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Review Article

Osteoporosis Management in Patients with Chronic Kidney Disease

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Abstract

The definition of osteoporosis in the general population according to the World Health Organization (WHO) is a T-score ≤ -2.5, or the presence of a low trauma fracture irrespective of bone mineral density (BMD). Osteopenia is defined by the WHO as T-score between -1 to -2.5. The prevalence of osteoporosis is higher in women with and without chronic kidney disease (CKD). In patients with CKD, osteoporosis falls within the spectrum of chronic kidney disease mineral and bone disorder (CKD-MBD). Kidney Disease Improving Global Outcome (KDIGO) CKD-MBD guidelines recommend measurements of BMD in patients with stage 3 or higher CKD to assess fracture risk. Many pharmacological options exist for the treatment of osteoporosis in the general population. There are no clinical trials in patients with CKD-MBD. Recommendations are based on expert opinion and post hoc analyses of major osteoporosis trials in the general population.

Keywords: Osteoporosis; Osteopenia; Chronic Kidney Disease; CKD-MBD; Renal Osteodystrophy

1. Osteoporosis in the General Population

The definition of osteoporosis in the general population according to the WHO is a T-score ≤-2.5 standard deviations (SDs) based upon BMD measurement by dual-energy x-ray absorptiometry (DXA), or the presence of a low trauma (fragility) fracture irrespective of BMD. T-score ≤-2.5 SD is BMD that is 2.5 or more SD below the young adult female reference

mean. BMD measures the amount of bone mass per unit volume (volumetric density), or bone mass per unit area (areal density) [1]. The National Health and Nutrition Examination Survey (NHANES 2005 - 2008) evaluated bone density of the lumbar spine and hip via DXA in women and men aged ≥ 50 years. It showed that the prevalence of osteopenia and osteoporosis was 61% and 16% for women, and 38% and 4% for men respectively [2]. In (NHANES 2017–2018) the prevalence of age adjusted osteoporosis at either the hip or lumbar spine or both among adults aged ≥ 50 years was 12.6%. It was higher among women (19.6%) compared with men (4.4%) [3]. The prevalence of osteopenia was 43.1%. It was higher among women (51.5%) compared with men (33.5%). Therefore, Osteoporosis prevalence increased from 2007–2008 through 2017–2018 among women but not men. Osteopenia prevalence was somewhat lower for both men and women.

Compared to men in the same age group, women ≥ 50 years of age have two times higher rate of osteopenia, four times higher rate of osteoporosis, and a tendency to get fractures 5 - 10 years earlier [2]. Most current guidelines recommend osteoporosis screening with DXA for women > 65 years. Although the diagnosis of osteoporosis is based on BMD, there are three major characteristics of osteoporosis: low bone mass (osteopenia), microarchitectural disruption, and increased skeletal fragility. Osteoporosis increases the risk of fracture due to decreased bone strength. Bone strength is a function of BMD, bone turnover (formation and resorption), and bone microarchitecture [4]. Fracture risk is increased in osteoporosis due to compromised bone strength (bone quality and density). BMD is assessed clinically by dual energy x-ray absorptiometry (DXA) [5]. Bone quality (turnover, mineralization, mass, architecture) can be measured by performing a bone biopsy. Bone biopsies are labor-intensive and are rarely done in clinical practice due to cost, the need for specialized centers, and patients' discomfort. Primary osteoporosis is common in post-menopausal women, as well as older men and women. Secondary osteoporosis can be due to medications such as corticosteroids [5]**.** The WHO has developed a clinical risk prediction algorithm that will help physicians determine the risk of a fracture within the subsequent decade: https://www.sheffield.ac.uk/FRAX/. Lifestyle interventions are recommended in all patients with osteoporosis and are summarized in Table 1 [1, 6]. Pharmacological management of osteoporosis in the general population is summarized in Table 2 [1, 5].

