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Updates in CKD-associated osteoporosis

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Abstract

PURPOSE OF REVIEW—Chronic kidney disease (CKD) is associated with bone loss and fractures. The purpose of this review is to provide clinicians with an overview of the underlying pathogenesis of CKD-associated osteoporosis, and a summary of the current diagnostic and therapeutic approaches to this disease.

RECENT FINDINGS—In 2017, the Kidney Disease Improving Global Outcomes Committee on Bone Quality updated their guidelines to include screening for osteoporosis and fracture risk by dual energy X-ray absorptiometry in patients with CKD. Once a diagnosis of osteoporosis and/or fracture risk is established, it is not clear how nephrologists should manage their patients.

SUMMARY—Patients with CKD should be screened for CKD-associated osteoporosis and considered for strategies that prevent bone loss and fractures. Assessment of bone turnover via imaging, biochemical testing or bone biopsy can help guide the choice of therapy. Ran-domized controlled trials are needed to assess safety and efficacy of treatments to prevent bone loss and fractures.

Keywords

CKD-MBD; Renal Osteodystrophy; Osteoporosis

INTRODUCTION

Chronic kidney disease (CKD) affects over 20 million individuals in the United States, and 752 million individuals worldwide (Table 1) [1]. Individuals with CKD have a high prevalence of CKD mineral and bone disease (CKD-MBD). CKD-MBD encompasses a range of abnormalities including derangements in mineral metabolism, vascular and soft tissue calcifications and skeletal abnormalities. In patients with CKD, osteoporosis and fracture risk are higher than in the general population[2], have negative effects on quality of life and increase the risk of mortality[3]. While the pathophysiology of bone disease in patients with CKD is complex and not completely clear, clinicians are faced with the need to manage the

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Compliance with Ethical Standards

Conflict of Interest

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Human and Animal Rights and Informed Consent

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disorder and initiate patients on treatments to improve their bone health. While the need to develop treatments that decrease risk of fracture in CKD patients is of paramount importance, there have not been advances in the discovery of new treatments and pharmacologic agents that are directed at the CKD population. This review will discuss the effects of CKD on bone, the definition of CKD-associated osteoporosis, invasive and non-invasive diagnostic methods of assessing bone health in CKD, and the currently available therapies for the management of CKD-associated osteoporosis.

BONE STRENGTH IN CHRONIC KIDNEY DISEASE

Osteoporosis is defined by the National Institutes of Health (NIH) Consensus Development Panel on Osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture[4]. Bone strength is determined by bone quantity and bone quality (Figure 1). Bone quantity can be assessed by 2-dimensional areal bone mineral density (BMD) by dual energy X-ray absorptiometry or by 3-dimensional volumetric BMD of cortical and trabecular bone by quantitative computed tomography. Bone quality pertains to bone material properties and includes bone turnover, mineralization, microdamage, collagen properties and cortical and trabecular microarchitecture (Figure 1). CKD is associated with global impairments in bone strength; therefore, bone disease in patients with CKD may be classified as CKD-associated osteoporosis.

Several studies using the National Health and Examination Survey (NHANES) reported that prevalence rates of osteoporosis in patients with GFR < 60mL/minute were double those in patients with GFR > 60 mL/minute[5], and that more than 80% of women and 50% of men over age 65 years with osteoporosis had a GFR < 35 mL/minute[6]. Cortical bone comprises around 80% of the skeleton and contributes largely to bone strength[7]. Hyperparathyroidism of kidney disease leads to increased cortical porosity and to de-creased cortical thickness[7–9]. Cortical bone loss subsequently results in loss of areal BMD[7,10]. Trabecular bone also contributes to bone strength. In patients with CKD, older age, hypogonadism and medications used to treat kidney diseases (i.e., glucocorticoids and calcineurin inhibitors) may result in loss of trabeculae. Mineralization defects (i.e., osteomalacia) are not uncommon in CKD; though widespread use of vitamin D analogues seems to have decreased the prevalence of mineralization defects in recent years[8]. Bone quality in CKD is further impaired as advanced glycation products accumulate and weaken the collagen network[11], as damaged bone and microcracks are not adequately repaired, and as oxidative stress levels are heightened[12].

In health, bone remodeling is balanced between bone formation by osteoblasts and bone resorption by osteoclasts; mineralization of bone is also necessary to form mature bone. The metabolic derangements present in CKD alter both remodeling and mineralization and are increasingly recognized as occurring in early kidney disease when function is considered normal, even before the development of biochemical evidence of CKD-MBD[13–15]. Klotho deficiency occurs in CKD and is one of the first derangements of CKD-MBD[16]. Low expression of Klotho induces fibroblast growth factor (FGF23) resistance, resulting in increased FGF23 levels[17]. Both FGF23 and Klotho are expressed in osteocytes with a complex inter-relationship, their effects on bone being both dependent and independent of

each other[18]. Klotho deficiency decreases the number and surface area of both osteoblasts and osteoclasts while also enhancing osteoblast activity therefore affecting bone turnover[18,19]. The exact role of Klotho on bone at different stages of CKD is not well understood yet[19]. The increased expression of FGF23 expression in CKD negatively impacts bone health by suppressing osteoblast differentiation and matrix mineralization[20].

