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STATE-OF-THE-ART REVIEW IN ENDOCRINOLOGY

Clinical approaches to osteoporosis in patients with chronic kidney disease: A comprehensive review

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Abstract. Chronic kidney disease (CKD) induces secondary osteoporosis, characterized by an imbalance between bone formation and resorption due to kidney dysfunction; the result is a reduction in both bone mineral density and quality. This condition is compounded by disruption of bone metabolic turnover, abnormalities in bone microstructure and collagen cross-linking, and compromised bone quality, all of which contribute to increased bone fragility. Reduced kidney function is complicated by secondary hyperparathyroidism, which exacerbates bone fragility. Managing osteoporosis in patients with CKD is challenging because drugs may be contraindicated or require cautious administration, particularly those with high urinary excretion rates. In addition, severe hypercalcemia or hypocalcemia may develop in these patients following administration of active vitamin D or denosumab, respectively. The choice of pharmacotherapy depends on the stage of CKD; however, evidence for the safety and efficacy of osteoporosis drugs in moderate to severe cases of CKD, particularly stages G4, G5, and G5D (*i.e.*, dialysis patients), is limited. This article focuses on the pathophysiology of CKD-associated osteoporosis, as well as the increased fracture risk, and provides a concise overview of safety considerations regarding administration of osteoporosis drugs in Japan. The data presented highlight the complexities associated with drug use in patients with CKD.

Key words: Chronic kidney disease, Osteoporosis, Fracture, Metabolic bone marker, Denosumab

Introduction

Osteoporosis is a systemic disorder characterized by reduced bone strength, leading to an increased risk of fracture; the condition is caused by an imbalance between bone deposition and resorption, which results in decreased bone mineral density (BMD) and weakened bone structures; the latter is caused primarily by abnormalities in bone microarchitecture, collagen cross-linking, and cortical bone porosity [1]. The primary complication of osteoporosis is fragility fractures, which compromise quality of life (QOL) [2] and reduce overall life expectancy [3, 4]. Moreover, there is an increased risk of developing immobilization syndrome, particularly following proximal femoral fractures that require prolonged bed rest. Primary osteoporosis arising from factors such as menopause, aging, and genetic predisposition is different from secondary osteoporosis, which has a different underlying cause that includes endocrine disorders, metabolic disorders, renal disorders and so on (Table 1).

In Japan, a diagnosis of osteoporosis relies on criteria established for primary osteoporosis [5]. A thorough examination, along with blood and urine tests, is conducted to differentiate primary from secondary osteoporosis, as well as other conditions that can result in low bone mass (Table 1). Once secondary osteoporosis or other conditions causing low bone mass are ruled out, the diagnosis of primary osteoporosis is based on the presence of fragility fractures and low BMD. BMD measurements are typically performed using X-ray bone density measurement devices such as dual-energy X-ray absorptiometry (DXA), and measurements focus on the vertebral bodies and/or the proximal femur [5, 6].

CKD and CKD-mineral and bone disorder (CKD-MBD)

In Japan, CKD is diagnosed when there is clear evidence of kidney impairment, including urinary abnormalities such as proteinuria, as well as imaging studies,

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Table 1 Causes of secondary osteoporosis

Endocrine disorders	Hyperthyroidism, primary hyperparathyroidism, secondary hyperparathyroidism (uremic and others), Cushing syndrome, Cushing disease, hypogonadism, Type 1 diabetes.
Metabolic disorders	Type 2 Diabetes, dyslipidemia
Renal disorders	Chronic kidney disease (CKD)
Cardiovascular and respiratory disorders	Hypertension, chronic obstructive pulmonary disease (COPD)
Nutritional	Post-gastrectomy state, neurogenic anorexia, malabsorption syndrome, vitamin C deficiency, excess of vitamin A or D.
Drug-induced	Corticosteroids (glucocorticoids), thiazolidinediones, beta-blockers, loop diuretics, proton pump inhibitors (PPIs), heparin, warfarin, sedative-hypnotics and anxiolytics, anticonvulsants, selective serotonin reuptake inhibitors (SSRIs), methotrexate.
Immobility	Systemic (bed rest, paralysis, disuse syndrome, spaceflight); localized (immobilization due to fracture fixation).
Congenital	Osteogenesis imperfecta, Marfan syndrome.
Metabolic bone diseases	Rickets/osteomalacia, multiple myeloma, bone metastasis, Paget's disease of bone, fibrous dysplasia, ankylosing spondylitis.
Others	Rheumatoid arthritis, severe liver disease, dementia, sarcopenia, frailty excessive alcohol consumption, insomnia.

blood work-up, and/or pathological findings. In particular, proteinuria (urinary protein levels >0.15 g/gCr, or albuminuria >30 mg/gCr) is considered significant. Additionally, CKD is diagnosed when either or both of the following conditions persist for more than 3 months: 1) the presence of urinary abnormalities, or 2) a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 [7]. Furthermore, classification of CKD is based on the underlying disease, kidney function (*i.e.*, GFR), and the level of proteinuria. As kidney function declines and proteinuria becomes more severe, the risk of mortality increases [7]. The prevalence of CKD among the global population is approximately 11% [8]. In 2017, the age-adjusted prevalence of CKD in Japan was 71.8 per 1,000 people aged <75 years [9].

The kidneys play a central role in regulating mineral metabolism. As CKD progresses it can manifest as CKD-MBD [10, 11]. Hormones such as parathyroid hormone (PTH), active vitamin D (1,25-$(OH)_2$D), and fibroblast growth factor 23 (FGF23) maintain homeostasis of serum calcium and phosphate concentrations *via* formation of feedback loops (Fig. 1). As CKD progresses and kidney function declines, a reduction in urinary phosphate excretion leads to elevated serum phosphate levels. In response, FGF23 levels start to increase before the increment of serum phosphate level, followed by a rise in PTH, to suppress the increase in serum phosphate. In CKD stage G4 and beyond, hyperphosphatemia is observed. The initial increase in FGF23 promotes phosphate excretion by the renal tubules, as well as inhibiting activation of vitamin D, resulting in reduced intestinal absorption of phosphate. As CKD progresses further, increased stress caused by elevated serum phosphate levels trigger secondary hyperparathyroidism, further promoting phosphate excretion. Eventually, the regulatory mechanisms involving FGF23 and PTH break down, resulting in permanent elevation of serum phosphate levels. Ultimately, this leads to bone disorders such as renal osteodystrophy (ROD), as well as ectopic calcification of blood vessels and soft tissues [12].

