

[REVIEW ARTICLE]

Management of Osteoporosis in Chronic Kidney Disease

Kosaku Nitta¹, Aiji Yajima¹ and Ken Tsuchiya²

Abstract:

Chronic kidney disease (CKD) patients with coexisting osteoporosis are becoming common. Many of the therapeutic agents used to treat osteoporosis are known to be affected by the renal function. It is generally thought that osteoporosis in G1 to G3 CKD patients can be treated as in non-CKD patients with osteoporosis. In stage 4 or more advanced CKD patients and CKD patients on dialysis with osteoporosis, however, bisphosphonates must be used with caution, bearing in mind the potential development of such disorders as adynamic bone disease. The use of vitamin D preparations in low doses is relatively safe. In postmenopausal women, raloxifene must be administered with caution. When using denosumab, the serum calcium concentrations should be monitored carefully to prevent the development of hypocalcemia, and active vitamin D preparations should be administered concomitantly. The present article provides an overview of the management of osteoporosis in CKD patients.

Key words: CKD-MBD, osteoporosis, bisphosphonate, denosumab, SERM, adynamic bone

(Intern Med 56: 3271-3276, 2017)

(DOI: 10.2169/internalmedicine.8618-16)

Introduction

Due to the rapidly aging population, the number of patients with osteoporosis has been increasing annually, and is currently estimated to be 13 million in Japan (1). Postmenopausal women are particularly prone to suffering from bone fractures such as vertebral and hip fractures; therefore, the treatment of osteoporosis represents an important current clinical issue. Furthermore, the increasing prevalence of chronic kidney disease (CKD) in patients with underlying lifestyle-related disorders such as hypertension and diabetes mellitus has also become a major social problem (2).

In patients with CKD, CKD-mineral bone disorder (MBD) develops in association with secondary hyperparathyroidism due to phosphorus (P) accumulation in the circulating plasma, leading to an increase in the risk of cardiovascular disease and bone fracture (3). It has been reported that the treatment/management of osteoporosis in CKD patients has a bearing on the progression of atherosclerosis, including vascular calcification, in that calcium (Ca) overload, or hypercalcemia, coupled with the consequent suppression of bone turnover give rise to adynamic bone (4). Since a no-

ticeable proportion of elderly female patients with osteoporosis have CKD, it is considered to be of vital importance to select appropriate drugs and treatment strategies with the aim of avoiding Ca and P strain and concomitant excessively high or low bone turnover in the treatment of these patients.

Due to alterations in the pharmacokinetics of drugs for patients with a decreased kidney function, we should pay special attention when administering medications for osteoporosis to CKD patients.

Definition of Osteoporosis

A working group of the World Health Organization (WHO) published their criteria for the diagnosis of osteoporosis by bone mineral density (BMD) in individuals who have not yet suffered a fragility fracture (5). According to the WHO criteria, osteoporosis is defined as “a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk”. They go on to provide a more technical definition: “Osteoporosis is defined as bone mineral density (BMD) T-score -2.5 and below” (6). This

¹Department of Medicine, Kidney Center, Tokyo Women's Medical University, Japan and ²Department of Blood Purification, Kidney Center, Tokyo Women's Medical University, Japan

Received: November 28, 2016; Accepted: April 16, 2017; Advance Publication by J-STAGE: October 11, 2017

Correspondence to Dr. Kosaku Nitta, knitta@twmu.ac.jp

Table 1. Diagnostic Criteria for Primary Osteoporosis in Japan (2012 Revised Edition).

I. Fragility fracture ^{#1}
1. Vertebral fracture ^{#2} or proximal femoral fracture
2. Other fragility fracture ^{#3} , bone density ^{#4} YAM<80%
II. No fragility fracture ^{#1}
Bone density ^{#4} YAM≤70% or less than -2.5SD

YAM: Young Adult Mean (lumbar spine 20-44 years old, proximal femoral 20-29 years old)

#1: A traumatic bone fracture caused by slight external force.

#2: In two-thirds of cases, vertebral body bone fractures are asymptomatic, and it is desirable to confirm the radiographic appearance of the spine from the viewpoint of differential diagnosis

#3: Other fragility fracture: A traumatic bone fracture caused by slight external force. The bone fracture sites are the ribs, pelvis (including the pubic bone, a hip bone, and sacrum), proximal part of the humerus, and distal end of the radius, and the crus bone.

