ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

INVITED REVIEW
Endocrinol Res Pract. 2025;29(1):52-58

Navigating Bone Health in Chronic Kidney Disease: A Comprehensive Review of CKD-MBD and Osteoporosis

ABSTRACT

Chronic kidney disease (CKD) is a common and progressive disorder associated with significant alterations in bone morphology and mineral metabolism, leading to a complex syndrome known as CKD-mineral and bone disorder (CKD-MBD). This condition involves biochemical, skeletal, and vascular abnormalities, all of which have been independently related to cardiovascular events and elevated mortality. Renal osteodystrophy (ROD) is bone component and related with increased fracture risk. Reduced bone quality and low bone mass in osteoporosis induce fragility fractures, and both ROD and osteoporosis independently contribute to higher fragility fracture risk, particularly in older individuals, posing diagnostic and management challenges due to the interplay between traditional osteoporosis and CKD-specific bone disorders.

This review summarizes the pathophysiology, diagnostic challenges, and management approaches for osteoporosis and CKD-MBD. It emphasizes the importance of distinguishing osteoporosis from other elements of CKD-MBD to accurately assess fracture risk and optimize treatment. The complexity of these conditions necessitates a nuanced approach that considers both CKD-specific and traditional risk factors. Advances in diagnostic tools, including biomarkers and imaging techniques, have improved the evaluation of bone health in CKD; nevertheless, some limitations and caveats should be considered. Pharmacological agents such as bisphosphonates, denosumab, and anabolic agents have demonstrated varying efficacy and safety profiles across different CKD stages.

Overall, managing bone health in CKD requires personalized treatment strategies to address both osteoporosis and CKD-MBD. Continued research is essential to refine diagnostic approaches and develop targeted therapies that minimize fracture risk and improve clinical outcomes in this high-risk population.

Keywords: Chronic kidney disease, CKD-MBD, osteoporosis, fracture risk

Introduction

Chronic kidney disease (CKD) is a progressive disorder affecting over 10% of the world population, which amounts to more than 800 million people.[1] As CKD progresses, disruptions in bone morphology and changes in mineral metabolism become increasingly prevalent, leading to a clinical syndrome known as CKD-mineral and bone disorder (CKD-MBD). This disorder is associated with a range of laboratory abnormalities, including disturbances in mineral metabolism (calcium and phosphorus), alterations in parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) levels, and vitamin D metabolism. These abnormalities contribute to various skeletal complications, such as renal osteodystrophy (ROD) and osteoporosis, as well as extraskeletal calcifications, all of which are associated with an increased risk of cardiovascular morbidity and mortality.[2]

Osteoporosis is a prevalent chronic disease characterized by trabecular thinning, decreased cortical thickness, and increased cortical porosity. This reduction in bone mass and microstructural disruption leads to increased bone fragility. Osteoporosis and CKD both have an independent impact on bone health, and elevated fragility fracture risk is associated not only with ROD but also with osteoporosis, especially in older ages. Despite the significant clinical impact of CKD-MBD and osteoporosis, diagnosing and managing these complications remain challenging. The complexity of evaluating and managing osteoporosis in CKD-MBD arises from the interplay between traditional osteoporosis and bone disorders specific to CKD, necessitating a comprehensive understanding of the pathophysiology, diagnostic approaches, and treatment strategies.

Ozlem Turhan Iyidir

Department of Endocrinology and Metabolism, Başkent University Faculty of Medicine, Ankara, Türkiye

Corresponding Author:
Ozlem Turhan Iyidir
✉ oturhaniyidir@yahoo.com

Received: August 31, 2024
Accepted: September 11, 2024
Publication Date: November 4, 2024

Cite this article as: Turhan Iyidir O. Navigating bone health in chronic kidney disease: A comprehensive review of CKD-MBD and osteoporosis. *Endocrinol Res Pract.* 2025;29(1):52-58.

DOI: 10.5152/erp.2024.24514

This review aims to present a detailed overview of the pathophysiology, difficulties in diagnostic approaches, and management strategies of osteoporosis and CKD-MBD, highlighting the complexities of evaluating and treating bone health in CKD.

Abnormalites in Parathyroid Hormone, Vitamin D Fibroblast Growth Factor-23, and Mineral Metabolism