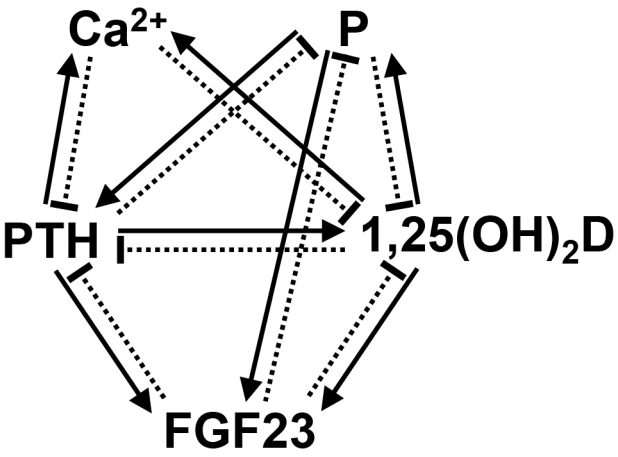


Fig. 1 Maintenance of serum calcium (Ca) and phosphate (P) homeostasis (created based on [111, 112])

Three hormones, parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), and fibroblast growth factor 23 (FGF23), act collaboratively to regulate serum Ca and P levels. Feedback loops among these factors play crucial roles in maintaining serum Ca and P homeostasis. A solid arrow indicates stimulation; a dotted line ending in a flat-head (T-bar) indicates suppression.

Abnormalities in calcium-phosphate metabolism are implicated in some cardiovascular events. The concept of

CKD-MBD was proposed because abnormal laboratory values, altered bone metabolism, and vascular calcification have a marked effect on cardiovascular events, fractures, and mortality [13].

CKD-MBD encompasses abnormalities in calcium, phosphate, and PTH levels, abnormal bone metabolism, and ectopic calcification [11]. Within this framework, ROD is classified as a "bone metabolism abnormality," exhibiting a specific histological pattern associated with moderate to end-stage CKD [14]. Histological diagnosis of ROD is crucial for prevention and treatment; as such, it plays a significant role in selection of therapeutic agents for osteoporosis. Evaluation of ROD involves bone biopsy and bone morphometry of bone tissue, which is an assessment of bone turnover (T), mineralization (M), and volume (V) [13, 15]; these indicators, known as the TMV classification, are used for histological classification of ROD [16].

Fracture risk in patients with CKD

Increased fracture risk in patients with CKD is well-documented, and is attributed to the presence of various comorbidities [16]. CKD poses an independent fracture risk beyond a simple reduction in BMD. Constant bone remodeling, which involves bone resorption by osteoclasts and bone formation by osteoblasts, is disrupted by factors such as estrogen deficiency post-menopause and age-related changes (reduced calcium reabsorption and diminished vitamin D production due to declining kidney function), all of which lead to osteoporosis as bone resorption surpasses formation. Additionally, CKD is associated with deteriorating bone quality [17]. Bone quality is defined by its structural characteristics (*i.e.*, microstructure, presence of microfractures) and material properties (*i.e.*, bone turnover rate, mineralization status, collagen cross-linking).

Anomalies in cross-linking of bone collagen structures contribute to bone deterioration. A comparison of collagen cross-linking structures in bone tissues from postmenopausal osteoporotic patients with and without fractures revealed diminished physiological cross-linking in highly mineralized bone tissues in the fracture group. Conversely, poorly mineralized tissues contain more immature collagen cross-links, including advanced glycation end products (AGEs). Therefore, the reduction in physiological cross-linking combined with a rise in AGEs contributes to a decline in bone quality [18]. In patients with CKD stage G5D, AGEs cross-linking is associated with a decline in kidney function, further contributing to deterioration of bone quality [19].

The Trabecular Bone Score (TBS), calculated from DXA images, is used along with BMD assessments to evaluate bone quality [20]. TBS analyzes bone microstructure by measuring variations in pixel intensity on DXA images, thereby allowing assessment of bone strength. High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) is a non-invasive technique used to analyze bone microstructure, allowing evaluation of parameters such as cortical bone porosity. The progressive cortical bone porosity resulted in the decreased bone quality are observed in patients with CKD [21].

Therefore, it is crucial to be attentive to bone fragility arising from decreased bone quality in patients with CKD. Despite efforts to treat CKD-MBD by controlling PTH and serum phosphate levels through phosphate binders, active vitamin D supplements and calcium-sensing receptor modulators (calcimimetics), bone quality does not improve. Therefore, to further reduce fracture risk in patients with CKD, it is imperative to increase BMD and bone quality through use of bone-active agents; however, caution is warranted.

The risk of fracture increases as CKD progresses [22-33]. Moreover, the clinical risk factors associated with fracture differ between primary osteoporosis and CKD [34]. Primary risk factors associated with osteoporosis include female sex, advanced age, early menopause, low BMI, smoking, excessive alcohol consumption (≥60 g/day), hypogonadism, and glucocorticoid use; secondary risk factors include inflammatory disorders, malabsorption, and rheumatoid arthritis. Factors prevalent in patients with CKD include secondary hyperparathyroidism, dialysis-related factors, uremic toxins, metabolic acidosis, malnutrition, peripheral neuropathy, muscle weakness, balance issues, sarcopenia, increased fall risk, cognitive impairment, diabetes, cardiovascular diseases, and vascular calcification.

A cross-sectional study focusing on elderly osteoporotic patients revealed a significant increase in fracture risk when creatinine clearance was <65 mL/min [26]. A study from the United States showed that elevated cystatin C levels correlate significantly with proximal femur fractures in women but not in men, suggesting sex-specific differences in fracture risk associated with CKD [35]. Additionally, several studies reported a higher risk of proximal femur fractures in individuals with an estimated GFR (eGFR) <60 mL/min/1.73 m^2 (CKD stage G3 or above) [36-38]. For example, in a case-cohort study within a cohort of 9,704 women 65 years or older, compared with women with an eGFR 60 mL/min/1.73 m^2 or greater, the hazard ratio (95% confidence interval [CI]) for hip fracture was 1.57 (95% CI, 0.89–2.76) in those with an eGFR 45 to 59 mL/min per 1.73 m^2 and 2.32 (95% CI, 1.15–4.68) in those with an eGFR less than 45 mL/min/1.73 m^2 [36].

The standardized incidence ratio for proximal femur

fractures in men and women undergoing maintenance dialysis (*i.e.*, CKD stage G5D) are 6.2 and 4.9 times higher, respectively, than in the general population [39]. Therefore, patients with CKD stage G5D have a significantly elevated risk of fractures at the start of dialysis, which increases with dialysis duration.