#4: The bone density is, as a general rule, measured at the lumbar spine or proximal part of the femur. It is important to adopt a lower % or SD level when the measurements were made at multiple sites. It is assumed that the values at L1-L4 or L2-L4 as the standard values.

cut-off was chosen based on the relationship between the lifetime risk of hip fracture in Caucasian women and the average T score from women aged 50-85 years which is -2.5 at the hip (7). In Japan, the diagnostic criteria for primary osteoporosis were established and revised previously (8). Table 1 shows the diagnostic criteria for primary osteoporosis in Japan (2012 revised edition). The criteria were divided into two major items: I (with fragility fracture) and II (no fragility fracture). Item I was further classified into minor items of I-1 (vertebral fracture or proximal femoral fracture) and I-2 [other fragility fracture, BMD<80% of the young adult mean (YAM)]. Item II was characterized by a BMD<70% of the YAM or a T-score of less than -2.5 standard deviations (SDs) in patients without fragility fractures.

Osteoporosis and Coexisting CKD

The frequency of coexisting CKD and osteoporosis increases with advancing age, and the morbidity rates of both of these disorders increase with age. A recent report showed that CKD patients had a marked increase in the risk of hip fracture, with a reported incidence of up to 5.2% (9). It has been reported that G5 CKD patients have a 4.4-fold higher risk of fractures than the general population (10). A wide range of pathophysiological states may account for the increase in the risk of fracture in CKD patients, including (i) secondary hyperparathyroidism, (ii) adynamic bone, (iii) hemodialysis-associated amyloidosis, (iv) vitamin D deficiency, (v) hypocalcemia, (vi) changes in the bone architecture, (vii) nutritional disturbance, and (viii) increase in oxidative stress. Hyperparathyroidism and accelerated bone metabolic turnover associated with renal dysfunction begin to develop in G3 CKD patients with an estimated glomeru-

lar filtration rate (eGFR) of <60 mL/min/1.73 m². Hyperparathyroidism gives rise to an increase in the risk of hip fracture and forearm fracture (11). The risk of hip fracture in women increases by 16% with every 1-SD elevation of the serum cystatin C, even after adjustments have been made for classic risk factors related to fragility fractures (12). The increase in the rate of falling due to an impaired visual function, hypoglycemia and an impaired motor function provoked by coexisting diseases such as diabetes, hypertension and cerebral infarction may strongly influence the increased fracture rate for BMD, given the increased rate of diabetes and hypertension as causes of CKD.

Furthermore, it has been reported from a case-cohort study of women ≥65 years of age with hip or vertebral body fractures that the risk of trochanteric fracture was increased by 5- and 3.5-fold in patients with eGFR between 45 and 49 mL/min/1.73 m², compared with women with eGFR ≥60 mL/min/1.73 m² (13). A cross-sectional study in older men and women revealed an increased risk of hip, vertebral and radial fractures in those with a creatinine clearance (Ccr) of <65 mL/min as estimated by the Cockcroft-Gault formula (14). The BMD determined by dual-energy X-ray absorptiometry (DXA) does not necessarily serve as a risk factor for fractures in CKD patients. However, recent review papers have shown that the BMD predicted fractures across the spectrum from CKD G3a to G5 (15-18). A recent meta-analysis of studies in hemodialysis patients revealed a significant relationship between a low BMD at the lumbar spine and femoral neck and the risk of bone fracture (19). This is further supported by another well-known meta-analysis regarding the association between the BMD and fracture risk among CKD G3-G5 (20). However, there has also been a report purporting to demonstrate that findings by peripheral quantitative computed tomography (pQCT) do not reflect decreases in the bone mass of cortical bones, suggesting that changes in the cortical bone due to the hypersecretion of parathyroid hormone (PTH) in CKD may not be able to be detected by DXA (21).