The decline in Klotho and the rise in FGF23 is followed by a rise in parathyroid hormone (PTH) levels, a decline in vitamin D levels and abnormalities in calcium and phosphorus homeostasis. Moreover, metabolic acidosis alters the balance between resorption and formation. CKD is additionally accompanied by chronic inflammation that can be deleterious to bone health via pathways that effect the WNT/β-catenin signaling pathway[21,22]. The WNT/β-catenin signaling pathway regulates osteogenesis and decreases bone resorption[22]. The regulation of this pathway is known to occur by two proteins, sclerostin and Dickkopf-related protein 1 (DKK1)[22]. Sclerostin inhibits WNT/β-catenin signaling via binding to low-density lipoprotein receptor-related protein 5/6 (LRP5/6), a component of the Wnt receptor complex that activates the β-catenin signaling pathway[23], thereby inhibiting osteoblast differentiation and causing low bone turnover. Sclerostin also plays a role in stimulating osteoclast activity[24]. DKK1 is an LRP5/6 antagonist whose role is not completely well characterized in osteoporosis, but which is upregulated in inflammatory diseases such as rheumatoid arthritis and may be a mediator of bone erosions in rheumatoid arthritis[25]. TNF-α levels and other inflammatory cytokines' levels are higher at lower levels of kidney function[26]. Moreover, the expression of TNF-α is related to overexpression of sclerostin and DKK1[27]. This may explain why both sclerostin and DKK1 levels are elevated early in the course of CKD[28,29], and can at least partially account for the effect of chronic inflammation of CKD on bone health.

Together, these skeletal abnormalities result in an increased risk of fractures. Fracture risk increases as estimated glomerular filtration rate (eGFR) decreases. The 3-year cumulative incidence of fractures is as high as 5% in men and as high as 9.6% in women aged greater than 65 years with eGFR <15mL/min per 1.73 m^2 as compared to 1.6% in men and 4.3% in women with eGFR ≥60mL/min per 1.73 m^2 [30]. In NHANES III, participants with CKD had a >2-fold greater prevalence of hip fracture as compared to participants without CKD[31]. Fractures in CKD patients are associated with increased economic burden related to hospitalizations, morbidity and mortality. The annual costs for management of fractures in patients with CKD stages 3–5D are estimated to be as high as 556 million dollars[3]. In the dialysis population, those who sustained a hip fracture had a median survival time of 289 days as compared to a survival time of 714 days in controls matched by age, cardiovascular disease and dialysis duration who had not sustained hip fractures[32].

DIAGNOSIS OF RENAL OSTEODYSTROPHY (AND ASSESSMENT OF FRACTURE RISK)

It is important for clinicians to make an accurate assessment of skeletal health in CKD patients. This assessment will guide the therapeutic approach that may mitigate the burden of fractures and other morbidity and mortality associated with CKD-associated osteoporosis.

INVASIVE DIAGNOSIS OF Renal Osteodystrophy

BONE BIOPSY

Renal Osteodystrophy (ROD) refers to abnormal bone pathology in kidney disease[33]. ROD was historically classified into hyperparathyroid bone disease (osteitis fibrosa cystica), mild hyperparathyroid bone disease, mixed osteodystrophy, low turnover/adynamic bone disease and osteomalacia. High turnover disease results from excessive activity of both osteoclasts and osteoblasts. In contrast, low bone turnover disease is characterized by the absence of osteoclast and osteoblast activity. Tetracycline double-labeled iliac crest bone biopsy is the gold standard for evaluating ROD type and mineralization.

Bone biopsy data from cohorts of patients both with CKD stages 3–5 and CKD stage 5D have elucidated the prevalence of histomorphometric abnormalities in both groups of patients[9,34–36]. In patients with CKD stages 3–5, normal bone followed by adynamic bone disease are the most common histomorphometric findings[34,35]. At least in one cohort, osteitis fibrosa cystica was the most common histomorphometric abnormality occurring in 47% of patients in CKD stages 3–4[36]. In CKD stage 5D, the most common type of ROD is low turnover/adynamic bone disease (~60%) and the prevalence of osteomalacia is low (~3%)[8,37]. In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) committee proposed a new classification system to better describe the bone abnormalities present in CKD and to assist with clinical decision-making. This system was based on the three key histologic features of renal osteodystrophy, bone turnover, mineralization and volume (TMV system; Table 2); histomorphometric abnormalities are reported using standard nomenclature as recommended by the American Society of Bone and Mineral Research[38]. This shift in classification recognized that the historical definition could not accommodate advances in our understanding of the diverse and complex pathobiology of bone disease in CKD patients. For example, the historic renal osteodystrophy classification system relied on assessments of bone turnover and mineralization but was unable to appreciate the increasingly recognized and important role of bone volume as indicators of bone disease and fracture risk in CKD[39]. The TMV classification system provides a clinically relevant description of the underlying bone pathology as assessed by histomorphometry, which in turn helps define the pathophysiology and thereby guide therapy. KDIGO recommends performing a bone biopsy in CKD stages 3a-5D if knowledge of the type of bone disease will affect treatment decisions. However, bone biopsy is not routinely used in the clinic because it is costly, invasive, painful, requires time consuming measurements, is only available at few centers worldwide and has not been shown to predict fracture risk. Therefore, non-invasive methods are more commonly used to identify fracture risk and underlying ROD type and inform treatment.