Intervention	**Comments**
Calcium from dietary sources	Use calcium carbonate or citrate if needed
Nutritional Vitamin D: Ergocalciferol (D2) Cholecalciferol (D3)	Keep 25-hydroxyvitaminD >30 ng/ml (normal range 30-80 ng/ml)
Exercise	Weight-bearing exercise is paramount
Fall prevention	Assess gait, vision, and hearing
Tobacco smoking cessation	
Alcohol intake moderation	

Balanced general nutrition	

Table 1. Lifestyle recommendation in patients with osteoporosis

Supplements	**Bisphosphates**	**RANKL inhibitors**	**SERMs**	**Parathyroid hormone and parathyroid hormone-related protein analogues**	**Sclerostin inhibitors**
Calcium & vitamin D were used as co-therapy in all major clinical trials	Alendronate	Denosumab	Raloxifene	Teriparatide	Romosozumab
Calcium from dietary sources. Use calcium carbonate or citrate if needed	Ibandronate			Abaloparatide	
Nutritional Vitamin D:					
Ergocalciferol (D2) Cholecalciferol (D3)	Risedronate Zoledronic acid				

Table 2. Medications for treatment of osteoporosis. RANKL: Receptor activator of nuclear factor kappa-B ligand (NF-κB), SERM: selective estrogen receptor modulator.

2. Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD)

Chronic kidney disease mineral and bone disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism due to chronic kidney disease (CKD) characterized by one or more of the following [7]:

- Abnormalities of vitamin D, calcium, phosphorus, or parathyroid hormone (PTH) metabolism [8].
- Abnormalities in bone strength, linear growth, turnover, mineralization, or volume.
- Vascular or other soft tissue calcifications.

Renal osteodystrophy (ROD) is the bone abnormalities component of CKD-MBD which increases the fracture risk in patients with CKD [4]. Renal osteodystrophy is a complex disorder of bone density and quality and is a form of osteoporosis. Therefore, the spectrum of CKD-MBD includes osteoporosis, but involves other complex abnormalities as well [9]. Adynamic bone disease is a form of CKD-MBD characterized by low bone turnover and low bone formation [7]. Management strategies for CKD-MBD are summarized in Table 3 [8, 10, 11]. Bone histomorphometry in renal osteodystrophy is class-ified based on bone turnover, bone mineralization, and bone volume [TMV classification] (Figure 1, Figure 2, Table 4) [7].

The last update of the Kidney Disease Improving Global Outcome (KDIGO) CKD-MBD guidelines published in 2017 recommended measurements of BMD to assess fracture risk [12]. It suggests measure-

ment of BMD via DXA in patients with stages 3-5 CKD and those on renal replacement therapy if they have risk factors for osteoporosis or evidence of CKD-MBD provided that outcome of the testing will affect treatment decisions. This recent recommenddation was based on longitudinal studies demonstrating the validity of T scores in patients with and without CKD [13-15].

2.1 Mechanisms of Osteoporosis in Chronic Kidney Disease

Different mechanisms are at play in patients with CKD and osteoporosis [8, 10, 16]. These mechanisms are summarized in Figure 3.

2.2 Prevalence of Osteopenia and Osteoporosis in Chronic Kidney Disease

A systematic review by Tariq et al. included 8 studies in patients with CKD [17]. It reported a prevalence of osteopenia between 33.3% and 81% (average of 45.91%), and a prevalence of osteoporosis between 2.24% and 31.3% (average of 23.29%). Females and CKD patients with low Body Mass Index had a higher prevalence. Therefore, the prevalence of osteoporosis in CKD patients is higher than the general population [16]. In the majority of studies, lumbar spine was the most susceptible site for osteoporosis.

2.3 Fracture Risk in Chronic Kidney Disease Patients

Alem et al. used data from the United States Renal Data System (USRDS) and concluded that the risk of hip fracture in Caucasian patients with ESRD was about four times higher than the general population irrespective of age or gender. The report was in Caucasians because ESRD patients were compared to the general population of Olmstead County in Minnesota, USA, which is >90% Caucasians [18]. Nickolas et al. studied hip fracture incidence in CKD patients [19]. They obtained data from the The Third National Health and Nutrition Examination Survey (NHANES) which was done between 1988-1994. Subjects with eGFR <60 ml/min had an increased risk of hip fracture (odds ratio [OR] 2.12; 95% confidence interval [CI] 1.18 to 3.80). Conversely, subjects aged 50-74 years with hip fracture were three times more likely to have CKD. The association of moderate to severe CKD with hip fracture was independent of hip fracture traditional risk factors.

Phosphate binders	**Active vitamin D sterols**	**Calcium sensing receptor activators (calcimimetics)**	**Correction of metabolic abnormalities**
Calcium carbonate	Calcitriol (D3)	Cinacalcet	Alkylating agents such as sodium bicarbonate in metabolic acidosis
Calcium acetate	Doxercalciferol (D2)	Etelcalcetide	Correction of hyponatremia
Sevelamer carbonate	Paricalcitol (D2)		
Ferric citrate	1-alpha-calcidiol (D3)		
Lanthanum carbonate			

Table 3. Medications for the treatment of CKD-MBD.

