



Diagnosis and management of osteoporosis in chronic kidney disease stages 4 to 5D: a call for a shift from nihilism to pragmatism

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Abstract

The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) CKD-MBD working group, in collaboration with the Committee of Scientific Advisors of the International Osteoporosis Foundation, published a position paper for the diagnosis and management of osteoporosis in patients with CKD stages 4–5D (eGFR < 30 ml/min 1.73 m²). The present article reports and summarizes the main recommendations included in this 2021 document. The following areas are reviewed: diagnosis of osteoporosis; risk factors for fragility fractures; fracture risk assessment; intervention thresholds for pharmacological intervention; general and pharmacological management of osteoporosis; monitoring of treatment, and systems of care, all in patients with CKD stages 4–5D. Guidance is provided for clinicians caring for CKD stages 4–5D patients with osteoporosis, allowing for a pragmatic individualized diagnostic and therapeutic approach as an alternative to current variations in care and treatment nihilism.

Keywords Chronic kidney disease · Osteoporosis

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Introduction

Chronic kidney disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. Disturbances in mineral and bone metabolism occur early in the course of CKD, to become almost universal in patients with advanced disease. The term CKD–mineral and bone disorder (CKD-MBD) is currently used to describe a broader clinical syndrome that develops as a systemic disorder in CKD, manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcifications. CKD-MBD associates with fractures as well as cardiovascular morbidity and mortality. The term renal osteodystrophy (ROD) specifically denotes alterations in bone morphology associated with CKD [1].

Osteoporosis is a condition characterized by low bone mass and qualitative bone deterioration that leads to bone fragility and fracture susceptibility [2, 3]. The economic and societal burden of fragility fractures is massive and is set to rise owing to an increasing skew towards an older population [4]. Over the last two decades, the ability to predict those at risk has developed enormously through the use of fracture prediction tools and an increasing understanding of scanning modalities, such as dual-energy X-ray absorptiometry (DXA). Alongside, the armamentarium to tackle osteoporosis continues to expand. However, a huge treatment gap exists between those at risk of fracture and those receiving treatment for the prevention of fragility fractures [5].

This treatment gap may be hypothesized to be even wider in patients with CKD stages 4–5D, i.e., patients with an estimated glomerular filtration rate (eGFR) below 30 ml/min 1.73 m². In these patients, impaired bone strength, related to low bone mass and impaired bone quality, and an increased propensity to fall cumulate in an excessive fracture risk [6]. At the same time, doubts about the optimal diagnostic and therapeutic approach fuel therapeutic inertia. These doubts find their origin in (a) the complex pathophysiology of bone fragility and (b) the lack of data on efficacy and safety of osteoporosis medications in patients with CKD stages 4–5D [7].

In 2018, the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) CKD-MBD working group, in collaboration with the International Osteoporosis Foundation, convened a working group to inventory evidence gaps with regard to the diagnosis and treatment of osteoporosis in patients with CKD stages 4–5D. The aims were to list important research questions and to provide some guidance in the absence of hard evidence. A literature review, a survey on the topic, a face-to-face meeting in Leuven (including 8 experts), and a review/approval by a larger group of experts worldwide were conducted.

The full position paper was recently published in *Nephrology, Dialysis and Transplantation* [8]. We herein present an executive summary of the main recommendations (Fig. 1).

Diagnosis of osteoporosis

1. Osteoporosis is a condition characterized by low bone mass and micro-architectural and qualitative bone deterioration that leads to bone fragility and fracture susceptibility.
2. The operational definition of osteoporosis is based on an areal bone mineral density (BMD) assessed by DXA at the spine or hip < -2.5 SD from the BMD in young female adults (T-score).

The diagnosis of osteoporosis in CKD stages 4–5D is often considered one of exclusion — when neither ROD nor CKD-MBD is the cause of low BMD or fragility fractures [9]. We stand for an inclusive operational definition of osteoporosis according to the WHO, including patients with CKD 4–5D, in spite of the contributions of ROD/CKD-MBD to decrease bone strength in this population. As CKD is a state of accelerated aging, primary osteoporosis likely plays a prominent role in bone fragility in CKD 4–5D patients and may eventually overcome the impact of ROD itself.

