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REVIEW

Chronic kidney disease and osteoporosis: evaluation and management

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Fractures across the stages of chronic kidney disease (CKD) could be due to osteoporosis, some form of renal osteodystrophy defined by specific quantitative histomorphometry or chronic kidney disease-mineral and bone disorder (CKD-MBD). CKD-MBD is a systemic disease that links disorders of mineral and bone metabolism due to CKD to either one or all of the following: abnormalities of calcium, phosphorus, parathyroid hormone or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth or strength; or vascular or other soft-tissue calcification. Osteoporosis, as defined by The National Institutes of Health, may coexist with renal osteodystrophy or CKD-MBD. Differentiation among these disorders is required to manage correctly the correct disorder to reduce the risk of fractures. While the World Health Organization (WHO) BMD criteria for osteoporosis can be used in patients with stages 1–3 CKD, the disorders of bone turnover become so aberrant by stages 4 and 5 CKD that neither the WHO criteria nor the occurrence of a fragility fracture can be used for the diagnosis of osteoporosis. The diagnosis of osteoporosis in stages 4 and 5 CKD is one of the exclusion—excluding either renal osteodystrophy or CKD-MBD as the cause of low BMD or fragility fractures. Differentiations among the disorders of renal osteodystrophy, CKD-MBD or osteoporosis are dependent on the measurement of specific biochemical markers, including serum parathyroid hormone (PTH) and/or quantitative bone histomorphometry. Management of fractures in stages 1–3 CKD does not differ in persons with or without CKD with osteoporosis assuming there is no evidence for CKD-MBD, clinically suspected by elevated PTH, hyperphosphatemia or fibroblast growth factor 23 due to CKD. Treatment of fractures in persons with osteoporosis and stages 4 and 5 CKD is not evidence based, with the exception of *post hoc* analysis suggesting efficacy and safety of specific osteoporosis therapies (alendronate, risedronate and denosumab) in stage 4 CKD. This review also discusses how to diagnose and manage fragility fractures across the five stages of CKD.

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Introduction

The prevalence of chronic kidney disease (CKD) is increasing in the worldwide population. Osteoporosis prevalence is also increasing on a global scale. These increases are, in part, related to the increase in aging of human beings and to the increase in the prevalence of obesity and its associated diabetes mellitus, and unrecognized hypertension.[1–3]

Glomerular filtration rate (GFR) declines as age increases, even in the absence of concomitant intrinsic renal disease or systemic disease. The mechanism(s) of age-related reductions in GFR are not well defined but may be related to changes in vascular blood flow associated with the aging and atherosclerotic process.[1–5]

The National Kidney Foundation (NKF) has moved to incorporate estimated (calculated) GFR (eGFR) on all routine biochemical profiles carried out by all physicians during the annual health examination. The eGFR inclusion is an attempt to identify (e.g. screen) the largest growing segment of the CKD population (stage 3) with eGFR 60–30 ml min^{-1}.[6]

The NKF classifies five stages of CKD (**Figure 1**).[6] Stages 1 and 2 CKD must have an associated urinary microscopic change (either hematuria and/or proteinuria) in addition to an eGFR <110 ml min^{-1} to fulfill those diagnostic criteria of stage 1 or 2 CKD. However, based on reduced eGFR alone, without needing accompanying proteinuria or hematuria, stages 3–5 CKD can be diagnosed on the basis of reduced eGFR alone (stage 3: eGFR <60–30 ml min^{-1}; stage 4: eGFR 30–15 ml min^{-1} and stage 5: eGFR <15 ml min^{-1}) and/or end-stage renal disease (ESRD). Stage 5D stands for ESRD in patients on dialysis.[7,8] The presence of proteinuria defined as a first morning voided spot urine albumin/creatinine ratio >500 mg g^{-1} creatinine carries a poorer prognosis for the