The retrospective cohort study analyzed data from April 1, 2008, to April 30, 2023, to examine fracture risk in Japanese patients with CKD stages G3–5 [40]. Non-dialysis CKD patients were matched 1:1 with age- and sex-matched controls without CKD. Among 76,598 individuals (38,299 per group), the incidence of all fractures was similar between groups (5.7% *vs.* 5.8%; hazard ratio [HR] 1.022, 95% confidence interval [CI] 0.952–1.098, $p = 0.542$). However, hip fracture risk was significantly higher in the CKD group (1.7% *vs.* 1.3%; HR 1.415, 95% CI 1.234–1.622, $p < 0.001$), especially in younger patients. Osteoporosis treatment and bone mineral density (BMD) assessment were more frequent in CKD patients (10.0% and 5.3%) than controls (4.4% each) but remained insufficient. Japanese CKD patients face a higher risk of hip fractures, highlighting the need for improved management through enhanced use of osteoporosis treatments and BMD assessments.

Assessment of fracture risk

DXA scans are a reasonable method of assessing fracture risk in postmenopausal women or men aged 50 and above with CKD stage G4–G5D, although DXA scans are not recommended for all patients at these stages of the disease [6]. DXA evaluation primarily provides BMD measurements at the proximal femur and lumbar spine. While it is possible to include the forearm in DXA scans, caution is needed due to measurement variability and difficulty of accurate measurements due to the effects of the arteriovenous fistula (AVF).

Other recommended methods include vertebral fracture assessment and lateral radiographs of the spine. These are particularly useful for patients undergoing DXA scans, those with height loss of >4 cm, those with spinal deformities, and those with a history of long-term glucocorticoid therapy. Additionally, it is preferable to include abdominal aortic imaging to determine the presence of vascular calcification. Furthermore, the FRAX® (fracture risk assessment tool) program developed by the World Health Organization international collaborative research group allows clinicians to calculate the probability of osteoporotic fractures occurring within the next 10 years in individuals aged 40 and above. This tool can predict the probability of fracture across all CKD stages [41].

In addition to these methods, measurement of bone turnover can be used to assess fracture risk. Bone alkaline phosphatase (BAP) and intact N-terminal propeptide of type I collagen (intact P1NP) are markers of bone formation, while tartrate-resistant acid phosphatase 5b (TRACP-5b) serves as a marker of bone resorption. These markers are not affected by impaired renal function, making them suitable for evaluating bone turnover in cases of renal dysfunction. Otherwise, osteocalcin, pyridinoline, deoxypyridinoline, type I collagen cross-linked N-telopeptides and type I collagen cross-linked C-telopeptides are influenced by renal function, making them unsuitable for assessing bone metabolism in CKD.

CKD patients are also at risk of falls due to gait abnormalities. Research in the United States indicates that walking speed decreases, stride length shortens, single-leg stance time during walking shortens, and double-leg stance time during walking increases as CKD progresses, resulting in an abnormal walking rhythm [42]. These abnormal gait rhythms lead to an increased risk of falls during walking, thereby contributing to an elevated risk of fracture. CKD-MBD itself can also contribute to muscle weakness and an increased risk of falls by following reasons. Hypocalcemia can directly impair muscle contraction and strength, while hyperphosphatemia can contribute to vascular calcifications and reduced muscle perfusion, leading to muscle weakness. High PTH levels are associated with decreased muscle mass and strength, contributing to frailty and increased fall risk. CKD results in reduced activation of vitamin D. Deficiency in active vitamin D can lead to muscle weakness and impaired balance, increasing the risk of falls. CKD-MBD can cause bone pain and skeletal deformities, which can affect mobility and increase the risk of falls. Dialysis-related factors such as protein-energy wasting, inflammation, and physical inactivity, further increase the risk of falls.

Evolution of guidelines for patients with CKD and osteoporosis

In 2002, the concept of CKD was first proposed by the National Kidney Foundation [43]. A new disease concept, CKD-MBD, was introduced in 2006 [13]. In 2009, The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the management of CKD-MBD provided treatment guidelines based on CKD stage. It recommended bisphosphonate agents as the first choice for treating osteoporosis associated with CKD stages G1 and G2, while treatments for CKD stage G3-associated osteoporosis should consider factors such as fracture risk, PTH level, and progression of CKD [10]. In 2017, the revised Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD presented specific criteria for treatment of osteoporosis based on CKD stage and CKD-MBD status

[11]. With respect to management of osteoporosis in patients with CKD stage G4 and G5, the European Renal Osteodystrophy (EUROD) workgroup suggested optimizing CKD-MBD treatment through evaluation of BMD, vertebral fracture (VF), and FRAX scores, taking into consideration lifestyle improvements and other factors [44]. With respect to treatment, the initial focus should be on adequately correcting CKD-MBD through the use of phosphate binders, active vitamin D supplements, and calcimimetics. This is crucial for reducing occurrence of cardiovascular events, fractures, and mortality.

Studies report an increased risk of fracture among the patients with post-kidney transplantation [45-49]. The risk of fracture within the first 3 years post-kidney transplantation is approximately 30% higher than that in patients with CKD [24]. During the first 5 years following transplantation, up to 25% of patients may experience fractures. DXA measurements have identified osteoporosis in 44% of kidney transplant recipients [50]. Risk factors for post-transplant fracture include persistence of secondary hyperparathyroidism (frequently observed in patients with CKD) and low levels of vitamin D [51, 52]. A prospective study of kidney transplant recipients revealed that 7.3% experienced fragility fractures during an average follow-up period of 5.2 years [53], which is equivalent to 14.2 fractures per 1,000 person-years. The median time from transplantation to the first fracture was 17.1 months, and the prevalence of osteoporosis ranged from 10–35%. These results show that kidney transplantation is a significant risk factor for fracture.

In Japan, CKD-MBD began gaining attention in 2006 [13], when The Japanese Society for Dialysis Therapy promptly addressed CKD-MBD in the "Guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients." The "Clinical Practice Guideline for CKD-MBD" in 2012 further deepened the understanding of CKD-MBD; however, guidelines such as the "Diagnostic criteria for primary osteoporosis: year 2012 revision" [5] published by the Japanese Society for Bone and Mineral Research, and the "Clinical practice guide 2011 on fracture risk in lifestyle diseases" published by the Japan Osteoporosis Society do not contain diagnostic or intervention criteria for osteoporosis associated with CKD.