Risk factors for fragility fractures

1. Clinical risk factors for osteoporosis in CKD patients comprise traditional risk factors including older age, female sex, low body mass index, fragility fracture history, glucocorticoid treatment, and CKD-specific risk factors such as long dialysis duration.
2. BMD as assessed by DXA predicts fractures in patients with CKD stages 4–5D. However, DXA probably underestimates the actual fracture risk in patients with CKD 4–5D, as it does not account for impaired bone quality. The consistency of the risk prediction across stages of disease and degree of parathyroid hormone (PTH) control remains to be documented.

Bone fragility in CKD is a composite of primary osteoporosis and adverse skeletal effects of drugs, disturbances of calcium metabolism, and the uremic milieu itself (Fig. 2). As CKD is a state of premature aging, primary, age-related osteoporosis may manifest at an earlier chronological age. Traditional risk factors for osteoporosis apply to patients with CKD stages 4–5D as well. Additionally, longer duration of dialysis therapy is consistently associated with increased fracture risk in CKD.

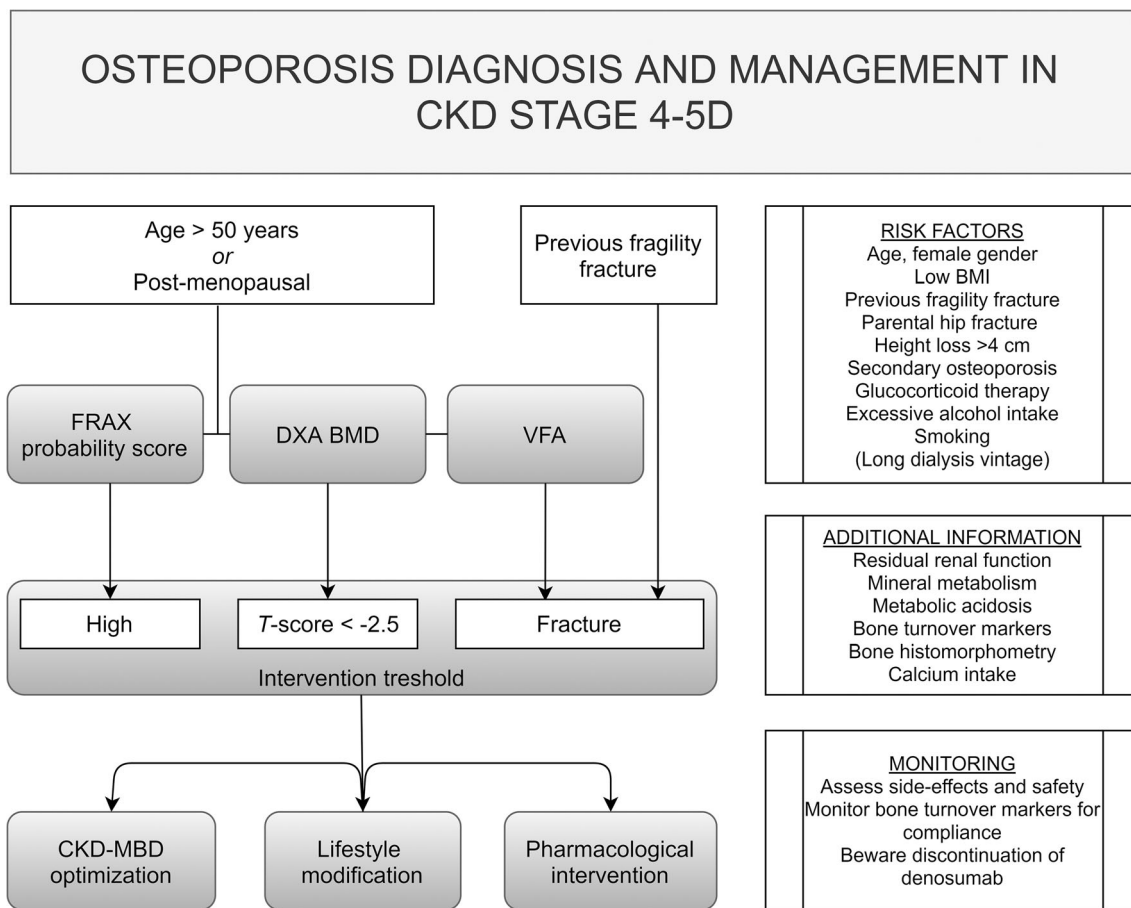


Fig. 1 Algorithm for the diagnosis and management of osteoporosis in patients with chronic kidney disease (CKD) stages 4–5D