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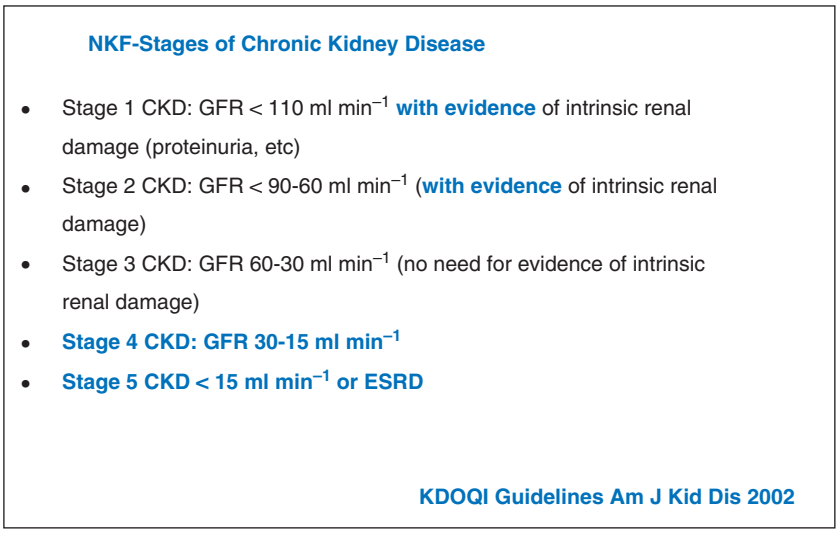

Figure 1 The NKF five stages of CKD[6]. CKD, chronic kidney disease; GFR, Glomerular filtration rate; NKF, National Kidney Foundation.

progression of CKD than in persons with decreased GFR without proteinuria. The presence of significant proteinuria implies intrinsic renal damage and renal disease beyond age-related reductions in GFR.[8] In addition, the National Kidney Foundation has subdivided stage 3 CKD (eGFR 60–30 ml min^{-1}) into two subtypes: stage 3A (eGFR 60–45 ml min^{-1}) and 3B (eGFR 45–30 ml min^{-1}).[9] The purpose of this division is to acknowledge that stage 3 CKD encompasses a broad range of renal function and that there may be clear biologic distinctions in the renal-bone-vascular calcification pathophysiology between stages 3A and 3B CKD. Early CKD is also associated with a progressive rise in osteocyte-derived fibroblast growth factor 23 (FGF-23), and later, a progressive rise in endogenous parathyroid hormone production (PTH), which are higher in stage 3B vs 3A CKD.[10–12] The progression of these metabolic abnormalities is also seen on bone histomorphometry (renal osteodystrophy) associated with progressive CKD: osteitis fibrosa cystica (severe hyperparathyroid bone disease) is more severe the higher the PTH (especially PTH values $>6\times$ the upper limit of normal).[12,13] Additionally, sustained hyperphosphatemia is more persistent and is associated with increased vascular calcification, which is seen in subjects with more severe reductions in GFR.[13] In addition, renal adynamic renal bone disease, a very low or absent bone turnover disease, is suggested in those with low PTH and low bone-specific alkaline phosphatase (BSAP) values, and is seen more often in the lower stages of the NKF classification (stage 3B and lower).[14–17]

Osteoporosis is defined by the National Institute of Health (NIH) as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength is a composite of bone density and bone quality.[18] In subjects with CKD there may be two forms of renal bone disease: one defined by quantitative histomorphometry (renal osteodystrophy) and the other defined by the discovery of persistent hyperphosphatemia, elevated, parathyroid hormone or FGF-23 that leads to the systemic bone-vascular disease termed CKD-MBD (chronic kidney disease-mineral and bone disorder).[13,19] Management of fractures in subjects with CKD may differ if a low trauma fracture is due to osteoporosis as opposed to fractures due to renal osteodystrophy or CKD-MBD.[19–24]