NON-INVASIVE DIAGNOSIS OF ROD

SKELETAL IMAGING

Non-invasive skeletal imaging can be used to assess the presence of skeletal abnormalities and to classify fracture risk. Measurement of areal bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) risk stratifies patients with CKD for fracture [40–42]. In

clinical practice, osteoporosis is detected by a DXA T-Score ≤ −2.5 or the presence of a low trauma fracture at any T-Score (Figure 2). In patients with CKD stages 3a5D with evidence of CKD-MBD and/or risk factors for osteoporosis, KDIGO recommends "*BMD testing to assess fracture risk if results will impact treatment decisions*"[43]. The optimal frequency of measurement of BMD in CKD patients is unknown. In clinical practice in the general population, BMD is tested every 1–2 years.

DXA is helpful in assessing areal BMD or bone quantity. However, it is unable to assess bone quality. Peripheral quantitative computed tomography (pQCT) and high resolution pQCT (HRpQCT) are imaging techniques that can assess the skeleton in three dimensions, providing information on microarchitecture and mineral density of both trabecular and cortical bone[44]. pQCT is widely available while HRpQCT is limited to research settings. The more widespread use of these techniques is limited by the absence of studies showing their superiority over DXA in predicting fractures or in guiding therapy[44].

BIOCHEMICAL AND BIOMARKER ASSESSMENT OF BONE TURNOVER

Although bone biopsy is the gold standard for the diagnosis and classification of bone disease, its use in the clinic is limited due to lack of performance by nephrologists and endocrinologists and few centers internationally that process and read bone histomorphometry. Alternatively, assessment of turnover type can also be based on bone turnover markers with a moderate degree of accuracy (Table 3) (Figure 2). The most commonly used marker of turnover by nephrologists is PTH. Bone formation markers, which are markers of osteoblast function, include bone specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type-1 N-terminal propeptide (P1NP). Bone resorption markers, which are markers of osteoclast number and function, include tartrate-resistant acid phosphatase 5b (Trap-5b) and C-terminal telopeptides of type I collagen (CTX).

Bone turnover markers can be useful when they are at the extremes of their ranges[45]. At those extremes, they can help distinguish between low and non-low turnover and high and non-high turnover bone disease with an area under the curve >0.67 (Table 2). Their correlation with bone histomorphometric parameters from bone biopsies is moderate (Table 4).

MANAGEMENT OF KIDNEY RELATED BONE DISEASE AND THERAPEUTIC CONSIDERATIONS

VITAMIN D, PHOSPHORUS AND PTH MANAGEMENT AND LIFE-STYLE MODIFICATION

The first-line therapy for the management of CKD-associated osteoporosis is treatment of the mineral and metabolic abnormalities associated with CKD-MBD. Management of hyperparathyroidism, hyperphosphatemia and vitamin D deficiency need to occur before initiation of medications that are used to treat osteoporosis (see Treatment Section) [43]. Secondary hyperparathyroidism has long been considered a major feature of CKD-MBD. It begins early in the course of CKD. Secondary hyperparathyroidism prevalence and severity increase as kidney function declines. In early stages of CKD, management strategies aim at

preventing the rise of PTH levels. The KDIGO 2017 guidelines recommend managing hyperphosphatemia, hypocalcemia, high phosphate intake and nutritional vitamin D (25-hydroxy vitamin D) deficiency in CKD stage 3–5 patients with rising PTH levels or PTH levels consistently above the upper limit of normal[46]. In patients with CKD stage 5D, KDIGO recommends targeting PTH levels of 2 to 9 times the upper normal limit of the assay. Lowering plasma phosphate levels with phosphate binders can partially reverse hyperparathyroidism. When PTH levels fail to decrease or continue to rise, vitamin D receptor activators (VDRA) should be used[4647–49]. Using nutritional vitamin D, such as ergocalciferol or cholecalciferol, is possible but not recommended by the guidelines because of unproven benefit[46]. The optimal serum concentration of nutritional vitamin D is unknown but data in patients with CKD stage 5D suggest that levels of 25hydroxy D > 30 ng/mL may be sufficient[50]. When PTH levels remain elevated despite sufficient 25-hydroxy D levels, calcimimetics are added. Calcimimetics, such as cinacalcet, can increase BMD[51], normalize bone histology[52] and may reduce the risk of fractures in CKD patients[53]. Whether this translates into improved mortality in CKD stage 5D patients is less clear[54]. Etecalcetide is an intravenous calcimimetic that was recently approved for the treatment of secondary hyperparathyroidism. When compared to cinacalcet in CKD stage 5D patients with PTH levels> 500pg/mL, etecalcetide was superior to cinalacet in reducing PTH levels (p for superiority 0.04)[55]. Long term effects and safety of eticalcetide have yet to be studied. Finally, non-pharmacologic interventions that include modifying dietary calcium and nutritional vitamin D, smoking cessation, weight bearing exercise, and moderating alcohol intake [56] should be discussed with all patients.

ANTI-RESORPTIVE AGENTS

Antiresorptive agents include bisphosphonates and denosumab. These agents inhibit osteoclast mediated bone resorption making them advantageous for the treatment of patients with high turnover bone disease; they are contraindicated in patients with low turnover or adynamic bone disease. Trials in patients with CKD-MBD are needed to determine their skeletal and extra-skeletal safety[57].