An increasing body of evidence indicates that DXA may predict incident fractures in CKD as in the non-CKD

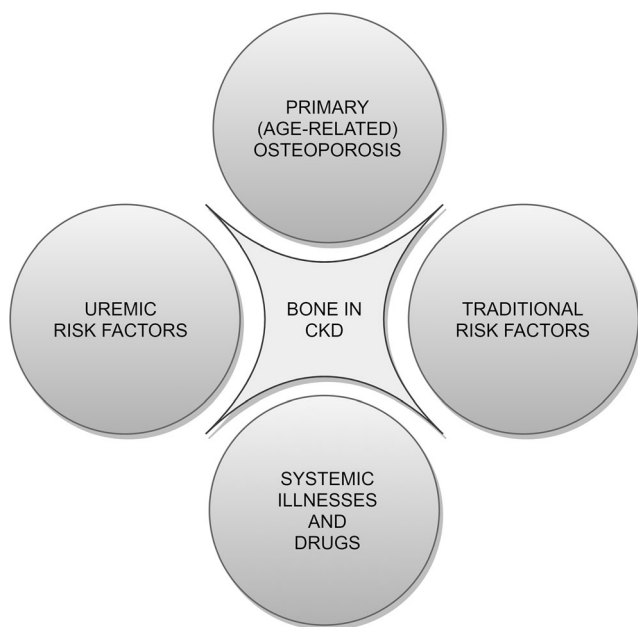


Fig. 2 Risk factors for osteoporosis in patients with chronic kidney disease (CKD)

population, although some doubt remains as to the consistency of this fracture risk prediction across stages of CKD and categories of circulating PTH levels [10–14]. Accounting for these data, KDIGO now supports BMD testing in patients with CKD 3a–5D with evidence of CKD-MBD and/or risk factors for osteoporosis [15]. The association of bone turnover markers (BTMs) with fracture risk, overall, is inconsistent. In a large epidemiological study in Japanese hemodialysis (HD) patients, a linear relationship between plasma total alkaline phosphatase (ALP) levels and fracture risk was observed [16], and in another Japanese study, bone-specific ALP (BALP) outperformed DXA in fracture risk prediction [10]. In clinical practice, PTH levels are often used as a surrogate of bone turnover. PTH levels show a complex J- or U-shaped relationship with fracture risk in CKD stage 5D [17–19], with both very high and low levels conferring an increased fracture risk.

Assessment of fracture risk

1. In patients with CKD stages 4–5D, DXA may be considered in postmenopausal women, or men > 50 years of age.

Routine DXA testing (screening) in all CKD 4–5D patients is not supported by current evidence.

2. The hip and the lumbar spine are the primary skeletal sites to evaluate BMD by DXA.
3. The forearm may be included in the DXA evaluation skeletal site panel, but one should be aware of operator-dependent variability and potential bias by arteriovenous fistula.
4. Trabecular bone score and alternative imaging techniques need further clinical evaluation prior to clinical implementation.
5. Vertebral fracture assessment (VFA), and/or lateral spine imaging, is recommended in all patients undergoing DXA evaluation, and in patients with a history of ≥ 4 cm height loss, kyphosis, or recent or current long-term oral glucocorticoid therapy. Imaging should include the abdominal aorta for determination of vascular calcification.
6. FRAX® predicts fracture probability in all CKD stages. Additional evidence is required to define whether further arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of advanced CKD.
7. Non-kidney-retained BTMs, especially BALP, may be useful for fracture risk prediction in CKD 4–5D, awaiting further confirmation.

The implementation of BMD testing for CKD patients in clinical practice raises several practical questions: Who to test, which skeletal site(s) to select, and what time interval to adopt for repeat testing? Extrapolating guidelines for the general population, DXA testing in patients with CKD stages 4–5D may be considered in postmenopausal women and patients > 50 years of age. The hip and the lumbar spine are the primary skeletal site to evaluate BMD by DXA. Since secondary hyperparathyroidism primarily affects cortical bone, DXA at cortical rich skeletal sites (such as the distal third of the radius), in addition to femoral neck, which is standard, may be interesting adjuncts, but clinical data confirming superiority or equivalence (if neither spine nor hip measurements are available) are still awaited. Dialysis patients show a 1.2% decline of BMD at the total hip per year [20]. This is well below the least significant change (LSC), averaging 2–3% for most DXA machines at the total hip.