Diagnosis in Stages 1–3 CKD

There is agreement that either the WHO BMD (*T*-score) criteria for osteoporosis or a low trauma fracture can be used to establish a diagnosis of osteoporosis as long as there are no biochemical abnormalities suggesting CKD-MBD.[13,19,23] The major justification for retaining the WHO densitometric diagnosis of osteoporosis in stages 1–3 is that all of the registration trials for postmenopausal osteoporosis treatments included subjects randomized on the basis of the WHO criteria, and with a GFR <30 ml min^{-1}. The WHO classification was established in 1994 and the KDIGO (kidney disease improving global outcome) bone working group that coined the term CKD-MBD was published in 2009.[13,21] Hence, 15 years separated the development of the BMD WHO criteria for PMO from the pathophysiologic systemic process defined as CKD-MBD. The traditional histomorphometric forms of renal bone diseases, defined by the term renal osteodystrophy (osteitis fibrosa cystica, osteomalacia, mixed renal bone disease and adynamic bone disease), are associated with a higher risk for fractures.[13,15–17] The challenge lies in discriminating traditional renal osteodystrophy bone diseases from CKD-MBD or osteoporosis. Making these diagnostic discriminations may be accomplished by biochemical markers of bone turnover and/or quantitative histomorphometry. The clinical syndrome of CKD-MBD can be assumed to be occurring in subjects with stages 3–5 CKD and may coexist with any of the forms of renal osteodystrophy or osteoporosis. Management of osteoporosis differs from that of CKD-MBD management or the various forms of renal osteodystrophy. Presently, the diagnosis of osteoporosis can be made in stages 1–3 CKD, as it is in subjects without CKD, as long as there are no biochemical abnormalities suggesting the presence of CKD-MBD, which are: sustained hyperphosphatemia, secondary hyperparathyroidism that is due to CKD and not due to other recognizable and reversible

causes of secondary hyperparathyroidism; or elevated serum FGF-23.[25] In animal models, CKD-MBD may be seen as early as stage 2 CKD, and thus measurement of the biochemical markers that may define CKD-MBD in early CKD is an important consideration.[26]

Diagnosis in Stages 4, 5 and 5D CKD

The differential diagnosis of the etiology for low BMD and/or fractures in patients with stage 4 (eGFR 30–15 ml min^{-1}) or 5 (eGFR $<$15 ml min^{-1}) or 5D (dialysis) is more complex. Osteoporosis diagnosis in stages 4 and 5 CKD is one of the exclusion. This observation is based on the data showing that all forms of severe renal bone disease defined by renal histomorphometry (renal osteodystrophy) may have low BMD and or fragility fractures.[19] Therefore, neither the WHO BMD criteria nor the presence of low trauma fractures can be used to make the diagnosis of osteoporosis in stages 4 and 5/5D CKD until one of the other forms of renal bone disease has been eliminated.[16,17,19] Exclusion is best accomplished by measuring specific biochemical markers of bone turnover (BTM) and/or quantitative bone histomorphometry. The gold standard for the diagnosis of specific renal bone diseases is double tetracycline-labeled quantitative bone histomorphometry.[27,28] Quantitative histomorphometry can objectively discriminate between adynamic bone disease, osteomalacia, mixed renal osteodystrophy and hyperparathyroid bone disease.[14,25] Since the NIH Consensus Conference on osteoporosis states that osteoporosis is, in part, an abnormality in bone quality, all forms of renal bone disease have a component of osteoporosis that include the microarchitectural deterioration embodied in the NIH definition of osteoporosis.[18] Likewise, the bone aspects of CKD-MBD (abnormalities in turnover, mineralization and volume) may also coexist with either renal bone disease or osteoporosis. They may coshare some pathophysiologic abnormalities, especially altered microstructural deterioration and cortical porosity. They differ in that osteoporosis and renal osteodystrophy are bone-specific diagnosis and CKD-MBD embodies the systemic pathophysiology that links bone metabolism to vascular calcification. The clinical management point is that by excluding adynamic, osteomalacic and hyperparathyroid renal bone disease, the fractures can be attributed to osteoporosis.

Biochemical BTM

Systemic as well as local regulators of bone turnover can be measured.[29,30] In addition, bone resorption and bone formation markers can be measured.[31–33] Data suggest that specific serum bone marker (BTM) levels, including serum PTH and tissue-specific alkaline phosphatase, may help to discriminate among the heterogeneous forms of renal bone disease.[34] In addition, specific biochemical markers of bone turnover—the resorption marker, C-telopeptide, and the bone formation marker, propeptide type I collagen (PINP), are valuable in assessing systemic bone turnover in postmenopausal or male osteoporosis, or in response to agents that inhibit bone turnover (antiresorptive agents) or stimulate bone turnover (anabolic agents).[31–33] **Figure 2** lists the BTM and divides measureable BTM into 'resorption' and 'formation' markers, recognizing that either group may be used interchangeably owing to the inherent coupling between bone cell lines: osteoclasts, osteoblasts and osteocytes.[32]