Relationship between Osteoporosis and Renal Osteopathy

Once CKD has advanced beyond stage 3, the urinary P excretion diminishes to an extent that the decreased P excretion cannot be compensated by urinary P excretion via fibroblast growth factor 23 (FGF23) secreted from the bones. This results in an elevation of the serum P concentration with a consequent increase in the serum PTH levels. Furthermore, the depressed urinary tubular function and elevated serum FGF23 in CKD lead to decreased vitamin D activation and enhanced PTH secretion under conditions of relative Ca deficiency, thereby giving rise to secondary hyperparathyroidism. In relation to bone lesions, the condition takes the form of fibrous osteopathy with a high bone metabolic turnover (22). Other bone lesions associated with CKD include adynamic bone and osteomalacia (22). Adynamic

Table 2. Influence of the Renal Function on Bone Metabolic Marker.

Bone metabolic markers	Influence of the renal function
Bone formation markers	
Alkaline phosphatase (ALP)	-
Bone model alkaline phosphatase (BAP)	-
Osteocalcin (OC)	+
Type I procollagen-C-propeptide (P1CP)	-
Type I procollagen-N-propeptide (P1NP)	-
Bone resorption markers	
Tartaric acid-resistant acid phosphatase (TRACP)	-
Bone-specific tartaric acid-resistant acid phosphatase (TRACP-5b)	-
Pyridinoline (PYD)	+
Deoxypyridinoline (DPD)	+
Type I collagen-C-telopeptide (1CTP)	+
Type I collagen cross-linked C-telopeptide (CTX)	+
Type I collagen cross-linked N-telopeptide (NTX)	+

bone is characterized by a condition whereby the bone turnover is low. This condition occurs after prolonged high-dose vitamin D therapy, the use of P binders containing Ca, and PTH resistance in advanced CKD patients. Osteomalacia is an increase in unmineralized bone due to aluminum deposition in bone. This condition is currently uncommon since aluminum-containing antacids are rarely used anymore as P binders in Japan, even though these agents are still being used in several countries.

The liberation of P from the bones in osteoporosis induces hyperparathyroidism via P loading. Since P additionally influences vascular damage, it also induces arteriosclerosis or functional impairment of the kidney, a vascular-rich organ (23). Indeed, the treatment of osteoporosis with bisphosphonates results in the suppression of arterial thickening and stiffening (24) in addition to reducing the incidence of myocardial infarction (25). Bone metabolic abnormalities in patients with CKD include osteoporotic elements besides renal osteodystrophy. With the advent of novel therapeutic agents for osteoporosis such as denosumab and the recombinant parathyroid hormone teriparatide, it has become practicable to treat osteoporosis even in CKD patients. Therefore, use of therapeutic agents for osteoporosis should also be considered for CKD patients, in addition to the management of P abnormalities and parathyroid functions.

Selection of Bone Metabolism Markers Taking into Account Coexisting CKD

Bone metabolism markers that directly reflect the state of bone metabolism are more useful than the serum PTH level as a means of evaluating bone metabolism, in that the PTH responsiveness of the bones decreases in the following order: postmenopausal women > premenopausal women > men, showing individual differences. It is possible to use several biochemical markers of bone turnover to assess or guide the care of CKD patients. As shown in Table 2, sev-

eral bone metabolic markers are independent of the renal function. Bone alkaline phosphatase (BAP) and Type I procollagen-C-propeptide (P1NP) have shown to be bone formation markers independent of the renal function status, thereby showing no change in the reference values. Tartaric acid-resistant acid phosphatase (TRACP-5b) is a bone resorption marker that is not influenced by the renal function. For these markers that are independent of the renal function status, the reference values in healthy normal subjects can also be applied to dialysis patients, and the interpretation of their levels requires no consideration of age-related renal impairment (26).

It then feasible to judge the bone metabolic turnover status using the normal reference values. It therefore becomes important to recognize the limited frequency of bone resorption marker measurements and the restriction of the same kind of bone metabolic markers to single measurements performed at one time according to the guidelines of the Japanese Health Insurance System. In contrast, bone metabolism markers accumulating in the circulation as a result of the depression of the renal function demonstrate an apparent increase in levels independent of the actual bone metabolic turnover status. We must bear in mind the above when interpreting the values in CKD patients (27).