The "Evidence-based Clinical Practice Guideline for CKD 2013" published by the Japanese Society of Nephrology recommend bisphosphonate agents as a treatment for osteoporosis in elderly patients with CKD (Grade B). The "Evidence-based Clinical Practice Guideline for CKD 2018" expanded the recommendations to include pharmacotherapy for osteoporosis in patients with non-dialysis CKD; treatments include bisphosphonate agents, vitamin D supplements, selective estrogen receptor modulators, PTH agents, and anti-RANKL antibodies [6]. The "Executive summary of clinical practice guide on fracture risk in lifestyle diseases" published in 2019 suggested that patients with bone loss at the level of osteopenia without frailty fractures begin drug therapy if they have an eGFR <60 mL/min/1.73 m^2 [54]. The "Evidence-based Clinical Practice Guideline for CKD 2023" recommended cautious administration of osteoporosis treatments to patients with non-dialysis CKD (*i.e.*, CKD stages G1–3b) due to the possibility of specific drug-related side effects; these guidelines provide explicit recommendations for each drug; however, there is a lack of clear evidence-based recommendations regarding treatment of osteoporosis in Japanese patients with CKD stages G4 and G5 [55].

The concentration of a drug in the bloodstream after administration depends on the speed at which it is eliminated (Fig. 2). The capacity of an organism to remove a drug is expressed in terms of total body clearance, which is the sum of kidney clearance and non-kidney clearance. In the case of drugs with a high urinary excretion rate, kidney clearance mainly correlates with the GFR, and decreases in cases of kidney impairment. Additionally, various factors lead to reduced non-kidney clearance of drugs; these include reduced hepatic clearance and increased bioavailability due to a reduced first-pass effect during oral administration. Since therapeutic drug doses are calculated to safely maintain a particular concentration without excessive accumulation, drugs showing slower total body clearance in the context of kidney impairment may result in sustained high blood concentrations, particularly after repeat administration. Therefore, measures such as dose reduction, extended dosing intervals, or non-administration are implemented.

Therapy for patients with CKD and osteoporosis

Bisphosphonate agents commonly used to treat osteoporosis are excreted *via* the kidneys. Moreover, many clinical trials investigating osteoporosis drugs, including bisphosphonates, typically excluded individuals with impaired kidney function. This is part of the reason for insufficient evidence supporting pharmacotherapy for CKD-associated osteoporosis. Currently, treatment aligns with the general diagnostic criteria for osteoporosis. Indeed, the "2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)" recommends standard osteoporosis treatments for patients with CKD Stage G1 and G2, which is similar to that recommended for non-CKD patients [11]. Additionally, a systematic review evaluating drug therapy for female patients with CKD Stage G3–5D

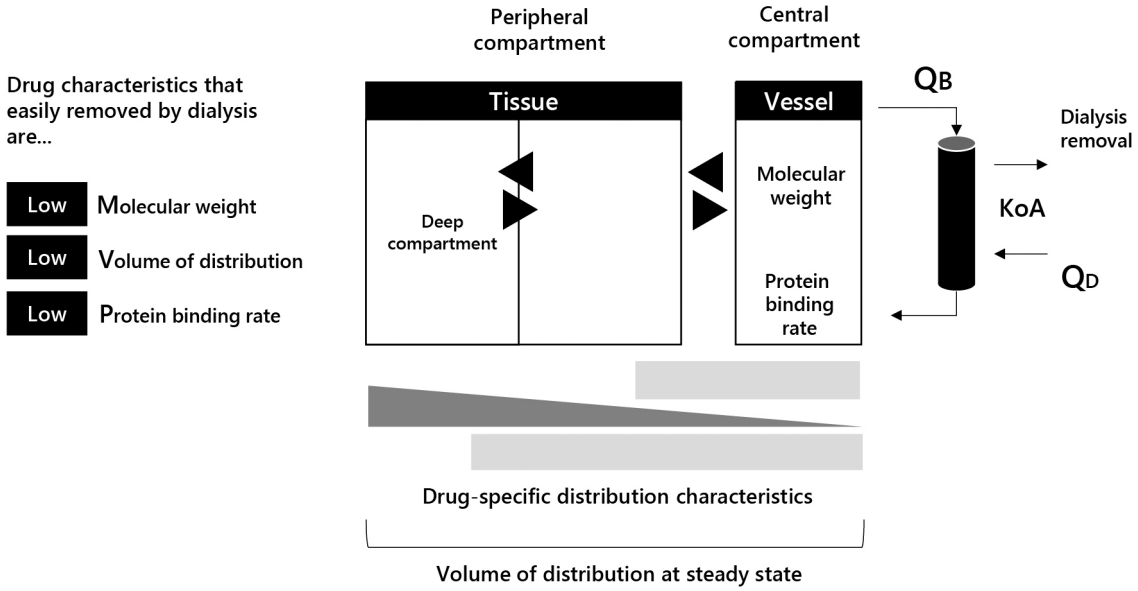


Fig. 2 Factors Related to the Dialyzability of Drugs (created based on [113])

Drugs with high dialyzability are characterized by having a low molecular weight, low plasma protein binding rate, and a small distribution volume. Regarding dialysis conditions, the factor that regulates the smallest value among blood flow rate (QB), dialysis fluid flow rate (QD), and the mass transfer area coefficient (KoA) determines the dialyzability. Generally, water-soluble drugs require dosage reduction in renal failure due to delayed elimination, but they are often easily removed by dialysis, so it is necessary to adjust the timing of administration according to their dialyzability.

demonstrated a potential reduction in the risk of VF in those with CKD Stage G3–4, with little difference compared with CKD5D in the risk of clinical fractures or adverse events [56].

For patients in CKD Stage G5 and 5D, the efficacy of osteoporosis drug therapy with respect to reducing the risk of clinical fracture or death remains uncertain. Evidence regarding the efficacy and safety of drug therapy in patients with severe osteoporosis and advanced CKD is scarce. Consequently, many osteoporosis medications are contraindicated, or require careful administration, in patients with impaired kidney function. Below, we describe the various osteoporosis medications. These medications are ordered according to CKD stage (according to the information provided in the package inserts). We also discuss specific considerations and features associated with each drug.

(1) Calcium preparations

Because calcium is a major constituent of bones, inadequate intake upsets the balance between bone formation and resorption, leading ultimately to loss of bone mass. Administration of calcium preparations restores the balance and prevents bone loss [5]. Possible side effects include hypercalcemia, as well as ectopic calcification due to decreased urinary calcium excretion associated with decreased kidney function.