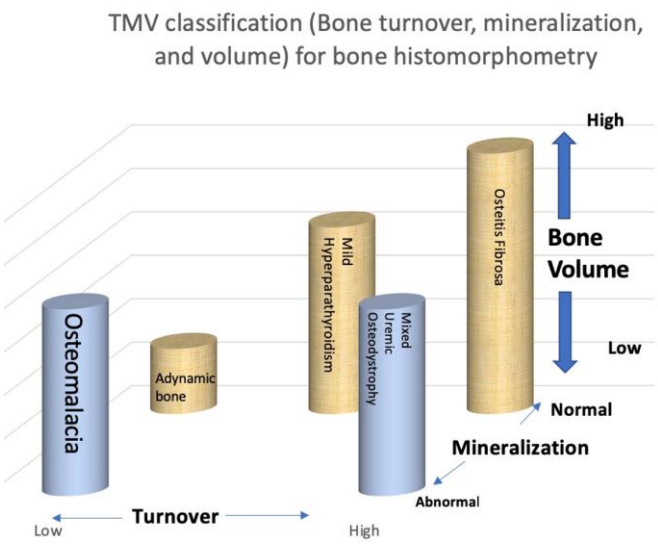

Figure 1. Schematic representation of TMV (bone turnover, mineralization, volume) classification for bone histomorphometry in renal osteodystrophy.

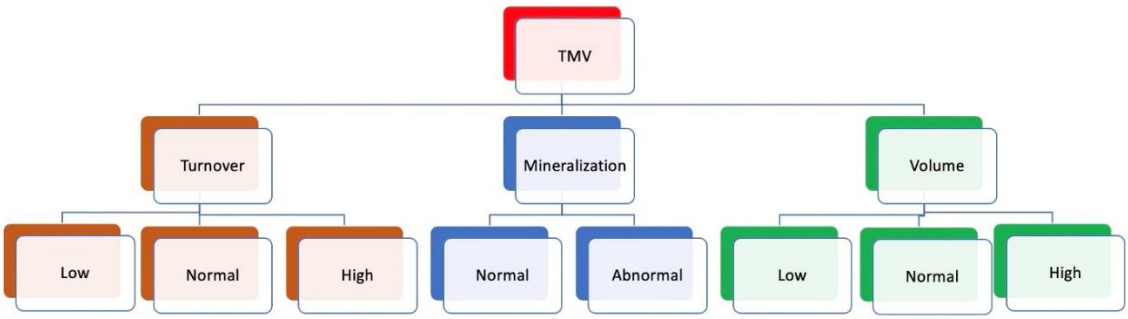

Figure 2. TMV (bone turnover, mineralization, volume) classification of renal osteodystrophy.

Condition	Bone turnover	Mineralization	Bone volume
Osteomalacia	Low	Abnormal	Low to medium
Adynamic bone disease	Low	Normal	Low to normal
Mild hyperparathyroidism	Medium	Normal	Variable
Advanced hyperparathyroidism (Osteitis fibrosa)	High	Normal	Variable
Mixed uremic osteodystrophy	High	Abnormal	Normal

Table 4: The TMV classification system allows accurate characterization of bone and mineral disorders in CKD patients.

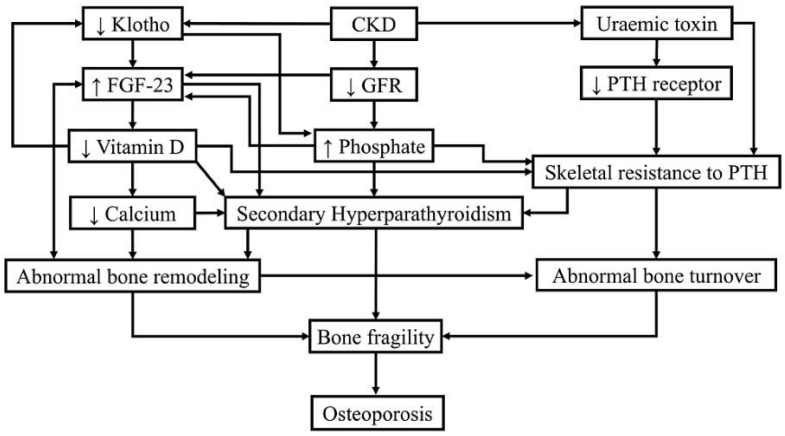

Figure 3. Different mechanisms in CKD lead to osteoporosis. FGF-23: fibroblast growth factor, GFR: glomerular filtration rate, PTH: parathyroid hormone. Diagram is courtesy of: Tasnim et al. Cureus 13(10): e18488. 2021. DOI 10.7759/cureus.18488, under the terms of the Creative Commons Attribution License CC-BY 4.0.