Two markers that are not cleared by the kidney are: a resorption marker (or more accurately, an osteoclast cellular number marker), tartrate-resistant acid phosphatase 5b; and the formation marker (or more accurately, an osteoblast activity marker), BSAP. The osteoblast-derived marker PINP is currently assayed by two assays: one that measures the intact (monomer and trimer) form of PINP and the other that measures only the trimer form of PINP. The trimer is not cleared by the kidney, whereas the intact is cleared by the kidney. The only Food and Drug Administration (FDA)-approved assay for PINP (a radioimmunoassay) measures the trimeric form. Currently, there is insufficient data to know if these differences influence PINP clearance enough to influence clinical utilization of the intact PINP in determining osteoblast activity.[33]

Recently, there has been a pivotal publication that assessed the ability of the serum PTH and/or BSAP to discriminate among the different forms of renal bone disease.[34] In this study, a large sample size of quantitative bone histomorphometry was analyzed along with the assays for tissue-specific alkaline phosphatase and serum PTH. The authors concluded that a serum PTH below 150 pg ml^{-1} and even more so $<$100 pg ml^{-1} in dialysis patient's not receiving therapies to lower serum PTH (cinacalcet or vitamin D analogs) had a high positive predictive value for renal adynamic bone disease. Likewise, adynamic bone disease was suggested by a tissue-specific alkaline phosphatase in the lower quartile of the laboratory reference range. At the other end of the spectrum, a high (6 $\times$ above the upper limit of the reference range) serum PTH had a high PPV for hyperparathyroid bone disease (osteitis fibrisa cyctica) as did a high BSAP. However, it should be noted that a high BSAP may also be seen in a number of other metabolic bone diseases that are not hyperparathyroid bone disease, and can coexist in patients with stage 5 CKD, such as Pagets's disease or metastatic cancer to bone. In the management of patients with stages 4–5 CKD and low *T*-scores or fractures, where the diagnosis of osteoporosis may be a considered, renal adynamic bone disease and osteomalacia are the most important diseases to exclude. Both of these bone disorders show very low bone turnover states, where reducing bone turnover further may not be beneficial, and osteomalacia always has a reversible cause (such as very low 25-hyroxy vitamin D levels or oncogenic osteomalacia). Serum tissue-specific alkaline phosphatase and serum intact PTH seem to be the most valuable tests to assess adynamic bone disease, and the causes of osteomalacia (suggested by an elevated BSAP) have a number of etiologies that can be defined clinically and biochemically.[19]

Bone Biopsy for Quantitative Purposes

Transiliac bone biopsy performed with prior double tetracycline labeling is the most sensitive and specific means of discrimination among the various renal bone diseases,[35–38] and also diagnosing osteoporosis by exclusion. Transiliac bone biopsies are safe and have a very low morbidity when carried out by experienced operators. Tetracycline goes into bone attached to calcium, and because it fluoresces under a fluorescent microscope, it is used as a means to quantify certain dynamic parameters of bone turnover. The science