DXA should only be repeated if the results will influence clinical management, or if changes in BMD are expected to exceed the LSC for the DXA equipment used.

Trabecular bone score, as well as other DXA-based bone texture measurements, may represent useful adjuncts to BMD to assess bone health [21, 22] but need further clinical evaluation before considering their implementation in clinical practice. Alternative imaging techniques such as (high resolution) peripheral quantitative computed tomography and magnetic resonance imaging, which are able to distinguish between cortical and trabecular bone, have been postulated to be

superior to DXA in discriminating fractures in CKD but so far yielded conflicting results [23–27].

Vertebral fractures (VFX) are common in patients with CKD but mostly do not come to medical attention and thus remain undiagnosed. Given the high prevalence of VFX in this patient group and their importance in predicting fracture risk, we recommend VFA or lateral spine imaging in all patients undergoing DXA evaluation, and in patients with history of ≥ 4 cm height loss, kyphosis, or recent or current long-term oral glucocorticoid therapy. The precise definition for a VFX vs. a non-fracture deformity was recently reviewed [28] but, briefly, should include evidence of fracture-related endplate deformity with height loss. Whenever available, DXA and VFA is preferred above lateral spine imaging, as this simultaneously inform on BMD. Lateral XR or DXA of the lumbar spine also allows assessment of abdominal aortic calcification [29] and may be useful in concomitantly stratifying cardiovascular risk.

Several tools have been developed for clinical fracture risk assessment. Of these, FRAX® (<https://www.sheffield.ac.uk/FRAX/tool.aspx>) has been the most extensively used [4]. FRAX® is a computer-based algorithm that calculates the 10-year probability of a major fracture (hip, clinical VFX, humerus, or wrist fracture) and 10-year probability of a hip fracture. As a unique feature, FRAX® considers competing mortality within the fracture risk estimation. The presence of CKD is noticeably absent in the list of secondary causes of osteoporosis in FRAX®. Despite this limitation, available evidence confirms that FRAX® performs as well in patients with CKD as in the general population for fracture discrimination [12, 30–32].

Intervention thresholds for pharmacological intervention

1. CKD patients > 50 years of age with a prior fragility fracture (major osteoporotic fracture [MOF]) may be considered for treatment without the need for further BMD assessment.
2. In the absence of a MOF, a DXA T-score threshold < -2.5 SD at the lumbar spine or hip is recommended, recognizing a higher threshold of -2.0 or -1.5 may be more appropriate.
3. FRAX® country-specific intervention thresholds are appropriate in CKD patients.

Both a BMD-centric and fracture risk-centric approach can be adopted when identifying patients for whom pharmacological intervention should be considered. A T-score < -2.5 SD at the hip or lumbar spine has been used as an inclusion criterion in most registration studies evaluating anti-osteoporotic drugs for postmenopausal osteoporosis and is widely adopted as

intervention threshold in osteoporosis literature. It should be acknowledged that the choice of this intervention threshold is purely arbitrary. Intervention thresholds have ranged from T-scores of -3.0 SD to -1.5 SD depending on clinical context, country, and health economic factors. In diabetics, the intervention threshold is set at -2.0 SD, accounting for the fact that fracture risk at -2.0 SD in diabetics is similar to the risk seen at -2.5 SD in non-diabetics [33]. Comparable data for CKD patients are, unfortunately, lacking. Therefore, a T-score intervention threshold < -2.5 SD at the lumbar spine or hip is recommended, recognizing that a higher threshold of -2.0 or -1.5 may be more appropriate.