In order to evaluate fracture risk in patients with CKD, it is essential to differentiate osteoporosis from other elements of CKD-MBD. Therefore, it is essential to understand abnormalities in mineral metabolism leading to skeletal changes. In normal physiology, calcium metabolism is tightly regulated by hormonal control involving the intestine, kidneys, and bones to regulate serum-ionized calcium levels within optimal ranges, mainly by the actions of two main hormones: PTH and 1,25-dihydroxyvitamin D (1,25D). A low calcium concentration is a common mineral abnormality in CKD patients. Total calcium concentration declines as CKD progresses due to increased phosphate binding to calcium, decreased levels of 1,25D, and skeletal resistance to PTH actions. Hypocalcemia leads to increased secretion of PTH and bone remodeling. A reduction in calcium levels is sensed by the calcium-sensing receptor (CaSR), which is a specific membrane receptor expressed on the surface of chief cells in the parathyroid gland. The fall in calcium levels potently stimulates PTH secretion. Serum phosphate levels remain within normal ranges mostly in the initial phases of CKD due to the counter-regulatory actions of FGF23 and PTH. Both of these hormones are stimulated as GFR decreases. Increased PTH secretion induces phosphaturia in the proximal renal tubules. Elevated levels of bone-derived hormone FGF23 inhibit phosphate uptake, increase phosphaturia, and decrease the renal synthesis of 1,25D. It is assumed that the increase in phosphate load per nephron stimulates FGF23 production from osteocytes; however, the details of this mechanism have not been fully understood.[3] Nevertheless, during the course of CKD, serum phosphate levels gradually rises despite the phosphaturic actions of both FGF23 and PTH. This, along with the deterioration of renal function, further inhibits the production of 1,25D, leading to decreased absorption of calcium in the intestines. This reduction in calcium levels further enhances PTH secretion and worsens secondary hyperparathyroidism (SHPT).[4] Prolonged SHPT leads to the development of diffuse or nodular hyperplasia in the parathyroid glands.

In addition to hypocalcemia and hyperphosphatemia, increased FGF23 levels and decreased 1,25D levels act as additional drivers of SHPT. Reduced expression of CaSR and vitamin D receptors in the parathyroid glands impairs the response of parathyroid cells to calcium and/or calcitriol.[5] Recent studies showed depressed expression of Klotho in the parathyroid gland. Klotho functions as a cofactor for FGF23. Therefore, downregulation of Klotho in the parathyroid gland is likely to cause resistance to the PTH-lowering effect of FGF23, resulting in further progression of SHPT.[4] Uncontrolled SHPT is a significant manifestation of CKD-BMD and is associated with fractures and mortality. Furthermore, FGF23 inhibits WNT pathways, which induces bone degradation and consequently increases susceptibility to fractures.

Chronic Kidney Disease-Mineral and Bone Disorder

The accepted definition of abnormalities of bone and mineral metabolism due to CKD includes one or more of the following 3 features: imbalances in the metabolism of calcium, phosphorus, PTH, fibroblast growth factor 23 (FGF23), and vitamin D, abnormalities in the bone due to impaired turnover, mineralization, volume and length, and extraskeletal (mostly vascular) calcifications. Previously, these disturbances were referred to as ROD. In the 2006 KDIGO Controversies Conference on "Definition, Evaluation, and Classification of Renal Osteodystrophy," this terminology was revised and the term CKD-mineral and bone disorder is recommended to be used to represent all 3 features. Chronic kidney disease-mineral and bone disorder is associated with higher incidence of fractures and also cardiovascular morbidity and mortality.[2]

Recently, ROD refers to pathological alterations in bone morphology in CKD, diagnosed through bone biopsy, and is related with a higher risk of fracture. The histomorphometry of the bone biopsy further identifies 4 types of ROD based on bone turnover, mineralization, and volume, known as the TMV classification.[6]

It is essential to assess mineral metabolism parameters, bone histomorphometry, and evaluate vascular calcification repeatedly to diagnose CKD-MBD. Since routine bone biopsies are not usually performed, clinicians prefer to follow the changes of biomarkers of bone and metabolism such as PTH, total or bone-specific alkaline phosphatase, and vitamin D. Thus, it is essential to understand abnormalities of these biomarkers throughout the progression of CKD. The biochemical alterations include decreased serum calcium, and elevated levels of serum phosphate, FGF23, and PTH.

Skeletal Abnormalites in CKD-MBD

Renal osteodystrophy is used to describe bone disease in CKD and is defined as any alteration in bone morphology due to disturbances in calcium and phosphorus metabolism.[2] Renal osteodystrophy encompasses a broad range of skeletal disorders. There are 4 types identified in CKD: hyperparathyroid bone disease (osteitis fibrosa), adynamic bone disease, mixed uremic osteodystrophy, and osteomalacia. Available biochemical markers are not useful to determine the different types of ROD; thus, bone biopsy at the iliac crest after tetracycline double labeling is the gold standard method.[7]

- Osteitis Fibrosa

  Hyperparathyroid bone disease, also known as osteitis fibrosa, is a high-turnover bone disease that is primarily associated with increased PTH secretion. Continuously high levels of PTH stimulate

MAIN POINTS

- CKD patients have a significantly higher risk of fractures compared to the general population, due to both traditional osteoporosis risk factors and CKD-specific complications.
- Standard fracture risk assessment tools have some limitations in the identification of patients with increased fracture risk in CKD.
- Managing bone health in CKD requires a tailored approach that addresses both CKD-MBD and osteoporosis.
- Personalized treatment strategies balancing the benefits and risks of therapy, particularly in advanced CKD, are crucial.