BISPHOSPHONATES

Bisphosphonates inhibit farnesyl pyrophosphate synthase, an important enzyme for osteoclast function. By inhibiting farnesyl pyrophosphate, they lead to osteoclast cell death. Long-term use of bisphosphonates is known to decrease the rate of bone turnover and remodeling[58,59]. As such, the duration of their use is controversial and they are not indicated in patients with low turnover or adynamic bone disease. Bisphosphonates are mainly cleared via the kidneys. Therefore, these agents have not been recommended in patients with CrCl < 30 mL/minute due to concern of excessive accumulation of bisphos-phonate in the skeleton, thus resulting in over suppression of bone remodeling. Finally, intravenous bisphosphonates have been associated with acute kidney injury.

Despite the safety concerns of using bisphosphonates in patients with CKD, a growing body of data suggest that these agents are safe in patients with an eGFR 15 to 59 ml/min/1.73 m^2 due to age-related declines in kidney function without CKD-MBD [60,61]. Miller et al. conducted a retrospective analysis evaluating the effect of risendronate on post-menopausal

women with creatinine clearance of <80 ml/min[62]. Women with lower creatinine clearance treated with risedronate had a significant increase in BMD and reduction in vertebral fractures compared to women treated with placebo. The rate of kidney and non-kidney adverse events was not higher in women with kidney failure. In Japanese subjects with osteoporosis and eGFR 30 to ≥ 90mL/min/1.73 m^2, risendronate administration improved lumbar spine BMD ($p<0.001$) and suppressed bone turnover markers urine N-terminal telopeptide of type 1 collagen, urine C-terminal telopeptide of type 1 collagen and BSAP ($p<0.001$). Importantly, kidney function was preserved throughout the treatment duration[63]. In a secondary analysis of the Fracture Intervention Trial, treatment with alendronate was safe and resulted in an increase in total hip and spine BMD and a reduction in spinal fractures in women with an eGFR <45 mL/minute[61]. Alendronate administration to patients with CKD stages 3–4 resulted in a significant increase in lumbar spine T-Score ($p=0.03$) as compared to patients who received placebo[64]. In CKD stage 5D patients, ibandronate significantly improved lumbar spine T score[65]. Despite these skeletal benefits, the major concern with the use of bisphosphonates is the development of adynamic bone disease. Ota et al.[66] investigated bone-tissue level safety of alendronate in 5/6 nephrectomized rats with CKD stage 4. Alendronate improved femoral trabecular bone volume fraction, the mineral-to-matrix-ratio of the endosteal and periosteal regions of cortical bone, and the carbonate-to-phosphate ratio of both trabecular and cortical bone[66]. These results are promising but cannot be generalized to our population since alendronate was only administered for 4 weeks, while our patients usually require longer treatment durations.

DENOSUMAB

Denosumab is a monoclonal antibody against the receptor activator of NF-κB ligand (RANKL). Denosumab does not act directly on bone but rather through mimicking the action of osteoprotegerin, a decoy receptor produced by osteoblasts that binds RANK and inhibits its binding to RANKL. Via this mechanism, denosumab inhibits osteoclast proliferation and development, making it a potent antiresportive agent. Denosumab is cleared by the reticuloendothelial system and not by the kidneys. In contrast to bisphosphonates, it does not accumulate in kidney failure, and therefore does not carry the risk of long-term oversuppression of bone turnover.

The role of denosumab in managing osteoporosis in patients with age-related kidney disease was explored in a *post-hoc* analysis of The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial [67]. The registration trial included 7868 postmenopausal women and demonstrated that treatment with denosumab for 36 months reduced vertebral, hip and non-vertebral fracture risk by 68%, 40%, and 20% respectively [68]. In another study, administration of denosumab to CKD stage 5D patients with PTH >1000 pg/mL resulted in an increase in femoral neck and lumbar spine BMD at 6 months[69]. The effects of denosumab on bone histology in patients with kidney failure have not been studied yet. In the FREEDOM trial, the rate of adverse events did not differ between patients with creatinine clearance less than as compared to greater than 30 ml/min/1.73 m^2 [67]. However, later studies and case reports demonstrated that the administration of denosumab is associated with a significant risk of hypocalcemia particularly at lower creatinine clearance[70–72]. These risks may be mitigated by adequate supplementation with calcium and

vitamin D prior to therapy initiation and by the use of high calcium dialysate baths in CKD stage 5D patients[73].

OSTEOANABOLIC AGENTS

Osteoanabolic agents refer to drugs that stimulate bone formation. Teriparatide and Abaloparatide are the two osteoanabolic agents currently used for the management of osteoporosis. They are forms of recombinant PTH that mimic PTH action on osteoblasts. Osteoblast formation is increased and osteoclast death is inhibited following PTH administration[74], making the administration of osteoanabolic agents ideal for increasing bone mass in low turnover or adynamic bone disease. However, their use is contraindicated in CKD patients with high turnover bone disease caused by elevated PTH levels, as high PTH levels can lead to CKD-associated osteoporosis via increases in cortical porosity and thinning due to endocortical trabecularization[10]. The long-term side effects of osteoanabolic agents in patients with CKD have not been studied. Since hyperparathyroidism is associated with cardiovascular calcification and mortality, then it is plausible that osteoanabolic agents would lead to the same consequences. Due to animal skeletal safety data, their use is currently limited to 2 years per lifetime duration. After holding these therapies, data suggest that women with postmenopausal osteoporosis will require another agent to prevent further bone loss[75].