Calcium preparations are contraindicated in patients with severe kidney impairment. In patients with CKD, calcium preparations are often used not for calcium supplementation but rather as phosphate-binding agents. In such cases, calcium carbonate is the most common formulation. A cross-sectional clinical study demonstrated that CKD stage G5D patients who received calcium-based phosphate binders (CPB) were associated with higher BMD compared with non-calcium-based phosphate binders (NCPB) [57], however, a meta-analysis of RCTs could not demonstrate significant benefit in BMD change or fracture incidence among patients who received CPB [58].

CPB such as calcium carbonate cause vascular calcification and ectopic calcification [59]. A randomized placebo-controlled non-blinded trial assigned patients with CKD stage G3–4 into one of two groups: one received CPB (calcium carbonate) and the other received NCPB (sevelamer hydrochloride). Fewer composite endpoints (such as all-cause mortality and initiation of dialysis) were observed in the group taking NCPB [60]. Additionally, a meta-analysis of patients with CKD stage G5D revealed that CPB are associated with poorer survival outcomes than NCPB [61]. NCPB improves survival outcomes not only in the patients with CKD stages G3–4 but also in the patients with CKD stage G5D compared to CPB. Therefore, NCPB should be selected over CPB, particularly in cases with high serum calcium levels or severe vascular calcification.

(2) Active vitamin D preparations (alfacalcidol, calcitriol, eldecalcitol)

Active vitamin D preparations such as alfacalcidol and calcitriol promote calcium absorption by the intestine, suppress PTH secretion from parathyroid glands, and attenuate skeletal resistance to the effects of PTH, leading to marked increases in BMD *via* regulation of bone turnover [62, 63]. Possible side effects include impairment of kidney function due to renal calcification caused by increased serum calcium and phosphate levels, as well as a risk of ectopic calcification.

These active vitamin D preparations can be used both pre-dialysis and during maintenance dialysis; however, caution is required with respect to patients with pre-dialysis kidney failure, as urinary calcium excretion decreases with declining kidney function [64], possibly leading to increased serum calcium levels without an increase in urinary calcium excretion. When using alfacalcidol, attention should be paid to development of acute kidney injury associated with increased serum calcium levels. When using eldecalcitol, caution is required regarding the risk of hypercalcemia due to increased serum calcium levels. When using calcitriol for patients with pre-dialysis kidney failure, there may be a decrease in peak blood concentration and an increased elimination time. In addition, there may be a delay in magnesium excretion from the kidneys during dialysis, necessitating caution when using the drug in combination with magnesium-containing preparations. For such reasons, KDIGO do not recommend routine use of calcitriol and vitamin D analogs among CKD G3a–G5 [11].

(3) Selective estrogen receptor modulators (SERMs: raloxifene, bazedoxifene)

The SERMs raloxifene and bazedoxifene exert estrogen-like effects on bone by binding to estrogen receptors [65], of which indication is postmenopausal osteoporosis. A placebo-controlled double-blind comparative trial involving 284 postmenopausal Japanese women with osteoporosis showed that raloxifene led to a significant increase in BMD at the lumbar spine and significant reduction in bone turnover markers [66]. Overall, 34.8% of patients in the raloxifene group experienced side effects, including hot flushes (4.3%), lower limb cramps, breast tension, and dermatitis (3.3% for each).

A double-blind dose-response comparison trial involving 423 postmenopausal Japanese women with osteoporosis who received bazedoxifene (20 mg or 40 mg) or placebo, reported significant increases in BMD at the lumbar spine (L1–L4) compared with the placebo group. Additionally, significant increases in BMD at the lumbar spine (L2–L4) and femoral neck, and significant decreases in bone turnover markers, were observed in the treatment group compared with the placebo group [67]. Overall, side effects were noted in 44.2% of patients, including muscle spasms in 2.5% and fibrocystic breast disease (mastopathy or breast cysts) in 2.5%.

A post-hoc analysis of the MORE trial, a large-scale clinical trial targeting postmenopausal women with osteoporosis, revealed that raloxifene slowed the decline of kidney function [68]. Additionally, in cases of normal kidney function and mild kidney impairment, bazedoxifene improved kidney function; the drug induces hypophosphatemia due to increased phosphate diuresis, thereby exerting a kidney protective effect [69].

Raloxifene increased the area under curve (AUC) and maximum plasma concentration (Cmax) in patients with kidney impairment compared with those with normal kidney function; therefore, dose reduction based on creatinine clearance (Ccr) is recommended when administering the drug to patients with kidney impairment. These issues have not been reported for bazedoxifene in cases of mild to moderate kidney impairment [70]. In patients with pre-dialysis kidney failure, raloxifene increases BMD and reduces fracture risk to levels similar to those in non-CKD patients [71]. Additionally, bazedoxifene is effective and safe in cases of mild to moderate kidney impairment [70]. Administration of raloxifene at 60 mg/day to female patients in maintenance dialysis increased BMD at the lumbar spine [72]; however, pharmacokinetic analyses in such patients suggest that a dose of 60 mg every 48–72 hours is appropriate, although there are no reports regarding effects on BMD under this regimen.

(4) Estrogen-related drugs and methenolone

Methenolone, a protein anabolic steroid, promotes protein synthesis in the liver and tissues, inhibits protein breakdown throughout the body, and contributes to tissue deposition of calcium and phosphorus. However, there is currently no specific evidence on its effects in patients with CKD.

Preparations containing estrogens such as estradiol and estriol may cause sodium and fluid retention when administered to patients with CKD or those undergoing maintenance dialysis. Similarly, methenolone may also cause sodium and fluid retention. These effects may lead to exacerbation of symptoms, particularly in patients with reduced kidney function. However, there are no established dosage criteria or contraindications based on the degree of kidney dysfunction.

(5) Bisphosphonates (alendronate, ibandronate, minodronate, risedronate, zoledronate)

The main mechanism of action of bisphosphonate drugs is believed to be inhibition of bone resorption through

induction of apoptosis and functional impairment of osteoclasts [73-75]. Regarding efficacy, reports from randomized controlled trials suggest that bisphosphonate drugs may reduce the risk of new vertebral fractures in patients with CKD to an extent equivalent to or greater than that seen in individuals with normal kidney function [76-78]; however, evidence for the use of bisphosphonates in CKD patients is limited because many clinical trials exclude patients with kidney dysfunction, and prescribing information may vary among different bisphosphonate drugs.