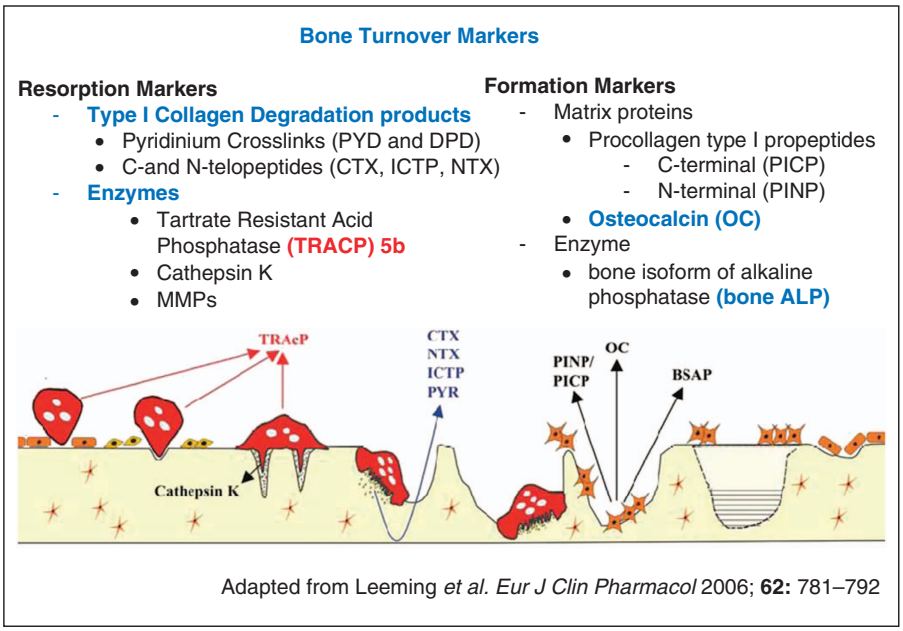

Figure 2 The bone resorption and bone formation markers.[32] Bone ALP, bone isoform of alkaline phosphatase; CTX, C-telopeptide; DPD, deoxypyridinoline; ICTP, type I collagen crosslinked C-telopeptide; MMP, matrix metalloproteinase; NTX, N-telopeptide; OC, osteocalcin; PICP, procollagen I C-terminal propeptide; PINP, propeptide type I collagen; PYD, pyridinoline; TRACP, tartrate-resistant acid phosphatase.

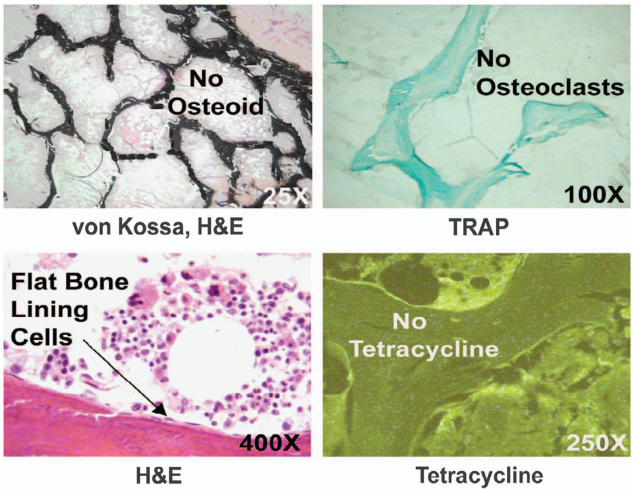

Figure 3 Renal adynamic bone disease.[21] TRAP, tartrate-resistant acid phosphatase.

underpinning quantitative histomorphomerty is rooted in robust data sets defining normal bone turnover and abnormalities in bone turnover.[14] Whereas hyperparathyroid bone parameters have a spectrum of histomorphometry according to the severity and longevity of the hyperparathyroid disorder, osteomalacia has a clear set of criteria required for its definition, and adynamic bone disease is generally considered to be a turnover disorder best defined by the absence of any single or double tetracycline labels (**Figure 3**).[27]

Management of Fractures in CKD

Stages 1–3 CKD

Management of osteoporosis does not differ in persons with known stages 1–3 CKD as in persons in whom renal function is either not known or measured. The justifications for this embrace the same justifications for the diagnosis of osteoporosis previously outlined as long as there is no biochemical evidence for CKD-MBD. In addition, dual-energy x-ray absorptiometry (DXA) is a strong risk factor for fracture risk prediction in stages 1–3 CKD.[23]

While the registered agents for osteoporosis include selective estrogen receptor modulators, bisphosphonates, denosumab and teriparatide, this discussion will highlight the latter three pharmacologic agents. As there has been abundant published literature on the use of these agents in populations that include subjects with GFR < 30 ml min^{-1}, the challenge for use of these agents lies in use in stages 4 and 5/5D CKD.[39–42]