TERIPARATIDE

Teriparatide is a recombinant peptide of the first 34 amino terminal residues of PTH. It was the first FDA approved osteoanabolic agent to treat osteoporosis and to prevent fractures in both age-related and glucocorticoid-induced osteoporosis [76,77]. Iliac crest bone biopsies in postmenopausal women treated with teriparatide for 19 months showed a significant increase in cancellous bone volume and connectivity density, cortical bone thickness[78] and trabecular morphology as compared to biopsies in postmenopausal women receiving placebo[79]. Our initial knowledge on the safety of use of teriparatide in kidney failure came from studies in post-menopausal women with age-related decline in kidney function. In a *post-hoc* analysis of the Fracture Prevention Trial[80], females with post-menopausal osteoporosis and eGFR 30 to 80 mL/min per 1.73 m^2 had significant increases in lumbar spine and femoral neck BMD. Compared to women with eGFR ≥ 80 mL/min per 1.73 m^2, they had similar reductions in the risk of vertebral and non-vertebral fractures. Importantly, the subjects with kidney dysfunction did not have a higher incidence of adverse events as compared to the group with normal kidney function. The pharmacokinetic safety profile of teriparatide in kidney failure has since been tested proving that there is no risk of accumulation of once weekly injections of teriparatide in kidney failure[81]. Data on the use of teriparatide in patients with moderate to severe CKD with MBD is available from small observational studies[67,70,82–86]. Daily administration of teriparatide for six months to CKD stage 5D patients with biopsy proven adynamic bone disease led to an increase in lumbar spine BMD with significant monthly increases in both lumbar spine and femoral neck BMD[84]. Administration of once-weekly teriparatide to CKD stage 5D patients with hypoparathyroidism and osteoporosis resulted in an increase in lumbar spine BMD. Resorption markers' levels increased significantly as well[87]. The most commonly seen adverse events included hypercalcemia and hyperuricemia, which were more common in

patients with the lowest levels of creatinine clearance[80]. Some patients with kidney failure also experienced transient hypotension[87].

ABALOPARATIDE

Abaloparatide is a recombinant PTH-related peptide analogue that shares the first 20 amino acids of the N terminus of PTH-rp. Abaloparatide was designed to have relatively greater affinity for the transient state of PTH/PTH1 receptor; thus, being more purely anabolic [88]. In ovariectomized rats, abaloparatide increased bone formation and mass without increasing bone resorption [89,90]. Similarly, in ovariectomized monkeys, abaloparatide administration led to increased bone formation and bone mass in vertebral and non-vertebral sites without influencing bone resorption markers[91]. Postmenopausal women receiving abaloparatide also had significant improvements in BMD at the total hip, femoral hip and lumbar spine[92,93]. In The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE)[93], postmenopausal women receiving subcutaneous abaloparatide for 18 months had a relative risk of vertebral fractures of 0.14 ($p<0.001$) as compared to women receiving placebo. Bone histomorphometry in post-menopausal women treated with 12–18 months of abaloparatide demonstrated no evidence of excessive osteoid, marrow fibrosis, or abnormalities in mineralization [94]. Furthermore, patients treated with abaloparatide had lower eroded surface on histomorphometry versus the placebo group [93], but had equivalent increases in cortical porosity compared to teriparatide [94]. These observations are consistent with the clinical trial bone turnover marker data showing that the rise in CTX, a resorption marker, was significantly less pronounced with abaloparatide than with teriparatide [94]. The risk of hypercalcemia with abaloparatide can be as much as 50% lower than the risk of hypercalcemia with teriparatide[93]. There are no published studies of abaloparatide in patients with kidney failure. However, the lower risk of hypercalcemia and hyperuricemia associated with its use in patients with healthy kidney function make it more attractive for use in CKD patients.

DEVELOPMENT OF NEW AGENTS

Inflammation's role in renal osteodystrophy and skeletal health is increasingly being studied (Refer to section: CKD effects on bone strength). Inhibition of TNF-α decreases levels of DKK1 in rheumatoid arthritis patients[95]. Similarly, rheumatoid arthritis patients receiving IL-6 inhibitors experience decreases in DKK1 levels and increases in the bone formation marker PINP[96].

Clinical trials involving sclerostin inhibitors in post-menopausal osteoporosis increase BMD and decrease the risk of vertebral and non-vertebral fractures [97–99]. Despite the large increases in bone mass seen with these agents, we do not recommend their use since the function of sclerostin in the vasculature is not well understood and in one clinical trial there were increased cardiovascular events among patients randomized to the monoclonal antibody against sclerostin[99,100].

Cathepsin K antagonists were also developed to decrease bone resorption by inhibiting Cathepsin K, a protease found in osteoclasts. These drugs never reached phase IV trials due to their association with increased risk of cerebrovascular events [101].

While none of these agents were developed with the CKD population in mind, their development sheds light on an exciting future for CKD-associated osteoporosis therapy. They highlight a departure from defining skeletal health in terms of systemic and hormonal derangements to a more bone-centric approach focused on osteocyte cell signaling and interactions. How these new approaches will affect the skeletal and extraskeletal manifestations of CKD needs to be investigated.