the proliferation of bone resorption units, leading to a significant expansion of resorptive areas and ultimately contributing to a negative bone balance. As a result of reduced cortical bone due to accelerated resorption, fibrous tissue containing cysts forms in place of the expected laminar osteoid.[8]

- Adynamic Bone Disease

  Adynamic bone disease is identified as low or absent bone formation and low cellularity. The low turnover is typically associated with the preservation of mineralization and the near-absence of osteoid accumulation. Bone volume and trabecular connectivity are usually diminished.[7] There are multiple factors involved in the pathogenesis of adynamic bone disease, including aluminum overload, accumulation of uremic toxins, relatively low PTH, and resistance to PTH. The balance between anabolic factors (i.e., insulin-like growth factor) and bone remodeling inhibitory factors (sclerostin, Dickkopf-related protein-1) is impaired. As a result, bone formation is suppressed through the repression of WNT/β-catenin signaling. Advanced age, diabetes, increased calcium load, malnutrition, and gonadal dysfunction are clinical conditions strongly associated with adynamic bone disease.[9]
- Osteomalacia

  Osteomalacia is defined as undermineralization of newly produced osteoid, primarily due to a lack of calcium, phosphorus, or vitamin D.[10] The discovery of aluminum-induced osteomalacia in the 1980s and decreased use of aluminum-containing phosphate binders have decreased the frequency of osteomalacia during the last years.
- Mixed uremic osteodystrophy

  Mixed uremic osteodystrophy is defined as increased bone turnover and impaired mineralization. Secondary hyperparathyroidism due to hypocalcemia, phosphate retention, vitamin D deficiency, and high FGF23 levels leads to an increase in bone formation and resorption. Furthermore, aluminum accumulation and amyloidosis disrupt mineralization in the bone. Bone biopsy reveals similar findings to those seen in osteitis fibrosa, which is marked by high turnover but with impaired mineralization.[11]

  The prevalence of ROD has undergone a notable shift over the past few decades, the underlying causes of which remain uncertain. This may be attributable to the utilization of novel pharmacological agents in the management of MBD, the advancement of dialysis techniques, and the enhanced survival rates of patients. Low bone turnover disease appears to be the main pattern in the early stages of CKD,[12] yet it is still unknown whether low bone turnover is a transitional state before high bone turnover, which is predominant in the advanced stages of CKD. Treatments to normalize PTH levels may have increased the incidence of adynamic bone disease.

Osteoporosis

Osteoporosis is a systemic condition marked by a reduction in bone mass and bone quality due to the microarchitectural deterioration of bone tissue, which leads to bone fragility and fracture susceptibility. Diagnosis of osteoporosis depends on bone mineral density (BMD) evaluated by dual-energy X-ray absorptiometry (DXA). The World Health Organization defines OP as a *T*-score ≤−2.5 at the spine or hip given by DXA.[13BMD]

Osteoporosis is likely to contribute to the bone component of CKD, especially in postmenopausal women and elderly men.[14] The coexistence of osteoporosis and CKD increases the risk of fragility fractures, with significantly worse clinical outcomes and considerable healthcare expenses. The prevalence of osteoporosis was 31.8% in patients with CKD G3-5, and there was a statistically significant relation between hip fractures and moderate to severe renal impairement.[15]

Patients with CKD are also subject to common risk factors, involving older age, hypogonadism, low body mass index (BMI), glucocorticoid treatment, and previous history of fragility fracture. Additionally, there are also risk factors specifically related to chronic kidney disease, such as long dialysis duration, acidosis, and uremia. Thus, decreased bone strength in CKD is a combination of primary osteoporosis and disturbances in mineral metabolism and the uremic environment.[16] Therefore, osteoporosis in CKD involves both primary bone loss due to aging and hypogonadism as in menopause and secondary bone damage specific to renal failure such as ROD, affecting diagnosis and treatment strategies (Figure 1).[17,18] Hence "uremic osteoporosis" or "CKD-induced osteoporosis" has been suggested as a new concept to differentiate osteoporosis in CKD patients recently.[6]

Osteoporosis vs Renal Osteodystrophy

In patients in the early stages of CKD and those without biochemical abnormalities, the diagnosis and management of osteoporosis are similar to those with normal renal function. However, in patients with G4-5D, it is essential to distinguish ROD from osteoporosis to determine the appropriate treatment option.