Management of Fractures in Stages 4 and 5/5D CKD

DXA underestimates the fracture risk in stages 4 and 5 CKD. The abnormalities in bone turnover and mineralization and bone microarchitecture are so deranged by these more advanced stages of CKD that DXA measurements of BMD cannot alone capture these additional bone quality abnormalities that add to reduced bone strength in stages 4 and 5 CKD[43] High-resolution peripheral quantitative computerized tomography (HRpQCT) of the forearm or tibia has been shown to be a better predictor of fracture risk in stages 4 and 5 CKD than DXA.[44,45] Until HRpQCT is available for widespread clinical use, combining DXA measurements along with clinical risk factors for fracture is the most pragmatic means of deciding management. The limitations in use of approved pharmacologic choices for osteoporosis is the lack of evidence for fracture risk reduction in patients with severe CKD, with the exception of a few *post hoc* analyses in smaller sample sizes of the registered cohorts for PMO.[46–48] Use of bisphosphonates in stages 4 and 5 CKD is 'off-label' and is predicated on the fact that fractures in this specific population has a far greater mortality than fractures in

subjects even with stage 3 CKD; that *post hoc* analysis show evidence for efficacy and safety of bisphosphonates and eGFR $<15\,ml\,min^{-1}$; and finally that the diagnosis of osteoporosis rather than renal osteodystrophy can be accomplished. Denosumab has no GFR restrictions as it is not cleared by the kidney, although a fracture benefit in stages 4 and 5 CKD is lacking.

Bisphosphonates are cleared by the kidney both by filtration and active proximal tubular secretion. Bisphosphonates are retained in bone in the remodeling resorption cavity and the amount of bisphosphonate retained is probably a function of the baseline remodeling space, the chronic rate of bone turnover and the GFR. While oral bisphosphonates are poorly ($<1\%$ of a single dose) absorbed and 50% of that excreted by the kidney, intravenous bisphosphonate show a 100% bioavailability with still 50% of an intravenous dose excreted by the kidney. Oral bisphosphonates have never been shown to have any renal toxicity while intravenous bisphosphonates, especially zoledronic acid, may acutely reduce the GFR via a tubular lesion that mimics acute tubular necrosis.[49] While intravenous ibandronate, the only other intravenous bisphosphonate registered for osteoporosis has not been shown in either clinical trials nor postmarketing reports to have a negative effect on the kidney, there have never been any head-to-head studies in normal, healthy subjects or in subjects with impaired GFR on renal effects between these two bisphosphonates.[50] Even zoledronic acid, when administered slower than the registered label (15 min) seems safe in clinical experience even in those patients with impaired GFR.[49]

Denosumab is cleared by the reticuloendothelial system and not the kidney, which forms the basis of the lack of a lower GFR limit with denosumab use. For the renal population, there are additional considerations to entertain with denosumab use. On quantitative bone histomorphometry in the original registration trials, there were significantly more subjects on denosumab that had no single tetracycline labels as opposed to the placebo groups that had tetracycline labels.[51] While absent single tetracycline labels may be seen in $<5\%$ of healthy normal subjects, the preponderance of absent labels with denosumab suggests the absence of bone mineralization during the administration in a subset of the clinical trial subjects. Although BTM rebound to even greater than baseline within 6 months after discontinuation of denosumab, it is unknown whether mineralization returned in the original registration cohort.[40] If suppression of remodeling is a concern in renal patients with adynamic bone disease, denosumab should be avoided in stages 4 and 5 CKD unless the managing physician knows that the patients do not have pre-existing adynamic bone disease. Additional considerations in use of denosumab are the relationships between the RANK ligand/osteoprotogerin (OPG) system and vascular calcification, and the induction of severe hypocalcemia in the stage 5/5D CKD population. Vascular calcification is the major cause of death in the CKD population. This is an important issue as serum OPG levels rise with denosumab administration as a regulatory response once RANK pathways are inhibited. There is conflicting and opposing data with regard to the influence of OPG on vascular calcification.[52] In the denosumab registration trial, vascular calcification was assessed by lateral lumbar spine X-rays carried out to assess the incident vertebral compression fracture. Data recently published suggest that vascular calcification scores measured by abdominal aortic calcification did not change between treated vs placebo groups over the 3-year duration of the trial.[53] Larger prospective trials are being designed to examine this relationship between denosumab use and vascular calcification by a variety of more sensitive means to measure vascular calcification.