CONCLUSION

CKD-associated osteoporosis is a complex disease that confers high morbidity and mortality to patients with kidney disease. Timely diagnosis of the underlying skeletal abnormalities identifies patients for treatments that may prevent future bone loss and decrease fracture risk. All patients with CKD should be managed with strategies that mitigate the derangements that are associated with declining kidney function and CKD-MBD, such as the use of phosphate binders, vitamin D analogs and/or calcimimetics. Based on the 2017 KDIGO Guidelines, fracture risk classification by DXA should be performed for patients with CKD-MBD and/or clinical risk factors for osteoporosis or fractures. The frequency of fracture risk assessment for CKD patients is not known, but based on the general population guidelines, every 2 years may be acceptable. Once fracture risk and/or a diagnosis of osteoporosis has been established, patients should be counseled on lifestyle modifications that are beneficial to the skeleton, including proper nutrition, weight bearing exercise, smoking cessation and limiting alcohol intake. Once the need for treatments that may mitigate bone loss and lower fracture risk are established, determination of ROD type is necessary to inform treatment. Bone turnover markers, when at the extremes of their ranges, can be helpful in distinguishing low from non-low turnover; thus, distinguishing which patients might benefit from an anabolic versus an anti-resorptive agent. When bone turnover markers are unable to assist with identification of underlying ROD type, bone biopsy is necessary. Ultimately, the development and study of treatments that are directed against fractures in patients with CKDassociated osteoporosis are needed to provide evidence-based recommendations that will both change nephrology practice patterns and lead to improved quality of life and decreased mortality in patients with CKD.

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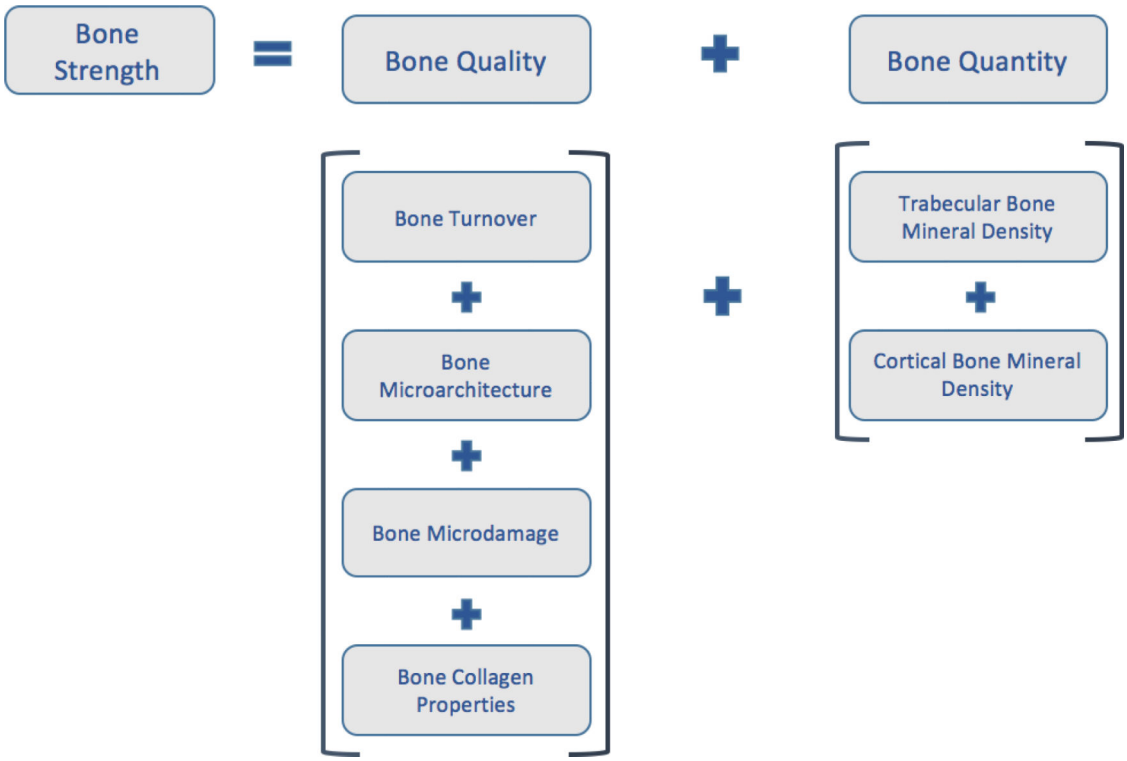

Figure 1. The Elements of Bone Strength

Bone strength is defined by bone quality and bone quantity. Bone quality pertains to bone material properties and includes bone turnover, microarchitecture, microdamange and collagen properties. Bone quantity pertains to the bone mineral density of trabecular and cortical bone.