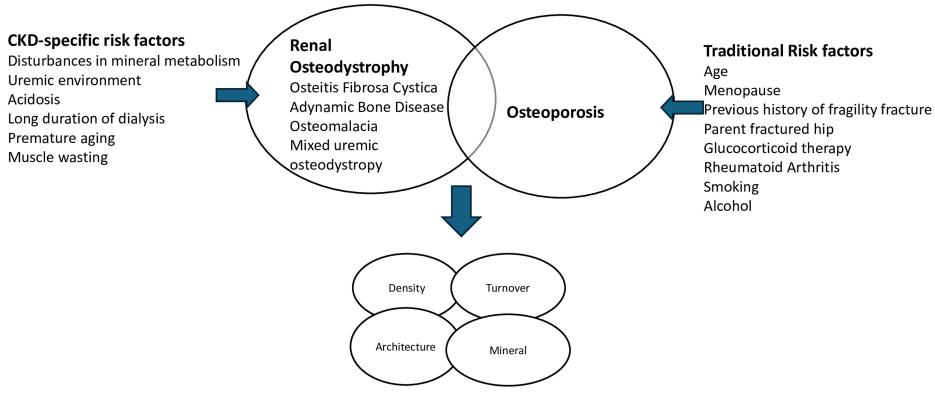

Figure 1. Interplay between CKD-MBD and osteoporosis in CKD and their impact on determinants of bone strength. Adapted from Bover et al[17] and West et al[18]

Osteoporosis is asymptomatic until the patient experiences a fracture. Patients with adynamic bone disease are also asymptomatic; however, bone pain and tenderness are the most frequent symptoms in patients with high-turnover bone disease. Diffuse bone pain is common in osteomalacia. Biochemical and non-invasive diagnostic tests, which are detailed in the next section, are unable to differentiate osteoporosis from the various types of ROD.[14]

Evaluation of Fracture Risk in CKD

The incidence of hip fractures among individuals with CKD is 2-4 times higher than in the non-CKD population. Vertebral fractures are very common and have similar prevalance in both CKD and non-CKD individuals, probably due to the underdiagnosis of vertebral fractures.

The presence of both traditional and non-traditional risk factors specific to CKD, including uremia, disturbances in mineral and Vitamin D metabolism, inflammation, premature aging, and chronic wasting, complicates the prediction of fracture risk in this population.

Low bone mass determined by DXA is a well-known major risk factor for fractures and is a very useful tool to predict incident osteoporotic fractures in non-CKD populations.[19] However, within the setting of CKD, as a result of additional CKD-specific risk factors that may impact bone strength and fracture susceptibility, the role of BMD through DXA might be limited. Therefore, after the introduction of new evidence suggesting a correlation between low BMD and increased fracture risk across the entire spectrum of CKD, the 2017 update of the KDIGO CKD-MBD guidelines recommends BMD testing in all stages of CKD, including in dialysis patients, if the results will impact treatment decisions.[20] Nevertheless, there are several important points to be considered in the interpretation of BMD.

First of all, a low *T*-score may not indicate osteoporosis. For instance, osteomalacia, a cause of impaired mineralization, will also lead to a low *T*-score, and in this condition, osteoporosis treatment might not be appropriate. Furthermore, many patients with a higher *T*-score can still have a high fracture risk, particularly those with a history of previous fractures. Using the *T*-score to diagnose osteoporosis is not appropriate, especially in children and young adults; the *Z*-score, which indicates a low bone density, is more appropriate. Finally, DXA does not identify the cause of low BMD, so it is crucial to evaluate other possible risk factors associated with low bone density, such as the nature of underlying ROD.[21]

FRAX is an online, computer-based fracture risk assessment tool that calculates the 10-year probability of major osteoporotic fractures and hip fracture.[22] In CKD, evidence suggests that FRAX may under or overestimate fracture risk, especially in patients with CKD G3; however, it can still can serve as a reliable tool for assessing fracture risk in early CKD stages.[23] There is insufficient evidence on the validity of FRAX in advanced stages and in dialysis patients, where ROD is common. The extent to which FRAX underestimates fracture risk in CKD patients with ROD remains uncertain.[21]

Trabecular bone score (TBS) is an indirect measure of bone microarchitecture derived from DXA spine scans. Trabecular bone score has been extensively studied in non-CKD population, and evidence shows a good correlation between bone resistance and fracture risk.[24] Trabecular bone score is frequently used for predicting fracture risk more accurately in the general population; however, evidence on the utility of TBS in CKD patients is insufficient. A recent meta-analysis of available data investigating the accuracy of TBS in the setting of CKD revealed a significant impairment of TBS values in patients with all stages of CKD as compared to the general population but the possible benefit as a potential adjustment for FRAX-calculated probability of fracture is not clear.[25]

Peripheral quantitative computed tomography, high-resolution peripheral computed tomography, and micro magnetic resonance imaging are new imaging modalities for evaluating bone microstructure non-invasively. Further research is needed to comprehend the roles of these alternative imaging methods in fracture prediction for CKD patients.[21]

Bone biopsy still remains the gold standard in the diagnosis and identification of specific forms of ROD. In order to understand bone biopsy findings in the assessment of ROD, KDIGO guidelines suggested using the TMV (bone turnover, mineralization, and volume) system to standardize histomorphometric analysis. However, the appropriate cut-off values to define the type of turnover, the amount of mineralization, and abnormal bone volume have not definitively determined.[26] The weak intercorrelation between biopsies taken from different sites at the same time in the same patients may limit the utility of bone biopsy.[27] Moreover, high cost, lack of expertise, the invasive character of the procedure, and limited patient acceptability are other limitations of bone biopsy.