3. Managing Osteoporosis as Part of CKD-MBD

Table 5. proposes a step-by-step approach to the management of osteoporosis in CKD-MBD [4].

3.1 Antiresorptive Agents

Antiresorptive agents include bisphosphonates, raloxifene, and denosumab [1]. BMD increases in osteoporosis with antiresorptive agents due to increased bone mineralization. Antiresorptive agents also decrease bone turnover [20]. Overall fracture risk decreases by approximately 50%.These agents may prevent bone loss in CKD patients with normal to high-turnover bone disease. There are no clinical trials in patients with CKD-MBD [4]. Recommendations are based on expert opinion and post hoc analyses of major osteoporosis trials in the general population. Note that post hoc analyses included patients with CKD, but it is unknown how many of them had CKD-MBD.

3.1.1 Bisphosphonates: Bisphosphonates are not FDA-approved for patients with eGFR < 30 ml/min [4]. These medications induce apoptosis of osteoclasts and are retained in bone for several years. The concern in patients with advanced CKD (eGFR < 30 ml/min including CKD-4, CKD-5, and patients on dialysis) is the development of adynamic bone disease due to suppression of bone remodeling. Miller et al. conducted a pooled analysis of nine randomized, double-blind, placebo-controlled phase III risedronate trials [21]. The goal was to study the effect of age-related reduction in renal function on the safety and effectiveness of risendronate in osteoporotic women. Renal function was measured via the Cockcroft and Gault equation. Adverse events, preservation of BMD, and reduction of vertebral fractures were similar irrespective of renal function. A limited number of subjects underwent transiliac bone biopsies. None of those biopsies showed adynamic bone disease.

3.1.2 Denosumab: Denosumab is a monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand [NF-κB]) [1]. Like bisphosphonate it is an anti-resorptive agent that

inhibits osteoclasts proliferation. However, unlike bisphosphonate, it is not renally cleared. Jamal et al. in a post hoc analysis of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial showed that the adverse effects and treatment benefit of denosumab were similar in patients with stage 3 and 4 CKD [22]. Creatinine clearance was estimated using the Cockcroft and Gault method. Patients should be monitored for hypocalcemia [23]. Two small studies (each had 12 patients) demonstrated the efficacy of denosumab for osteoporosis in end-stage renal disease patients on dialysis. Hypocalcemia was the most significant adverse event [24, 25].

3.2 Anabolic Agents

Anabolic agents should not be used in CKD patients with high bone turnover state such as secondary hyperparathyroidism [4]. Their use is a consideration in patients with low bone turnover state such as adynamic bone disease. In such patients they enhance bone turnover and improve BMD [6, 20]. As with antiresorptive agents more data from trials in CKD-MBD patients are needed.

3.2.1 Teriparatide: Miller et al. used data from the Fracture Prevention Trial to determine the safety and efficacy of teriparatide [rhPTH(1-34)] in postmenopausal women with osteoporosis and CKD [26]. GFR was calculated using the Cockcroft-Gault equation. Patients were randomized to receive daily subcutaneous injections of teriparatide 20 or 40 mcg/day or placebo. All patients had normal PTH. Therefore, as with the above-mentioned studies with antiresorptive agents, this is not an analysis in patients with CKD-MBD. All patients had creatinine ≤ 2.0 mg/dl. teriparatide-mediated reduction in vertebral and nonvertebral fracture was essentially the same independent of renal function. The main adverse events were hypercalcemia and hyperuricemia, both were more common in patients with lower creatinine clearance. Sumida et al. administered 56.5-µg teriparatide once-weekly for 48 weeks to 22 adult hemodialysis patients with hypoparathyroidism and low bone mass [27]. BMD did not change in the femoral neck and distal one-third radius but increased at the lumbar spine by 3.3 ± 1.9 % (mean ± SEM) and 3.0 ± 1.8 % at 24 and 48 weeks respectively. The most common adverse event was transient hypotension.