A randomized trial of alendronate *versus* placebo (Fracture Intervention Trial) in 6,458 postmenopausal women found that about 10% had severely reduced eGFR, however, alendronate increased BMD and reduced fracture risk regardless of kidney function, with no difference in side effects [77]. A Japanese phase III double-blind trial of alendronate involving 207 postmenopausal osteoporotic patients over 48 weeks reported that the drug induced a significant increase in BMD compared with the placebo [79]. Adverse event frequency was 18.6%, with the main side effects being gastrointestinal discomfort (2.9%), gastric pain (2.9%), loose stools (2.0%), dizziness (2.0%), and back pain (2.0%).

A 48-week phase III double-blind trial in Japanese postmenopausal osteoporotic patients reported that minodronate increased BMD at the lumbar spine and proximal femur. The drug also reduced expression of bone resorption markers. Adverse events occurred in 20.9% of cases, with gastrointestinal discomfort (5.2%), upper abdominal pain (3.7%), and increased serum creatine phosphokinase (3.0%) being the main side effects.

A Japanese phase II/III randomized double-blind trial of ibandronate (administered *via* injection) in patients aged ≥60 with primary osteoporosis revealed that the drug was not inferior to risedronate with respect to reducing the incidence of non-traumatic vertebral fractures over 3 years. Adverse events occurred in 25.1% of cases, with back pain (2.9%) being the main side effect according to the package insert provided by the pharmaceutical company.

A combined analysis of data from nine randomized, double-blind, placebo-controlled phase III trials of risedronate demonstrated that the incidences of overall adverse events and renal function-related adverse events were comparable between the placebo and risedronate 5 mg groups, irrespective of renal function. Furthermore, risedronate effectively preserved bone mineral density (BMD) and reduced the incidence of vertebral fractures [78]. A Japanese phase III double-blind placebo-controlled trial reported that risedronate showed efficacy in reducing non-traumatic vertebral fractures in patients with osteoporosis [80]. Adverse event occurred in 31.5% of cases, with upper abdominal pain (6.2%) and nausea (2.2%) being the main side effects according to the package insert provided by the pharmaceutical company.

A Japanese phase III double-blind trial in patients with primary osteoporosis reported that zoledronate led to a significant reduction in fracture compared with placebo. Adverse events occurred in 59.2% of cases, with fever (39.3%), arthralgia (10.8%), myalgia (8.1%), fatigue (7.8%), influenza-like illness (6.9%), hypocalcemia (6.3%), and headache (6.0%) being the main side effects according to the package insert provided by the pharmaceutical company.

While none of these drugs are contraindicated in patients with CKD stages G1–G3b, etidronate, risedronate, and zoledronic acid may exhibit delayed excretion. Etidronate and risedronate are contraindicated in patients with CKD stage G4 or higher, while zoledronic acid is contraindicated in those with a creatinine clearance <35 mL/min; however, epidemiological studies based on information stored in domestic medical information databases reported an increased risk of hypocalcemia in patients with advanced kidney impairment (eGFR <30 mL/min/1.73 m^2), or CKD stage G4 or higher, receiving bisphosphonate drugs to treat osteoporosis. Therefore, caution is required when using other bisphosphonate drugs that are not contraindicated in these patients.

Common side effects of bisphosphonate drugs include gastrointestinal disturbance and medication-related osteonecrosis of the jaw (MRONJ) and atypical fractures. Adequate medication counseling (taking the drug with a full glass of water and remaining upright for 30 minutes after ingestion) is crucial for preventing gastrointestinal disturbance. MRONJ occurs during invasive dental procedures such as tooth extraction; CKD stage 5D is a risk factor for MRONJ. Despite these risks, the latest position paper suggests not discontinuing bisphosphonate drugs even during tooth extraction.

(6) Denosumab: an anti-RANKL (receptor activator of nuclear factor-κB ligand) antibody

Denosumab is a human IgG2 monoclonal antibody that targets RANKL, thereby inhibiting osteoclast formation and bone resorption. A phase III trial in Japan involving patients with primary osteoporosis (472 patients in the denosumab group and 480 patients in the placebo group) reported that the incidence of vertebral fractures decreased in the former. Additionally, after 2 years of administration, the denosumab group showed significant increases in BMD at the lumbar spine (L1–L4), proximal femur, femoral neck, and distal third of the radius. Adverse events were observed in 18.0% of cases, with the main side effects being hypocalcemia (0.8%), back pain (0.8%), increased γ-GTP (0.8%), hypertension

(0.8%), eczema (0.7%), and joint pain (0.6%) according to the package insert provided by the pharmaceutical company.

The pharmacokinetics and pharmacodynamics of denosumab were evaluated in 55 subjects with renal function ranging from normal to dialysis-dependent kidney failure [81]. Participants received a single 60-mg subcutaneous dose of denosumab. The analysis revealed that renal function had no significant impact on the pharmacokinetics or pharmacodynamics of denosumab. These findings suggest that dose adjustment based on glomerular filtration rate is not necessary.

A sub-analysis of randomized controlled trials revealed that denosumab suppressed vertebral fractures, and increases BMD at the lumbar spine and femoral neck, significantly in patients with CKD stage G3 without secondary hyperparathyroidism [82]. Another prospective study of denosumab in hemodialysis patients demonstrated significant decreases in bone turnover markers, and increases in BMD at the lumbar spine, after 12 months [83]. A 3-year follow-up study of denosumab in osteoporotic dialysis patients showed significant reductions in bone turnover markers, TRACP-5b, and total P1NP. However, cases of osteonecrosis of the jaw due to denosumab administration have been reported.

A systematic review evaluating the effects of denosumab in kidney transplant recipients found that the drug effectively increased BMD and T-scores at the lumbar spine and femoral neck [84]. Regarding its impact on kidney function, a trial administering denosumab to osteoporotic patients with primary hyperparathyroidism showed increases in BMD and improvements in lumbar spine TBS, without a decrease in eGFR, compared with a control group undergoing parathyroidectomy [85].

Hypocalcemia is a significant adverse effect of denosumab; therefore, the drug is contraindicated in patients with hypocalcemia. Denosumab inhibits calcium mobilization from bone to blood, leading to transient hypocalcemia [86]. Risk factors for hypocalcemia associated with denosumab include reduced kidney function (Ccr <30 mL/min), serum calcium levels <8.5 mg/dL before denosumab initiation, and prior use of calcium and vitamin D supplements to prevent hypocalcemia. Elderly patients with denosumab-induced hypocalcemia often have pre-treatment-corrected serum calcium concentrations below 2.28 mmol/L (9.14 mg/dL) [87]. Studies conducted overseas also report an increased incidence of hypocalcemia with declining kidney function [81].