Several bone turnover markers (BTMs) have been suggested as non-invasive diagnostic markers to clinically differentiate high and low bone turnover in CKD. Parathyroid hormone and bone-specific ALP (BALP) are the most frequently used biomarkers in clinical practice. The correlation between PTH and bone turnover is rather weak and is not a good indicator of turnover unless at extreme concetrations. Parathyroid disease, responsiveness of bone to PTH, and biologically inert PTH molecules are additional confounders of the association between PTH and bone turnoner.[28] Bone-specific alkaline phosphatase (bone ALP) constitutes about 40% of serum total ALP, and in the absence of liver dysfunction, total ALP is a suggested marker to monitor bone formation in the CKD population. There is a direct and linear relationship between ALP and fracture risk in patients with CKD on maintenance dialysis; conversely, PTH shows a U- or J shaped correlation.[29] As markedly low or high values may be helpful to understand underlying bone turnover, the 2017 KDIGO guidelines recommend measuring PTH and BALP in CKD G3-5D.[20]

Not only lack of tissue specificity and high variability are limitations of BTMs, but also interpretation is restricted in the setting of CKD. Procollagen type I N-terminal propeptide (PINP) and tartrate-resistant acid phosphatase 5b (TRaP5b), reflecting bone formation and resorption respectively, have emerged as promising BTMs. In a cross-sectional retrospective study in patients with CKD3-5D and kidney transplant recipients, for high turnover, a diagnostic cut-off for PINP was >120.7 ng/mL while TRACP-5b <3.44 U/L was a better predictor for low bone turnover.[30] Although the combined utilization of BTM may improve their predictive value, especially in discrimination of low and high bone turnover, there are no consistent recommendations in clinical guidelines.[31]

Treatment Options

It is suggested to manage osteoporosis and/or high-risk fractures in patients with CKD G1-G2 and those with CKD-G3 who have PTH levels

in normal ranges, similar to the general populaton.[20] In patients with advanced stages of CKD, the major goal concerning bone disease should be to prevent or manage ROD by controlling SHP, managing acidosis, and appropriate replacement for vitamin D deficiency. Avoiding oversuppression of PTH is also important. Management of SHP in this setting is out of the scope of this review.

Non-pharmacological Interventions

Non-pharmacological strategies encompass appropriate nutrition, adequate calcium and vitamin D replacement, smoking cessation, limiting alcohol intake, engaging in regular physical activity, and fall prevention. A low-phosphorus diet is suggested since PTH concentrations can be lowered with phosphorus restriction in CKD. Lowering protein in daily nutrition may slow CKD progression, but there is insufficient evidence on the impact of these diets on BMD and reducing fractures.[32] Moreover, it is crucial to provide adequate caloric intake to avoid malnutrition because of the well-recognized direct association between BMI and bone mass.[33] For patients with CKD G1-3 and without biochemical evidence of CKD-MBD, recommendations for calcium and vitamin D intake are similar to general population. Excess calcium supplementation can be harmful, especially in patients with hypercalcemia, those on warfarin treatment, in adynamic bone, with low PTH levels, or in cases of cardiovascular calcifications. Intake of moderate doses of calcium (800-1000 mg/day), mostly through an appropriate diet, and, if required to consider modest supplementation, could be encouraged. Unfortunately, there is still a need for randomized controlled trials investigating the effect of calcium suppplementation on fractures.[34] Since 25OHD deficiency and insufficiency are common in patients with CKD, a daily intake of 800 IU vitamin D has been suggested, though this may need to be adjusted according to reach the desirable target level of 25OHD.[21] Chronic renal failure is associated with a higher fall risk. Thus, systemic muscle weakness should be evaluated, and exercises to enhance muscle strength, tone, and balance should be recommended to reduce probable falls and fracture rates. Secondary causes of increased fall risk, such as decreased vision, neuropathy, hypotension, bradycardia, and psychotic drugs, should also be revised.[35]

Pharmacological Interventions

The selection of appropriate pharmacologic treatment for osteoporosis in CKD is based upon fracture risk, BMD, and existence of CKD-MBD (e.g., high or low turnover bone disease). Before commencing a pharmacologic agent (antiresorptive or anabolic), biochemical abnormalities like vitamin D deficiency, hypocalcemia, SHPT, and hyperphosphatemia should be controlled. Phosphate-lowering therapies, calcium, calcimimetics, vitamin D, and vitamin D receptor activators are used to handle these abnormalities.