3.2.2 Abaloparatide

Abaloparatide is a new anabolic agents, it is an analog of PTH-related protein [20]. It is associated with a lower risk of hypercalcemia compared to teriparatide. The ACTIVE phase 3 study was an 18-month, randomized, double-blind, placebo-controlled trial of postmenopausal women with osteoporosis who received subcutaneous abaloparatide 80 µg, placebo, or open-label teriparatide 20 µg daily [28]. The trial excluded patients with serum creatinine >2.0 mg/dL or eGFR <37 mL/min based on Cockcroft-Gault formula. In patients with mild to moderate CKD, abaloparatide and teriparatide had similar efficacy and safety. Abaloparatide caused significantly less hypercalcemia compared to teriparatide in patients with CKD.

3.3 Romosozumab

Sclerostin is a protein secreted by osteocytes. It inhibits bone formation. Romosozumab targets sclerostin to support new bone formation. Romosozumab is a monoclonal antibody with a dual effect of increasing bone formation and decreasing bone resorption [20]. FRAME was a double-blind, randomized, placebo-controlled study involving 7,180 postmenopausal

women with osteoporosis [29]. Patients were injected subcutaneously on a monthly basis with either placebo or 210 mg romosozumab. At baseline, most subjects (88%) had mild or moderate renal insufficiency (stages 1,2, and 3); 0.3% had severe CKD (stage 4). No patients had stage 5 CKD [30]. At the end of study, the improvement in BMD, reduction in new vertebral fractures, cardiovascular events, and adverse events, were the same irrespective of baseline eGFR. These findings do not apply to patients with stages 4, and 5 CKD.

Step	**Comments**
Confirm the diagnosis of CKD	evidence of kidney damage or eGFR <60 ml/min/1.73 m^2 for 3 months or more.
Establish the diagnosis of CKD-MBD	Abnormal calcium, phosphorus, vitamin D, PTH, bone abnormalities, or tissue calcifications (see above)
Screen for osteoporosis with DXA scan every 1-2 years	If T-score ≤ -2.5, or if the patient has low trauma fracture irrespective of T-score, move to step 4
Obtain a bone biopsy to assess bone turnover if feasible to guide management decisions	Bone biopsies are not commonly done due to multiple logistical issues
Evidence of low bone turnover such as low intact PTH (e.g., below 100 pg/ml) in a dialysis patient and a low bone-specific alkaline phosphatase	Consider starting an anabolic agent
Evidence of normal or high bone turnover such as high intact PTH (e.g., above 600 pg/ml) in a dialysis patient and an above mid-range bone-specific alkaline phosphatase	Consider starting an anti-resorptive agent

Table 5: Bone-specific alkaline phosphatase (BAP) is synthesized by the osteoblasts, reference range is approximately 7-27mcg/L. Intact parathyroid hormone (PTH) reference range is 10-65 pg/ml. KDIGO guidelines recommend maintaining intact PTH in the range of 2-9 times the upper range of normal in dialysis patients. A low intact PTH (e.g., below 100 pg/ml) in a dialysis patient is consistent with low bone turnover state such as adynamic bone disease, while a high intact PTH (e.g., above 600 pg/ml) is consistent with high bone turnover state such as secondary hyperparathyroidism. Bone biopsy studies have shown significant overlap. African Americans dialysis patients tend to have higher intact PTH level. Oversuppression of intact PTH is undesirable as it may lead to adynamic bone disease.

4. Conclusions

- Compared to men in the same age group, women ≥ 50 years of age have two times higher rate of osteopenia, four times higher rate of osteoporosis and, and a tendency to get fractures 5 - 10 years earlier.
- Renal osteodystrophy (ROD) is the bone abnormalities component of CKD-MBD which increases the fracture risk in patients with CKD. Renal osteodystrophy is a

complex disorder of bone density and quality and is a form of osteoporosis.

- The prevalence of osteoporosis in CKD patients is higher than the general population.
- There are no osteoporosis clinical trials in patients with CKD-MBD. In case of osteoporosis and low bone turnover in a CKD-MBD patient consider starting an anabolic agent, and in case of normal or high bone turnover consider an anti-resorptive agent.
- Many major osteoporosis trials in the general population included patients with CKD. The results of post hoc analyses of these trials are encouraging and permit individualized treatment of osteoporosis in CKD patients.

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