When the circulating levels of the markers that accumulate under conditions of renal dysfunction are interpreted by applying the upper limit of the reference range for patients with a normal renal function, the bone metabolic turnover tends to be overestimated. This then means that the formulation of a treatment plan based on such data may carry a risk of the oversuppression of bone metabolic turnover, depending on the type of drug used. When the PTH and BAP values suggest adynamic bone, the use of anti-bone resorbing drugs should be avoided. Of note, it is reasonable to perform a bone biopsy in a number of settings including prior to therapy with bisphosphonates in patients with CKD-MBD (27).

Table 3. Caution in the Use of Therapeutic Agents for Osteoporosis in CKD Patients.

Drug	Renal insufficiency of preservation period		Dialysis (CKD-5D)
	eGFR \geq 35 mL/min/1.73 m 2	eGFR $<$ 35 mL/min/1.73 m 2	
Calcium L-aspartate	Contraindication (C)	Contraindication (C)	Careful administration (B) (Check the calcium concentration)
Alfacalcidol, calcitriol	Change dose depending on the condition of a patient (A)		
Eldecalcitol	Careful about rises in serum calcium concentration (B)		
SERM (Raloxifene, bazedoxifene)	Careful administration (B)		
Bisphosphonate	Alendronate	Careful administration (B)	Contraindication (C)
	Risedronate	Careful administration (B)	Contraindication (C)
	Minodronic acid	Careful administration (B)	Contraindication (C)
	Ibandronate	Careful administration (B)	Contraindication (C)
	Etidronate	Contraindication (C)	Contraindication (C)
Elcatonin	Normal dose possibility (for osteoporotic pain) (A)		
Denosumab	Careful administration (B) (Hypocalcemia should be watched for in patients with severe renal dysfunction)		
Teriparatide	Careful administration (B)		

A: Normal dose possibility, B: Careful administration, C: Contraindication. CKD: chronic kidney disease

Points to Consider When Using Therapeutic Agents for Osteoporosis Bearing in Mind the Possible Concurrent Presence of CKD

It is generally thought that the treatment of osteoporosis in patients with G1 to G3 CKD is the same as that in patients without CKD, unless there is elevation of the serum P and/or PTH (28). Active vitamin D administration is a more fundamental therapy mainly targeting the adjustment of serum Ca and P and then PTH levels. However, its effect on the improvement of BMD or the suppression of fracture rate is slight, and bisphosphonate and denosumab are more potent interventional treatments for BMD and the fracture rate.

The points that need to be considered when prescribing therapeutic agents for osteoporosis in patients with renal impairment are summarized by the stage of the renal disease in Table 3. The most problematic drug class in osteoporosis patients with renal impairment is likely bisphosphonates. All bisphosphonates, once absorbed from the intestine or injected into the blood, are excreted via the kidney. Therefore, the accumulation of these drugs in the bone is suspected to be faster in advanced-stage CKD patients than in those with a normal renal function, possibly due to the early development of adynamic bone disease in these patients. There are no large-scale clinical safety data on bisphosphonate use in patients with CKD G4 or eGFR $<$ 35 mL/min/1.73 m 2 . Therefore, the use of any bisphosphonate drug generally avoided in these patients (27). Etidronate occasionally precipitates serum P elevation. Therefore, this drug is contraindicated for the treatment of osteoporosis in patients with kidney disease. Alendronate (29) and risedronate (30) may be administered with caution if the Ccr is \geq 35 mL/min, but should be avoided in patients with Ccr $<$ 35 mL/min. Intravenous ibandronate injection in postmenopausal women with

osteoporosis showed comparable safety levels to that of alendronate, with only small changes in the serum creatinine (31), but should be carefully administered to patients with eGFR \leq 30 mL/min/1.73 m 2 . Minodronic acid should be used cautiously in patients with advanced CKD as well as in those on maintenance dialysis therapy (32). Zoledronic acid is an intravenous bisphosphonate approved worldwide for the treatment of primary or secondary osteoporosis (33) and is contraindicated for CKD patients with eGFR \leq 35 mL/min/1.73 m 2 . In elderly women who show a predilection for the development of osteoporosis accompanied by a decrease in muscle mass, it is of vital importance to evaluate the renal function precisely by calculating the eGFR, even when the serum creatinine level is normal, before prescribing any drugs. Selective estrogen receptor modulators (SERMs) must be administered with caution, since prolongation of the plasma elimination half-life has been reported in patients with CKD (34). Nevertheless, SERMS are thought to restore bone metabolic turnover to that of the premenopausal state from the postmenopausal state and are considered less likely than bisphosphonates to induce oversuppression of bone turnover due to drug accumulation in patients with kidney disease (35). SERMS are contraindicated in the patients who have or once had venous thrombosis as CKD patients, especially nephrotic patients who may suffer from coexisting venous thrombosis.