Bisphosphonates are safe and effective in osteoporosis management in the general population. Most of the absorbed bisphosphonate is cleared by the kidneys via glomerular filtration and active secretion; the remaining is taken up by the bone. Thus, they may remain in the bone for many years and are gradually released throughout the cycles of bone remodeling. In cases of impaired renal function, renal elimination diminishes, and increased skeletal accumulation may lead to greater suppression of bone remodeling.[36] Furthermore, renal accumulation may also have detrimental effects on kidney function. Data from post hoc analyses of pivotal clinical trials of bisphopsphonates found similar efficacy of these drugs in patients with mild or moderately impaired renal function compared to those with normal eGFR. However, based on concerns about potential impact on renal function and inadequate evidence on the efficacy and safety of bisphosphonates in patients with G4-G5D, these drugs are considered contraindicated in patients with GFR < 30-35 mL/min.[37]

Denosumab acts as a receptor activator of nuclear factor-κB ligand (RANK-L) inhibitor, which is an osteoclast differentiation factor. Thereby, denosumab impairs osteoclast formation and function, which results decreased bone resorption and increased bone density. It is eliminated by the reticuloendothelial system and can therefore be safely administered to patients with creatinine clearances below 35 mL/min.[38] The post hoc analysis of a clinical trial of denosumab, which stratified participants by their eGFR, showed reduced fracture risk among women with impaired renal function; however, the number of women with G4 CKD was small.[39] There is still a lack of specific trials evaluating the efficacy of denosumab in patients with G4-G5 CKD and those on dialysis, but available data suggest that denosumab improves BMD. Conversely, there is limited evidence about the effect of denosumab on fracture risk in this group.[40] Denosumab-induced hypocalcemia, especially in advanced stages of CKD, and potential rapid bone loss after cessation of denosumab are major concern. Low 25OHD, low baseline ALP and PTH, previous parathyroidectomy, acute medical illness, non-calcium-based phosphate binders, loop diuretic treatment, and insufficient supplementation of calcium and calcitriol were reported as risk factors for denosumab-induced hypocalcemia. Careful patient selection, repletion of calcium and 25OHD prior to and during treatment, and close monitoring of calcium levels during the first 2 months after administration are important to prevent severe hypocalcemia.[38] It is already well established that after withdrawal of denosumab, there is a rapid reduction in BMD, and subsequent multiple vertebral fractures may occur, which is defined as the rebound phenomenon. A sequential bisphosphonate treatment can attenuate this rebound phenomenon.[41] In a real-world setting study, patients with CKD have a greater risk of fractures after denosumab discontinuation.[42] There is a need for more direct evidence about appropriate subsequent treatment modalities after denosumab in patients with CKD.

Raloxifene is an oral selective estrogen modulator and is less commonly utilized because of its less potent antiresorptive activity. In clinical trials, raloxifene significantly improved BMD and reduced the incidence of vertebral fractures in postmenopausal women with CKD G1-4, irrespective of kidney function. Two small short-term trials showed the efficacy of Raloxifen in maintaining bone density in postmenopausal women with CKD G5-5D.[43] Additional studies are required to assess the benefits and risks of raloxifene in advanced stages of CKD.

Teriparatide (PTH 1-34) and Abaloparatide (PTH-related protein analog) are anabolic agents that increase remodeling-based formation and partially restore bone microstructure. In teriparatide clinical trials, patients with creatinin levels >2 mg/dL and high PTH were excluded. The post hoc analysis of the Fracture Prevention Trial, which required participants to have normal serum PTH concentrations, showed that teriparatide was both safe and effective in patients with mild to moderate renal insufficiency.[44] Small studies in patients on dialysis or with verified adynamic bone disease demonstrated that teriparatide may be beneficial in adynamic bone disease.[45,46] The optimal dosing regimen is still unclear. Once-weekly

teriparatide was associated with transient hypotension in patients on dialysis. The duration of therapy should not exceed 2 years.[35] Data regarding abaloparatide's efficacy in patients with CKD-MBD are lacking.

Romosozumab is a monoclonal antibody against sclerostin. Sclerostin is an inhibitor of Wnt signaling, which is a key negative regulator of bone formation; thus, inhibition of sclerostin favors bone formation. In clinical trials, romosozumab improved BMD and decreased vertebral fractures. Unfortunately, research in the setting of CKD is limited. In a retrospective analysis of 2 randomized trials of romosozumab, it was effective in reducing the risk of new vertebral fractures and was safe in postmenopausal women with mild to moderate loss of kidney function.[47] In a recent single-center observational Japan study in Japan, 1 year treatment with romosozumab increased BMD in patients on hemodialysis. The most frequent adverse effect was tolerable hypocalcemia, and there was no apparent increase in cardiovascular events.[48] Since concerns have been raised with regard to cardiovascular safety, it is important to emphasize that the utilization of romosozumab is strictly contraindicated for patients with high cardiovascular risk.[49] Further data on safety are required, especially for high-risk patients, which definetly comprises the CKD population

In summary, CKD significantly impacts bone and mineral metabolism, leading to an increased fracture risk. The coexistence of osteoporosis and CKD-MBD is evolving, and treating osteoporosis differs from the general population due to the complex impact of both CKD-specific and traditional risk factors on bone. There is no consensus on the optimal method to assess bone health and predict fracture risk in CKD, especially in CKD G4-5D. Despite advancements in understanding and treatment, challenges remain in accurately diagnosing and optimally managing these conditions. Post hoc analyses of randomized trials of osteoporosis therapies showed that the efficacy of these agents was similar to that of the general population in patients with mild to moderate CKD; nevertheless, data are limited in advanced stages. Therefore, the need for personalized treatment plans is critical, especially in advanced CKD stages, where balancing benefits and potential risks remain crucial.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.T.I.; Literature Search – O.T.I.; Writing – O.T.I.; Critical Review – O.T.I.