Symptomatic (e.g. tetany) response has been reported in studies of small sample sizes with denosumab administration in patients with stage 5D CKD. Hypocalcemia even in subjects with severe CKD may be mitigated by adequate vitamin D and calcium supplementation.[54]

The only anabolic agent FDA registered for the treatment of osteoporosis in women and men, as well as glucocorticoid-induced osteoporosis, is recombinant human 1–34 PTH (teriparatide) (Forteo, Eli Lilly and Company, Indianapolis, IN, USA).[55] Teriparatide stimulates the formation of new bone by other cellular as well as regulatory pathways.[56] The teriparatide registration trial, like other registration trials for osteoporosis, did not randomize subjects with known stages 4 and 5 CKD. However, like the previously mentioned *post hoc* analysis for alendronate, risedronate and denosumab that had subsets of the randomized population with eGFR values $<15\,ml\,min^{-1}$, the teriparatide trials had small subsets that had eGFR $<30\,ml\,min^{-1}$.[41] In these subsets, there were similar increases in BMD and PINP across tertiles of eGFR. Fracture numbers were too small to have power for statistical analysis across these three tertiles. There were no changes in renal function as assessed by changes in serum creatinine or serum calcium concentrations as a function of eGFR during the registration trial with the approved 20 μg per day or the higher 40 μg per day doses of teriparatide. While 24 h urine calcium excretion increased on average ~ 50 mg per day greater than placebo, there was no greater risk of clinical nephrolithiasis, although pre-existing kidney stones were an exclusionary criteria for trial randomization. Serum uric acid did rise significantly more than placebo, although the clinical consequences of this change in serum uric acid over the trial duration are unknown.

There are no data on the effect of teriparatide in subjects with stages 4 and 5 CKD nor in subjects with bone biopsy-proven adynamic renal bone disease. The use of teriparatide in stages 4 and 5 CKD is off-label and its use in known idiopathic adynamic bone disease is only predicated on the knowledge that an anabolic agent can increase bone turnover and improve bone microarchitecture and there is a strong correlation between teriparatide-induced increases in BMD and fracture risk reduction.[57] In addition, idiopathic (as opposed to iatrogenic) adynamic bone disease is a disease where therapies are unknown.[58,59] Hence, it is possible, although unproven, that teriparatide may have a beneficial role in idiopathic renal adynamic bone disease. It is also unknown if teriparatide will have the same anabolic effect in subjects with pre-existing secondary hyperparathyroidism. Baseline PTH levels were only measured in a small subset of the teriparatide PMO registration trials, and were normal. Hence, it is unknown if sustained and uncorrected elevated PTH levels could mitigate the anabolic effect of teriparatide.

Finally, serum sclerostin levels increase as GFR decreases.[60] Sclerostin inhibits osteoblastic activity and could be one of the factors inducing idiopathic renal adynamic bone disease. In this regard, the development of monoclonal antibodies to sclerostin that leads to increased osteoblastic activity might

hold promise to be a therapeutic agent for renal adynamic bone disease.

Conclusions

The management of patients with fragility fractures across the spectrum of CKD should not differ between persons without reductions in eGFR as compared with persons with stages 1 and 3 CKD. This suggestion is predicated on the absence of information that could suggest the presence of CKD-MBD. In patients with stages 4 and 5 CKD and who have fragility fractures, the first management step is making the correct diagnosis. Diagnosis of osteoporosis in stages 4 and 5 CKD is an exclusionary one. Exclusion is best made by quantitative histomorphometry. Biochemical markers of bone turnover, in particular serum PTH and tissue-specific alkaline phosphatase, may provide differentiation between biopsy-proven adynamic, hyperparathyroid and/or osteomalacia. The exclusion, in particular, of renal adynamic bone disease is important as even off-label use of antiresorptive agents may not, in theory, be beneficial in persons with no bone turnover to begin with. There is a great need to gain knowledge and evidence for a beneficial or non-beneficial effect of registered therapies for post-menopausal, male or steroid-induced osteoporosis in very high-risk stage 4 and 5 CKD subjects who have sustained a low trauma fracture. In addition, the treatment of idiopathic adynamic renal bone disease may be facilitated by better understanding of the regulation of osteoblast activity, including sclerostin and FGF-23.

Conflict of Interest

The author receives research grants from and is on the scientific advisory boards of Amgen, Lilly, Merck, and Radius Research. The author also receives research grants from Boeheringer-Manheim, Takeda pharmaceuticals.

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