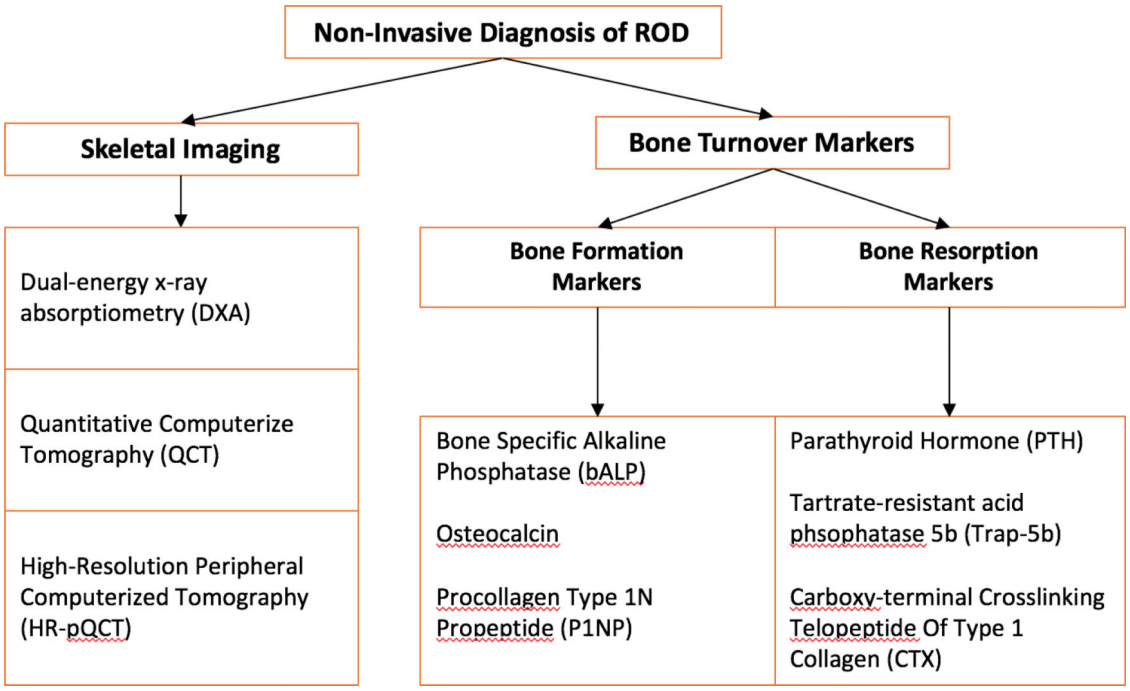

Figure 2. Non-Invasive Diagnosis of ROD

Non-invasive skeletal imaging can be used to assess the presence of skeletal abnor-malities and to classify fracture risk. Measurement of bone mineral density can be done by dual energy X-ray absorptiometry (DXA). Microarchitecture and mineral density of trabecular and cortical bone can be assessed by quantitative computerized tomography (QCT) and by high-resolution peripheral computerized tomography (HR-pQCT).

Alternatively, assessment of turnover type can also be based on bone turnover markers. Bone formation markers, which are markers of osteoblast function, include bone specific alkaline phosphatase (BALP), osteocalcin, and procollagen type-1 N-terminal propeptide (P1NP). Bone resorption markers, which are markers of osteoclast number and function, include tartrate-resistant acid phosphatase 5b (Trap-5b) and C-terminal telopeptides of type I collagen (CTX).

Table 1.

Stages of Chronic Kidney Disease

CKD Stages	Estimated Glomerular Filtration Rate (mL/min/1.73m^2)
1	≥90
2	60–89
3A	45–59
3B	30–44
4	15–29
5	<15
5D	On dialysis

Table 2.

TMV classification system for renal osteodystrophy

Turnover	Mineralization	Volume
Low	Normal	Low
Normal	Abnormal	Normal
High		High

From: Moe S, Drueke 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):1945–53.

Table 3.

AUROCs of Circulating Bone Biomarkers to Distinguish High and Low Bone Turnover from Non-high and Non-low Bone Turnover as Assessed by BFR/BS

Blood Sample Marker	N	AUROC (95% CI)	Best Cutoff
Low vs Non-low			
iPTH, pg/mL	280 vs 196	0.701 (0.653–0.750)	103.8
wPTH, pg/mL	260 vs 180	0.712 (0.662–0.761)	48.0
bALP, U/L	273 vs 190	0.757 (0.713–0.801)	33.1
P1NP, ng/mL	280 vs 1,197	0.650 (0.599–0.701)	498.9
Combined iPTH + bALP	272 vs 188	0.718 (0.670–0.767)	NA
Combined wPTH + bALP	257 vs 174	0.743 (0.695–0.790)	NA
High vs Non-hiah			
iPTH, pg/mL	81 vs 395	0.724 (0.663–0.786)	323.0
wPTH, pg/mL	75 vs 365	0.678 (0.611–0.746)	61.4
bALP, U/L	77 vs 386	0.711 (0.655–0.767)	42.1
P1NP, ng/mL	81 vs 396	0.743 (0.689–0.797)	621.1
Combined iPTH + bALP	76 vs 384	0.718 (0.658–0.779)	NA
Combined wPTH + bALP	72 vs 359	0.691 (0.628–0.725)	NA

Abbreviations: AUROC, area under the receiver operating characteristic curve; bALP, bone-specific alkaline phosphatase; BFR/BS, bone formation rate/bone surface; CI, confidence interval; iPTH, intact parathyroid hormone; NA, not available; P1NP, amino-terminal propeptide of type 1 procollagen; wPTH, whole parathyroid hormone. From Sprague et al, 2015. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. Am J Kidney Dis.

Table 4.