The performance of FRAX® in estimating the absolute fracture risk (fracture calibration) in CKD is as good as in the general population. However, evidence is still scarce, and both under- and over-estimation of fracture risk by FRAX® have been reported in CKD. CKD patients not only have an increased fracture risk but also a limited life expectancy. The impact of CKD on the FRAX® score may thus prove to be overall neutral over the longer term. Recently, it has become apparent that the imminent fracture risk after a sentinel fragility fracture is high, and during the 2 years following a fragility fracture, the risk of re-fracture vs. mortality is not well captured by FRAX [34]. Further evidence is needed to describe imminent fracture risk in the CKD 4–5D population and its attenuation by rapidly acting anti-osteoporosis medications. Awaiting further evidence and fine-tuning, conventional intervention and assessment thresholds, as defined for postmenopausal women, may be used as guides for patients with CKD stages 4–5D [4].

Individuals > 50 years of age with a history of a fragility fracture at the hip, lumbar spine, proximal humerus, or pelvis, or individuals with a history of multiple fragility fractures, may be considered for intervention without the necessity of BMD testing (other than to monitor treatment).

Non-pharmacological intervention

1. A sufficient supply of calcium should be guaranteed (800–1200 mg/day, preferentially through diet) and vitamin D stores should be replenished according to osteoporosis and CKD-MBD guidelines.
2. Regular weight-bearing exercise should be advised, tailored to the needs and abilities of the individual patient.
3. The falls risk needs to be evaluated regularly and acted upon.

Since patients with CKD are at risk of negative calcium balance and low vitamin D stores, it is advocated to assess daily calcium intake and circulating 25(OH)D levels. Supplementation of calcium (preferentially through diet) and vitamin D (supplements) should be considered in patients with a calcium intake below 800 mg/day and 25(OH)D levels below 30 ng/dL

[35]. Total exogenous elemental calcium input should not exceed 1200 mg per day to avoid accelerated vascular calcification.

Although supporting evidence is limited, regular weight-bearing exercise should be advised, tailored to the needs and abilities of the individual patient.

CKD patients have an increased falls risk [31, 36–38]. Key to minimizing falls risk is the evaluation of secondary causes — including (orthostatic) hypotension, bradycardia, psychotropic drugs, myopathy and neuropathy, and decreased vision. Exercises to improve muscle strength and balance may also reduce the likelihood of falls, recognizing that evidenced-based community programs have limited effectiveness due to poor participation and adherence rates.

Pharmacological intervention

1. CKD-MBD therapy should be optimized according to current guidelines before considering specific osteoporosis management.
2. Metabolic disturbances linked to bone fragility (acid-base, uremic toxicity) should be controlled at all time.
3. Risks and benefits of available pharmacological interventions need to be balanced at the individual level and discussed with the patient. Formal informed consent may be required when considering off-label use.
4. Evolving evidence indicates that antiresorptive agents may be effective in advanced CKD and that vascular and skeletal risks are not excessively high.
5. Renal risks of bisphosphonates are poorly explored in patients with CKD stages 4–5D, which calls for caution.
6. Denosumab confers no risk of kidney function decline, but the risk of severe hypocalcemia with denosumab is increased in CKD and needs to be addressed by concomitant vitamin D and calcium supplementation.
7. Withdrawal of denosumab therapy may be associated with an increased risk of vertebral fracture.

Prior to initiating anti-osteoporosis drugs, CKD-MBD therapy should be optimized and metabolic disturbances known to harm bone, such as metabolic acidosis, should be well controlled. A detailed discussion of the optimal treatment of CKD-MBD is beyond the scope of this position paper and can be found in recent guidelines and review papers [15]. Importantly, a bone biopsy is no longer deemed obligatory prior to initiating antiresorptive therapy in patients with CKD 4–5D but may be considered if a mineralization defect is suspected, or if the exact diagnosis of ROD has influence on the treatment decision.

Antiresorptive agents (nitrogen-containing bisphosphonates and denosumab) are first-line therapy in patients with postmenopausal and primary male osteoporosis. Post-hoc analyses of pivotal clinical trials evaluating antiresorptives demonstrate that these drugs have similar efficacy, improving BMD and reducing