To avoid denosumab-induced hypocalcemia, daily oral calcium supplementation, oral supplementation with active vitamin D (which does not require activation in the kidney), and regular monitoring of serum-corrected calcium levels are important. While denosumab administration does not affect Cmax or AUC in dialysis patients, 33% of patients with stage G5 CKD receiving denosumab experience hypocalcemia [81]. The incidence of hypocalcemia (<8.5 mg/dL) is significantly higher in dialysis patients than in non-dialysis patients; a median of 7 days from initial denosumab administration to the onset of hypocalcemia has been reported for dialysis patients [88].

Reports of hypocalcemia associated with denosumab correlate with two risk factors: low eGFR and high bone turnover. Pre-treatment with bone resorption inhibitors may reduce the risk of denosumab-induced hypocalcemia [86]. A meta-analysis of end-stage kidney disease patients receiving denosumab found an estimated incidence rate of denosumab-associated hypocalcemia of 42% in dialysis patients [89]. Therefore, close monitoring of serum calcium levels during the first few weeks after denosumab administration (even in cases receiving appropriate calcium/vitamin D supplementation), and gradual supplementation with calcium and active vitamin D as needed in cases that are not already receiving the supplements, are necessary. Despite adequate supplementation, the incidence rate of denosumab-associated hypocalcemia within 6 months of administration is around 14%, warranting caution [90]. Hypocalcemia may occur after initiating denosumab treatment in patients with impaired kidney function, necessitating monitoring of serum calcium levels and gradual supplementation with calcium and vitamin D if necessary [84].

In the FREEDOM study and its extension trial, an increased incidence of multiple vertebral compression fractures was observed in cases where denosumab 60 mg had been administered at least twice and subsequently discontinued for more than seven months [91]. A systematic review of 24 cases, comprising a total of 112 vertebral fractures (4.7 fractures per case), revealed that vertebral compression fractures occurred 8 to 16 months after the last denosumab administration, which corresponds to a delay of 2 to 10 months beyond the scheduled subsequent dose [92]. Notably, patients receiving denosumab treatment for more than two years were at higher risk of fracture compared to those treated for two years or less, warranting careful monitoring.

Furthermore, a report of nine cases indicated that vertebral compression fractures occurred even in patients whose bone mineral density had normalized and for whom denosumab treatment was discontinued, though no abnormalities were detected in their bone tissue [93]. The potential cause of the increased incidence of multiple vertebral compression fractures following denosumab discontinuation is thought to be a rapid increase in bone turnover after treatment cessation [94].

(7) PTH type 1 receptor agonist (teriparatide and abaloparatide)

Teriparatide comprises the N-terminal 1–34 peptide fragment of human PTH, while abaloparatide is a modified polypeptide derived from the N-terminal 34 amino acid sequence of human PTH-related protein. Both drugs promote bone formation by increasing the number of activated osteoblasts.

A phase III trial in Japan evaluated a recombinant teriparatide (daily subcutaneous injection formulation). This trial, known as the GHDB trial, was a placebo-controlled double-blind comparison trial targeting 203 osteoporotic patients at high risk of fractures. The results showed a statistically significant mean change in BMD at the lumbar spine (L2–L4) [95, 96]. Adverse events were observed in 16.9% of cases, with the main side effects being increased serum ALP (3.7%), increased serum uric acid (2.2%), and hyperuricemia (2.2%) according to the package insert provided by the pharmaceutical company.

The Fracture Prevention Trial assessed teriparatide in postmenopausal women with osteoporosis and renal impairment (GFR: normal ≥80, mild 50–79, moderate 30–49 mL/min) [97]. Patients with serum creatinine ≤2.0 mg/dL and normal PTH were randomized to placebo or teriparatide (20 or 40 μg daily). Teriparatide increased PINP, lumbar spine, and femoral neck BMD across all renal subgroups. Fracture risk reduction and adverse events, including renal-related events, were consistent across groups. Teriparatide 20 μg/day caused mild post-dose calcium elevations without significant effects on GFR, gout, or nephrolithiasis. Elevated uric acid was more frequent in moderate impairment and 40 μg/day groups. Even so, adverse event data did not suggest an increased incidence of gout or arthralgia or of nephrolithiasis events in teriparatide-treated patients with normal, mild, or moderate renal impairment.

A phase III double-blind trial in Japan involving 542 osteoporotic patients at high risk of fractures evaluated the efficacy of teriparatide acetate (a formulation delivered weekly *via* subcutaneous injection) over 72 weeks. The drug and placebo were administered as a dose of 56.5 μg. The results showed that the drug reduced the incidence of new vertebral fractures significantly according to the package insert provided by the pharmaceutical company. Moreover, there was a significant mean change in BMD at the lumbar spine (L2–L4) after 72 weeks compared with the placebo group. Adverse events were observed in 43.8% of cases, with nausea (18.6%), vomiting (8.6%), headache (7.6%), fatigue (6.2%), and abdominal discomfort (4.1%) being the main side effects. Another trial in Japan (non-blinded, non-controlled) evaluated the efficacy of the 56.5 μg dose of teriparatide over 24 months in osteoporotic patients at high risk of fracture. The results showed a mean 8.4% increase in BMD at the lumbar spine (L2–L4) at 72 weeks, and a 9.9% increase at 104 weeks. Adverse events were observed in 58.2% of cases, with nausea (33.3%), vomiting (20.6%), headache (16.4%), fatigue (16.4%), and abdominal discomfort (10.1%) being the main side effects.

A placebo-controlled randomized double-blind parallel-group comparison phase III trial in Japan, evaluating abaloparatide, enrolled 206 osteoporotic patients who had an LS BMD T score less than –1.8 with one or more fragility vertebral fractures or an LS BMD T score less than –3.0 [98]. The data suggested a significant increase in baseline BMD at the lumbar spine (L1–L4) compared with the placebo group. The frequency of adverse events was 32.1%, with nausea (5.7%), palpitations (5.0%), hematoma at the injection site (4.3%), increased serum calcium (4.3%), and increased serum uric acid (3.6%) being the main side effects.

