 and early decrements in kidney function: the Heart and Soul Study. *Nephrol Dial Transplant* 2010; 25: 993-997.
- [54] Kanda E, Yoshida M, Sasaki S. Applicability of fibroblast growth factor 23 for evaluation of risk of vertebral fracture and chronic kidney disease-mineral bone disease in elderly chronic kidney disease patients. *BMC Nephrol.* 2012; 13: 122.
- [55] Iwasaki Y, Kazama JJ, Yamato H, Fukagawa M. Changes in chemical composition of cortical bone associated with bone fragility in rat model with chronic kidney disease. *Bone* 2011; 48: 1260-1267.
- [56] Newman CL, Moe SM, Chen NX, Hammond MA, Wallace JM, Nyman JS, Allen MR. Cortical bone mechanical properties are altered in an animal model of progressive chronic kidney disease. *PLoS One* 2014; 9: e99262.
- [57] Saito M, Marumo K. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. *Osteoporos Int* 2010; 21: 195-214.
- [58] Mitome J, Yamamoto H, Saito M, Yokoyama K, Marumo K, Hosoya T. Nonenzymatic cross-linking pentosidine increase in bone collagen and are associated with disorders of bone mineralization in dialysis patients. *Calcif Tissue Int* 2011; 88: 521-529.
- [59] Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. *J Clin Endocrinol Metab* 2004; 89: 4246-4253.
- [60] Fang Y, Ginsberg C, Sugatani T, Monier-Faugere MC, Malluche H, Hruska KA. Early chronic kidney disease-mineral bone disorder stimulates vascular calcification. *Kidney Int* 2014; 85: 142-150.
- [61] Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB; Asturias Study Group. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. *Nephrol Dial Transplant* 2009; 24: 239-246.
- [62] Taal MW, Roe S, Masud T, Green D, Porter C, Cassidy MJ. Total hip bone mass predicts survival in chronic hemodialysis patients. *Kidney Int* 2003; 63:1116-1120.
- [63] Kohno K, Inaba M, Okuno S, Maeno Y, Maekawa K, Yamakawa T, Ishimura E, Nishizawa Y. Association of reduction in bone mineral density with mortality in male hemodialysis patients. *Calcif Tissue Int* 2009; 84: 180-185.
- [64] Nickolas TL, Cremers S, Zhang A, Thomas V, Stein E, Cohen A, Chauncey R, Nikkel L, Yin MT, Liu XS, Boutroy S, Staron RB, Leonard MB, McMahon DJ, Dworakowski

- E, Shane E. Discriminants of prevalent fractures in chronic kidney disease. *J Am Soc Nephrol* 2011; 22: 1560-1572.
- [65] KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int* 2009; 76 (Suppl 113) : S1-S130.
- [66] Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the Fracture Intervention Trial. *J Bone Miner Res* 2007; 22: 503-508.
- [67] LaCroix AZ, Lee JS, Wu L, Cauley JA, Shlipak MG, Ott SM, Robbins J, Curb JD, Leboff M, Bauer DC, Jackson RD, Kooperberg CL, Cummings SR; Women's Health Initiative Observational. Cystatin-C, renal function, and incidence of hip fracture in postmenopausal women. *J Am Geriatr Soc* 2008; 56: 1434-1441.