Declaration of Interests: The author has no conflicts of interest to declare.

Funding: This study received no funding.

References

1. Bello AK, Okpechi IG, Levin A, et al. An update on the global disparities in kidney disease burden and care across world countries and regions. *Lancet Glob Health*. 2024;12(3):e382-e395. [CrossRef]
2. Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: improving Global Outcomes (KDIGO). *Kidney Int*. 2006;69(11):1945-1953. [CrossRef]
3. Suzuki K, Soeda K, Komaba H. Crosstalk between kidney and bone: insights from CKD-MBD. *J Bone Miner Metab*. 2024;42(4):463-469. [CrossRef]
4. Komaba H, Fukagawa M. FGF23-parathyroid interaction: implications in chronic kidney disease. *Kidney Int*. 2010;77(4):292-298. [CrossRef]
5. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. *Clin J Am Soc Nephrol*. 2011;6(4):913-921. [CrossRef]
6. Moe SM. Renal osteodystrophy or kidney-induced osteoporosis? *Curr Osteoporos Rep*. 2017;15(3):194-197. [CrossRef]
7. Aguilar A, Gifre L, Ureña-Torres P, et al. Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis. *Front Physiol*. 2023;14:1177829. [CrossRef]
8. Santoso D, Thaha M, Empitu MA, et al. Brown tumour in chronic kidney disease: revisiting an old disease with a new perspective. *Cancers (Basel)*. 2023;15(16). [CrossRef]
9. Andress DL. Adynamic bone in patients with chronic kidney disease. *Kidney Int*. 2008;73(12):1345-1354. [CrossRef]
10. Modest JM, Sheth H, Gohh R, Aaron RK. Osteomalacia and renal osteodystrophy. *R I Med J (2013)*. 2022;105(8):22-27.
11. Santos MFP, Hernández MJ, de Oliveira IB, et al. Comparison of clinical, biochemical and histomorphometric analysis of bone biopsies in dialysis patients with and without fractures. *J Bone Miner Metab*. 2019;37(1):125-133. [CrossRef]
12. Drüeke TB, Massy ZA. Changing bone patterns with progression of chronic kidney disease. *Kidney Int*. 2016;89(2):289-302. [CrossRef]
13. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785-795. [CrossRef]
14. Pazianas M, Miller PD. Osteoporosis and chronic kidney disease-mineral and bone disorder (CKD-MBD): back to basics. *Am J Kidney Dis*. 2021;78(4):582-589. [CrossRef]
15. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol*. 2006;17(11):3223-3232. [CrossRef]
16. Evenepoel P, Cunningham J, Ferrari S, et al. Diagnosis and management of osteoporosis in chronic kidney disease stages 4 to 5D: a call for a shift from nihilism to pragmatism. *Osteoporos Int*. 2021;32(12):2397-2405. [CrossRef]
17. Bover J, Bailone L, López-Báez V, et al. Osteoporosis, bone mineral density and CKD-MBD: treatment considerations. *J Nephrol*. 2017;30(5):677-687. [CrossRef]
18. West SL, Patel P, Jamal SA. How to predict and treat increased fracture risk in chronic kidney disease. *J Intern Med*. 2015;278(1):19-28. [CrossRef]
19. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res*. 2005;20(7):1185-1194. [CrossRef]
20. KDIGO. Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–Mineral and bone Disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;7(1):1-59. [CrossRef]
21. Haarhaus M, Aaltonen L, Cejka D, et al. Management of fracture risk in CKD-traditional and novel approaches. *Clin Kidney J*. 2023;16(3):456-472. [CrossRef]
22. Kanis JA, Johansson H, Harvey NC, McCloskey EV. A brief history of FRAX. *Arch Osteoporos*. 2018;13(1):118. [CrossRef]
23. Desbiens LC, Sidibé A, Beaudoin C, Jean S, Mac-Way F. Comparison of fracture prediction tools in individuals without and with early chronic kidney disease: a population-based analysis of CARTaGENE. *J Bone Miner Res*. 2020;35(6):1048-1057. [CrossRef]
24. Goel H, Binkley N, Boggild M, et al. Clinical use of trabecular bone score: the 2023 ISCD official positions. *J Clin Densitom*. 2024;27(1):101452. [CrossRef]
25. Bioletto F, Barale M, Maiorino F, et al. Trabecular bone score as a marker of skeletal fragility across the spectrum of chronic kidney disease: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2024;109(7):e1534-e1543. [CrossRef]
26. Tartaglione L, Pasquali M, Rotondi S, Muci ML, Covic A, Mazzaferro S. Positioning novel BioLogicals in CKD-mineral and bone disorders. *J Nephrol*. 2017;30(5):689-699. [CrossRef]