Regular measurement of kidney function is recommended for patients receiving either of the above PTH drugs. While it is not necessary to adjust the dose according to the degree of kidney impairment, care should be taken when administering teriparatide or abaloparatide to patients with severe kidney impairment due to delayed elimination from the bloodstream. Teriparatide is contraindicated in CKD patients with secondary hyperparathyroidism [99], but it is recommended for CKD patients with suppressed PTH levels and adynamic bone disease [100]. Post-marketing surveillance of a recombinant teriparatide, involving 33 patients with CKD stage G4 and G5, showed a significant increase in BMD at the lumbar spine after 24 months of treatment, with no notable adverse effects [101].

There are no established criteria regarding administration of these drugs to patients on maintenance dialysis. Administration of teriparatide acetate (weekly subcutaneous injection) to patients with stage 5D CKD (*i.e.*, on maintenance dialysis) with suppressed PTH levels and adynamic bone disease increased BMD at the lumbar spine, but decreased serum calcium concentrations [102]. For non-CKD patients, caution is needed regarding elevated serum calcium levels, and use is contraindicated in patients with hypercalcemia. However, attention should also be paid to hypocalcemia in patients with stage 5D CKD on maintenance dialysis.

(8) Romosozumab: an anti-sclerostin antibody

Romosozumab binds to sclerostin, a classic Wnt/β signal inhibitor, thereby promoting bone formation and inhibiting bone resorption [103, 104].

An international multicenter placebo-controlled double-blind comparative trial targeting postmenopausal osteoporotic patients assigned to a romosozumab group (3,589

cases, including 247 Japanese patients) and a placebo group (3,591 cases, including 245 Japanese patients). The participants received romosozumab (210 mg) or placebo once monthly for 12 months; thereafter, by both groups received denosumab (60 mg) every 6 months for an additional 12 months [105]. The results showed a significant reduction in the incidence of new vertebral fractures at 12 and 24 months in romosozumab treatment group. Additionally, there were increases in BMD at the lumbar spine (L1–L4), proximal femur, and femoral neck at 12 and 24 months in romosozumab treatment group. Adverse events were observed in 16.6% of cases, with joint pain (2.0%), limb pain (1.6%), muscle pain (1.3%), injection site pain (1.2%), injection site erythema (1.1%), and nasopharyngitis (1.0%) being the main side effects.

The paragraphs below summarize studies that examined the efficacy and safety of romosozumab in patients with kidney impairment.

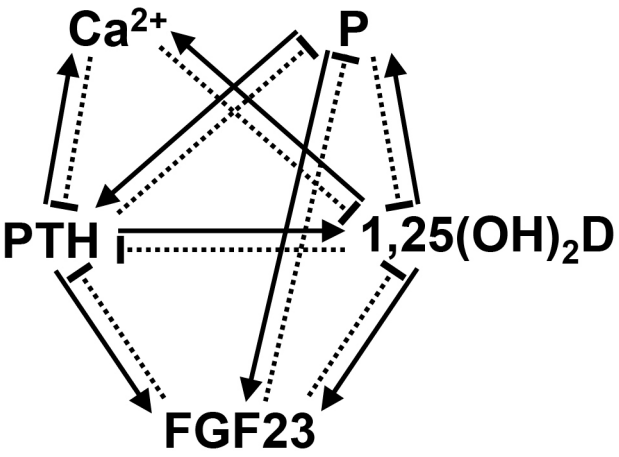
Kidney function in postmenopausal Japanese women with osteoporosis and CKD were classified as CKD (eGFR <90 mL/min/1.73 m^2) or normal kidney function (eGFR ≥90 mL/min/1.73 m^2), and the efficacy and safety of romosozumab were evaluated accordingly [106]. The romosozumab-treated group showed increased BMD at the lumbar spine, proximal femur, and femoral neck at 12 months from baseline; in addition, the incidence of new vertebral fractures was lower in the romosozumab group than in the placebo group, regardless of the eGFR. The incidence of adverse events was similar between the groups. Furthermore, an overseas study that classified kidney impairment as eGFR ≥90, 60–89, or 30–59 showed that romosozumab reduced the risk of new vertebral fractures and increased BMD, with similar safety profiles across all kidney function groups [107].

Administration of romosozumab to patients with severe kidney impairment or to those on dialysis requires caution due to the potential for hypocalcemia. AUC and Cmax increase in patients with severe kidney impairment or end-stage kidney disease. However, according to interview forms, the need for dose adjustment in patients with severe CKD or dialysis patients is considered low. Another report noted that romosozumab was well tolerated; although transient hypocalcemia and elevated parathyroid hormone levels were more common than in healthy individuals, all cases with hypocalcemia were asymptomatic and did not require treatment [108]. Regarding the efficacy of romosozumab in patients with severe kidney impairment or on dialysis, a randomized comparison of patients sub-grouped according to kidney function reported significant increases in BMD at the lumbar spine, proximal femur, and femoral neck, as well as a significant reduction in the incidence of new vertebral fractures after 12 months, in patients with CKD stage G3 treated with romosozumab [107].

With respect to patients on maintenance dialysis, romosozumab increased BMD at the lumbar spine and femoral neck significantly after 1 year [109]. Although hypocalcemia was observed, there was no apparent increase in cardiovascular events. Another report of treatment-naïve osteoporosis patients on maintenance dialysis who received romosozumab for 12 months, followed by denosumab for an additional 12 months, showed significant increases in BMD at the lumbar spine, proximal femur, and femoral neck; however, there was a slight increase in the coronary artery and thoracic aorta calcification scores. Romosozumab was more effective in patients with low baseline BMD at the proximal femur, low baseline BMD at the femoral neck, and high baseline TRACP-5b [110]. Although romosozumab appears to show efficacy in patients on hemodialysis, attention should be paid to development of hypocalcemia after initiation of treatment.

Conclusion

In healthy individuals, the collaborative action of three hormones, namely PTH, $1,25(OH)_2D$, and FGF23, orchestrates the regulation of serum Ca and P level, however, this homeostatic system becomes disrupted in patients with CKD (Graphical Abstract). This review summarizes the diagnosis and pharmacological treatment of osteoporosis in patients with CKD, including those on maintenance dialysis. Accumulating evidence suggests that osteoporosis should be managed at different CKD stages, particularly in patients with non-dialysis CKD; however, there is little evidence regarding pharmacotherapy during CKD stages G4 to G5, or during maintenance dialysis



Graphical Abstract In the treatment of osteoporosis in patients with CKD, consideration must be given not only to the reduction in bone mass and deterioration of bone quality but also to the abnormalities in this homeostatic system.

(G5D). Thus, established criteria regarding initiation of pharmacological treatment, as well as further evidence regarding management of osteoporosis in patients with CKD, are eagerly anticipated.

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