As the renal function declines, the renal excretion of both Ca and P decreases. Active vitamin D preparations are endowed with a blood Ca- and P-elevating effects coupled with a consequent increase in the Ca \times P product, thereby readily inducing renal and ectopic calcification. Caution should be exercised in patients with CKD, as serum Ca elevation occurs without a concurrent increase in the urinary Ca excretion and critical hypercalcemia can be provoked months after the administration of active vitamin D, potentially aggravating the renal function in predialysis CKD pa-

tients and inducing a comatose state. Eldecalcitol should be administered carefully to CKD patients, with an initial dose of 0.75 µg/day, as this drug has a more potent serum Ca- and P-elevating effect than conventional active vitamin D preparations (36). Careful administration is also imperative for parenteral teriparatide due to the potential for serum Ca elevation (37). Denosumab is effective at reducing the fracture risk and the efficacy is not influenced by the kidney function (38). However, this agent is liable to cause hypocalcemia in patients with an impaired renal function (39). Hypocalcemia induced by denosumab in CKD patients can be a critical issue and should be avoided by practicing appropriate precaution and preemptively administering active vitamin D to eligible CKD patients before starting denosumab. The serum Ca levels usually reach their nadir around seven days after administration, with a less-extensive Ca decrease with the second denosumab administration. This is considered to be because the serum Ca level is maintained by the Ca release from the bones through enhanced bone metabolism resulting from PTH elevation. Therefore, enhanced bone resorption is frequently seen in patients with a hypocalcemic response to denosumab administration. Such responders are considered to represent a group of patients in whom an increase in the bone mass may be expected from denosumab medication. In patients with G3 or more advanced CKD, the serum 1,25(OH)₂D concentration decreases linearly with decreasing eGFR despite elevation of the serum PTH. Therefore, natural-form vitamin D₃ supplementation is insufficient for obtaining adequate elevation of the serum Ca levels. Minimal supplementation with active-form vitamin D₃ is considered necessary to prevent hypocalcemia in CKD patients on denosumab therapy. Denosumab treatment spanning five years resulted in normal bone quality with a reduced bone turnover in the FREEDOM study extension (40).

The authors state that they have no Conflict of Interest (COI).