27. Thomsen JS, Ebbesen EN, Mosekilde L. Static histomorphometry of human iliac crest and vertebral trabecular bone: a comparative study. *Bone*. 2002;30(1):267-274. [CrossRef]
28. Evenepoel P, Cavalier E, D'Haese PC. Biomarkers predicting bone turnover in the setting of CKD. *Curr Osteoporos Rep*. 2017;15(3):178-186. [CrossRef]
29. Maruyama Y, Taniguchi M, Kazama JJ, et al. A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among patients receiving hemodialysis in Japan. *Nephrol Dial Transplant*. 2014;29(8):1532-1538. [CrossRef]
30. Jørgensen HS, Behets G, Viaene L, et al. Diagnostic accuracy of noninvasive bone turnover markers in renal osteodystrophy. *Am J Kidney Dis*. 2022;79(5):667-676.e1. [CrossRef]
31. Brouwers P, Bouquegneau A, Cavalier E. Insight into the potential of bone turnover biomarkers: integration in the management of osteoporosis and chronic kidney disease-associated osteoporosis. *Curr Opin Endocrinol Diabetes Obes*. 2024;31(4):149-156. [CrossRef]
32. Stremke ER, Biruete A, Hill Gallant KM. Dietary protein intake and bone across stages of chronic kidney disease. *Curr Osteoporos Rep*. 2020;18(3):247-253. [CrossRef]
33. Johansson H, Kanis JA, Odén A, et al. A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res*. 2014;29(1):223-233. [CrossRef]
34. Evenepoel P, Jørgensen HS, Bover J, et al. Recommended calcium intake in adults and children with chronic kidney disease-a European consensus statement. *Nephrol Dial Transplant*. 2024;39(2):341-366. [CrossRef]
35. Evenepoel P, Cunningham J, Ferrari S, et al. European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4-G5D. *Nephrol Dial Transplant*. 2021;36(1):42-59. [CrossRef]
36. Pereira A, Frazão J. Kidney-induced osteoporosis: a new entity with a novel therapeutic approach. *Port J Nephrol Hypertens*. 2020;34(2). [CrossRef]
37. Miller PD, Jamal SA, Evenepoel P, Eastell R, Boonen S. Renal safety in patients treated with bisphosphonates for osteoporosis: a review. *J Bone Miner Res*. 2013;28(10):2049-2059. [CrossRef]
38. Gopaul A, Kanagalingam T, Thain J, et al. Denosumab in chronic kidney disease: a narrative review of treatment efficacy and safety. *Arch Osteoporos*. 2021;16(1):116. [CrossRef]
39. Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res*. 2011;26(8):1829-1835. [CrossRef]
40. Simonini M, Bologna A, Vezzoli G. Is denosumab an efficient and safe drug for osteoporosis in dialysis patients? Considerations and state of the art about its use in this setting. *Int Urol Nephrol*. 2024;56(10):3285-3293. [CrossRef]
41. Tsourdi E, Zillikens MC, Meier C, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. *J Clin Endocrinol Metab*. 2020;106(1):264-281. [CrossRef]
42. Tripto-Shkolnik L, Fund N, Rouach V, Chodick G, Shalev V, Goldshtein I. Fracture incidence after denosumab discontinuation: real-world data from a large healthcare provider. *Bone*. 2020;130:115150. [CrossRef]
43. Zaimi M, Grapsa E. Current therapeutic approach of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial*. 2024;28(5):671-689. [CrossRef]
44. Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. *Osteoporos Int*. 2007;18(1):59-68. [CrossRef]
45. Cejka D, Kodras K, Bader T, Haas M. Treatment of hemodialysis-associated adynamic bone disease with teriparatide (PTH1-34): a pilot study. *Kidney Blood Press Res*. 2010;33(3):221-226. [CrossRef]
46. Sumida K, Ubara Y, Hoshino J, et al. Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: a prospective study. *Osteoporos Int*. 2016;27(4):1441-1450. [CrossRef]
47. Miller PD, Adachi JD, Albergaria BH, et al. Efficacy and safety of Romosozumab among postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease. *J Bone Miner Res*. 2022;37(8):1437-1445. [CrossRef]
48. Sato M, Inaba M, Yamada S, Emoto M, Ohno Y, Tsujimoto Y. Efficacy of Romosozumab in patients with osteoporosis on maintenance hemodialysis in Japan; an observational study. *J Bone Miner Metab*. 2021;39(6):1082-1090. [CrossRef]
49. Kawaguchi H. Global 'conditional' assurance of Romosozumab safety: international consensus on the uniqueness of adverse cardiovascular events in Japan. *Calcif Tissue Int*. 2024;115(4):455-458. [CrossRef]