Diagnostic performance of bone biomarkers compared to bone biopsy histomorphometry

Biomarker	Assay	Population (*N*)	Diagnosis	Cutoff	Prevalence (%)	Spec (%)	Sens (%)	NPV (%)	PPV (%)	AUC	Reference
Markers of bone turnover											
iPTH (pg/ml)	Roche Diagnostics	HD, 476	Low BFR	<103.8	59					0.70	Sprague et al. [7••]
iPTH (pg/ml)	Roche Diagnostics	HD, 476	High BFR	>323.0	17					0.72	Sprague et al. [7••]
iPTH (pg/ml)	Immulite, DPC	PD, 41	HTO	>386	49	62	70	80	77	0.77	de Oliveira et al. [17]
iPTH (pg/ml)	Roche Diagnostics	HD, 40	Non-LTO	NA	50					0.85	Haarhaus et al. [18]
iPTH (pg/ml)	Scantibodies	CKD-5, 60	Low BFR	<335	NA	80	40	53	72		Cejka et al. [19]
iPTH (pg/ml)	Scantibodies	CKD-5, 60	High BFR	>391	NA	80	43	84	38		Cejka et al. [19]
iPTH (pg/ml)	Immulite, DPC	hd, **n**	LTO	<150	60	50	85		83		Barreto et al. [20]
iPTH (pg/ml)	Immulite, DPC	HD, 97	HTO	>300	37	69	75		62		Barreto et al. [20]
iPTH (pg/ml)	Nichols Diagnostics	CKD 3–4, 26	HTO	>31	54	100	40			0.91	Lehmann et al. [21]
iPTH (pg/ml)	Nichols Diagnostics	HD - PD, 78	HTO	>27	69	100	18			0.85	Lehmann et al. [21]
iPTH (pg/ml)	Biosource	CKD 4–5, 84	ABD	<237	23	53	78			0.75	Bervoets et al. [22]
iPTH (pg/ml)	Nichols Diagnostics	HD, 103	ABD	<150	37	76	81	88	65		Couttenye et al. [23]
biPTH (pg/ml)	Scantibodies	HD, 440	Low BFR	<48	59					0.71	Sprague et al. [7••]
biPTH (pg/ml)	Scantibodies	HD, 440	High BFR	>61.4	17					0.68	Sprague et al. [7••]
biPTH (pg/ml)	Nichols Diagnostics	CKD 3–4, 26	HTO	>21	54	100	40			0.94	Lehmann et al. [21]
biPTH (pg/ml)	Nichols Diagnostics	HD + PD, 78	HTO	>15	69	100	9			0.86	Lehmann et al. [21]
PTH (1–841/C-PTH	Scantibodies/Nichols	D, 51	LTO	<1	55	83	100	100	88		Monier-Faugere et al. [24]
PTH (1–84)/C-PTH	Scantibodies/N ichols	CKD 3–4, 26	HTO	>0.76	54	100	0			0.54	Lehmann et al. [21]
PTH (1—84)/C-PTH	Scantibodies/Nichols	HD - PD, 78	HTO	>0.8	69	100	22			0.55	Lehmann et al. [21]
Sclerostin (pg/ml)	R&D Systems	CKD-5, 60	Low BFR	<2800	NA	80	35	66	57		Cejka et al. [19]
Sclerostin (pg/ml)	R&D Systems	CKD-5, 60	High BFR	>1925	NA	80	59	40	93		Cejka et al. [19]
Sclerostin (ng/dl)	Quidel/TECOmedical	PD, 41	HTO	>1.82	49	62	85	61	68	0.70	de Oliveira et al. [17]
Markers of bone formation											
BsAP (U/l)	Quidel	HD, 463	Low BFR	<33.1	59					0.76	Sprague et al. [7••]
BsAP (U/l)	Quidel	HD, 463	High BFR	>42.1	17					0.71	Sprague et al. [7••]
BsAP (U/l)	Metra Biosystems	PD, 41	HTO	>57	49	96	65	95	92	0.79	de Oliveira et al. [17]
BsAP	Quidel	HD, 40	Non-LTO	NA	50					0.89	Haarhaus et al. [18]

Biomarker	Assay	Population (*N*)	Diagnosis	Cutoff	Prevalence (%)	Spec (%)	Sens (%)	NPV (%)	PPV (%)	AUC	Reference
BsAP (U/l)	Electrophoretic[a]	CKD 4–5, 84	ABD	<23	23	66	83			0.79	Bervoets et al. [22]
BsAP (U/l)	Electrophoretic[a]	HD, 103	ABD	<27	37	86	78	88	75		Couttenye et al. [23]
Blx	HPLC[a]	HD, 40	Non-LTO	NA	50					0.83	Haarhaus et al. [18]
TAP (U/l)	[a]	PD, 41	HTO	>107	49	81	65	80	76		de Oliveira et al. [17]
TAP (U/l)	Kinetic method[a]	CKD 4–5, 84	ABD	<66	23	54	74			0.65	Bervoets et al. [22]
TAP (U/l)	Kinetic method[a]	HD, 103	ABD	<123	37	83	75				Couttenye et al. [23]
OC (ng/ml)	Biosource	CKD 4–5, 84	ABD	<41	23	67	83	94	47	0.80	Bervoets et al. [22]
OC (ng/ml)	Diasorin	HD, 103	ABD	<14	37	54	96	97	55		Couttenye et al. [23]
P1NP (ng/ml)	Unknown	HD, 477	Low BFR	<499	59					0.65	Sprague et al. [7••]
P1NP (ng/ml)	Unknown	HD, 477	High BFR	>621	17					0.74	Sprague et al. [7••]
Markers of bone resorption											
DPYD (nmol/1)	Quidel	PD, 41	HTO	>14	49	62	75	61	65	0.72	de Oliveira et al. [17]
DPYD/PYD (nmol/1)	HPLC[a]	CKD 4–5, 84	ABD								Bervoets et al. [22]

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