References

- Yoshimura N, Muraki S, Oka H, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. *J Bone Miner Metab* **27**: 620-628, 2009.
- Japanese Society of Nephrology. Evidence-based practice for the treatment of CKD. *Clin Exp Nephrol* **13**: 537-566, 2009.
- Chen NX, Moe SM. Pathophysiology of vascular calcification. *Current Osteoporos Rep* **13**: 372-380, 2015.
- Bover J, Urena-Torres P, Lloret MJ, et al. Integral pharmacological management of bone mineral disorders in chronic kidney disease (part II): from treatment of phosphate imbalance to control PTH and prevention of progression of cardiovascular calcification. *Expert Opin Pharmacother* **17**: 1363-1373, 2016.
- NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* **285**: 785-795, 2001.
- Schipper LG, Fleuren HW, van den Bergh JP, et al. Treatment of osteoporosis in renal insufficiency. *Clin Rheumatol* **34**: 1341-1345, 2015.
- Miller PD. Bone disease in CKD: a focus on osteoporosis diagnosis and management. *Am J Kidney Dis* **64**: 290-304, 2014.
- Orimo H, Hayashi Y, Fukagawa M, et al. Diagnostic criteria for primary osteoporosis: year 2000 revision. *J Bone Miner Metab* **19**: 331-337, 2001.
- Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* **17**: 3223-3232, 2006.
- Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* **58**: 396-399, 2000.
- Khosla S, Melton J 3rd. Fracture risk in primary hyperparathyroidism. *J Bone Miner Res* **2**(Suppl): N103-N107, 2002.
- Fried LF, Briggs MI, Shlipak MG, et al. Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol* **18**: 282-286, 2007.
- Ensrud KE, Lui LY, Taylor BC, et al. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* **167**: 133-139, 2007.
- Dukas L, Schact E, Stahelin 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* **16**: 1683-1690, 2005.
- Iimori S, Mori Y, Akita W, et al. 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* **27**: 345-351, 2012.
- Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* **7**: 1130-1136, 2012.
- Naylor KL, Garg AX, Zou G, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol* **10**: 646-653, 2015.
- West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* **30**: 913-919, 2015.
- Jamal SA, Haydenn JA, Beyene J. Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. *Am J Kidney Dis* **49**: 674-681, 2007.
- Bucur RC, Panjwani DD, Turner L, et al. Low bone mineral density and fractures in stage 3-5 CKD: an updated systematic review and meta-analysis. *Osteoporos Int* **26**: 449-458, 2015.
- West SJ, Jamal SA. Determination of bone architecture and strength in men and women with stage 5 chronic kidney disease. *Semin Dial* **25**: 397-402, 2012.
- Salam SN, Eastell R, Khwaja A. Fragility fractures and osteoporosis in CKD: pathophysiology and diagnostic methods. *Am J Kidney Dis* **63**: 1049-1059, 2014.
- Kuro-O M. A phosphate-centric paradigm for pathophysiology and therapy of chronic kidney disease. *Kidney Int* **3**(Suppl): 420-426, 2013.
- Okamoto K, Inaba M, Furumitsu Y, et al. Beneficial effect of risedronate on arterial thickening and stiffening with a reciprocal relationship to its effect on bone mass in female osteoporosis patients: a longitudinal study. *Life Sci* **87**: 686-691, 2010.
- Kang JH, Keller JJ, Lin HC. Bisphosphonates reduced the risk of acute myocardial infarction: a 5-year follow-up study. *Osteoporos Int* **24**: 271-277, 2013.
- Maeno Y, Inaba M, Okuno S. Significant association of fracture of the lumbar spine with mortality in female hemodialysis patients: a prospective observational study. *Calcif Tissue Int* **85**: 310-316, 2009.
- West SL, Patel P, Jamal SA. How to predict and treat increased fracture risk in chronic kidney disease. *J Intern Med* **278**: 19-28, 2015.

28. Miller PD. Bone disease in CKD: a focus on osteoporosis diagnosis and management. *Am J Kidney Dis* **64**: 290-304, 2014.
29. Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res* **22**: 503-508, 2007.
30. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* **20**: 2105-2115, 2005.
31. Miller PD, Raqi-Eis S, Mautalen C, et al. Effects of intravenous ibandronate injection on renal function in women with postmenopausal osteoporosis at high risk for renal disease-the DIVINE study. *Bone* **49**: 1317-1322, 2011.
32. Tanishima S, Morio Y. A review of minodronic acid hydrate for the treatment of osteoporosis. *Clin Interv Aging* **8**: 185-189, 2013.
33. Dhillon S. Zoledronic acid: a review in osteoporosis. *Drugs* **76**: 1683-1697, 2016.
34. Ishani A, Blackwell T, Jamal SA, et al. The effect of raloxifene treatment in postmenopausal women with CKD. *J Am Soc Nephrol* **19**: 1430-1438, 2008.
35. Melamed ML, Blackwell T, Neuqarten J, et al. Raloxifene, a selective estrogen receptor modulator, is renoprotective: a post-hoc analysis. *Kidney Int* **79**: 241-249, 2011.
36. Kondo S, Takano T, Ono Y, Saito H, Matsumoto T. Eldecacitol reduces osteoporotic fractures by unique mechanisms. *J Steroid Biochem Mol Biol* **148**: 232-238, 2015.
37. Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH. Teriparatide in postmenopausal women with osteoporosis and mild to moderate renal impairment. *Osteoporos Int* **18**: 59-68, 2007.
38. Jamal SA, Ljunqren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res* **26**: 1829-1835, 2011.
39. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res* **27**: 1471-1479, 2012.
40. Brown JP, Reid IR, Wagman RB, et al. Effects of up to 5 years of denosumab treatment on bone histology and histomorphology: the FREEDOM study extension. *J Bone Miner Res* **29**: 2051-2056, 2014.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).