fracture rates, in subjects with CKD up to stage 4, without biochemical evidence of CKD-MBD. Data in advanced CKD is scarce, limited by small sample sizes, and yielded inconsistent findings [39–45]. Suppression of bone turnover is inherent to bisphosphonates, and most osteoporosis patients develop a low bone formation rate during treatment. There is, however, no compelling evidence that (a) the level of remodeling suppression in CKD is greater than that in non-CKD counterparts [46] or that (b) iatrogenic suppressed bone remodeling associates with poor skeletal and cardiovascular outcomes. Ten-year follow-up data for denosumab suggests that strong, prolonged remodeling inhibition does not impair bone strength [47]. Data from post-hoc analyses of large registration trials [48, 49] and a recent RCT [42] are reassuring regarding vascular outcomes. Furthermore, adopting some simple precautions, renal risks (bisphosphonates), and risk of hypocalcemia (denosumab) can be minimized. Withdrawal of denosumab therapy is associated with a 30% increase in vertebral fractures in postmenopausal women [50]. Therefore, denosumab must either be administered continuously or followed by another antiresorptive therapy. As the type and timing of such a switch-over to bisphosphonates is currently unclear, therapy with denosumab must be considered long-term.

Acknowledging that low bone turnover is highly prevalent among patients with CKD stages 4–5D, anabolic agents could be considered promising. However, efficacy data are very poor (PTH-analogs), or non-existing (romosozumab) in patients with CKD stages 4–5D, and no safety data is available in this patient category. High serum sclerostin has been associated with both better and worse outcomes in advanced CKD, and some of the large registration trials raised concerns regarding the cardiovascular safety of romosozumab [51]. In an era in which personalized medicine is gaining importance, benefits and risks of anti-osteoporosis therapy need to be balanced at the individual level. Formal informed consent may be required whenever off-label use of anti-osteoporosis drugs is considered.

Monitoring

1. Non-kidney-retained BTMs, such as BALP, intact procollagen type I N-propeptide (PINP), and tartrate-resistant acid phosphatase 5b (TRAP5b), should be preferentially monitored in CKD patients.
2. Monitoring of BTMs may inform on the early therapeutic response.
3. Monitoring of BTMs after therapy withdrawal (offset of effect) may inform on the need for reintroduction.
4. Repeat DXA informs on the long-term treatment effect on BMD. The time interval when treatment effect can be detected may vary depending on treatment modality and underlying type of ROD.

Early monitoring of BTMs informs on the therapeutic response. Non-kidney-retained bone turnover markers (BALP, trimeric PINP, TRAP5b) are preferentially used in the setting of CKD, especially in patients with non-stable kidney function. Given the high biological variability of BTMs, LSC should be considered when evaluating treatment response. Biofeedback by BTMs only is only beneficial in those demonstrating a positive response [52]. The measurement of BTMs after withdrawal of osteoporosis therapy is potentially useful to evaluate offset of effect: An increase more than the LSC reflects loss of treatment effect and identifies patients that are likely to experience a decrease in BMD. Such changes could provide an indication for reintroduction of treatment [53]. A major caveat is that BTMs are grossly elevated 2 days after a fracture and remain elevated for at least 12 months [54]. This precludes their routine use in patients with a recent fracture. Repeat BMD informs on the long-term treatment effect; however, the time interval to when a treatment effect can be detected may vary depending on treatment modality and underlying type of ROD. As a guide, secondary analysis of the Fracture Intervention Trial showed that monitoring BMD in postmenopausal women during the first 3 years after starting treatment with a potent bisphosphonate was unnecessary and could be misleading [55].

Systems of care

1. Coordinator-based fracture liaison services (FLS) should be considered to systematically identify and guide CKD patients with fragility fractures, in close collaboration with nephrologists. The (cost-) effectiveness of FLS has been established in the general population.

Given that the complexity of optimizing these patients' bone metabolism is outside the competency of most general practitioners, these patients will need to be reviewed by a specialist bone metabolism unit once identified by the FLS.

Research questions and perspectives

- Determine whether arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4–G5D.
- Define whether ROD subtypes associate with fracture risk.
- Define the calcium balance in CKD G4–G5D and the optimal calcium supplementation strategy.
- Define the efficacy and safety of anti-osteoporosis agents (bisphosphonates, denosumab, PTH analogs, raloxifene, romosozumab) in patients with CKD G4–G5D.
- Better characterization of role of primary and secondary mineralization in ROD.

- Compare bone strength in iatrogenic (e.g., bisphosphonates) vs. idiopathic (e.g., CKD related) low bone turnover.
- Define whether antiresorptive therapy in patients with adynamic bone disease (ABD) or low bone turnover confers harm.

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