Fractures in Patients with CKD: Time for Action

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Fractures represent a debilitating injury with prolonged rehabilitation, long-term pain, and higher costs. Only 50% of patients with a hip fracture regain the mobility and independence that they had prefracture. As the population ages, it is predicted that the number of fractures worldwide will increase from 1.7 million fractures in 1990 to 6.3 million fractures in 2050 (1). Studies in patients with CKD stages 3 and 4, patients on dialysis, and patients post-transplant all show that patients with CKD have a two- to 100-fold higher incidence of fracture compared with age- and sex-matched individuals without CKD. As CKD progresses, there is an increase in prevalent hip fractures (Figure 1). A 40 year old on dialysis has a 100-fold higher risk of having a hip fracture compared with a 40 year old in the general population. Even at age 80 years old, the risk in patients on dialysis is substantially greater in patients with CKD compared with those without (2). Mortality doubles in patients on dialysis who sustain a major fracture that requires hospitalization (3,4). Fractures are one of many premature aging consequences observed in our patients. So why have we not paid more attention to fractures, and why are patients with CKD uniformly excluded from clinical trials evaluating pharmacotherapies? The answer is in the uniqueness of CKD in the pathogenesis of fractures. However, as our CKD population ages, there will be more mixing of age-related and postmenopausal causes of bone loss with CKD-specific causes of bone loss.

Many consider the diagnosis of osteoporosis to be synonymous with low bone mineral density (BMD) assessed by dual x-ray absorptiometry (DXA). However, in treatment studies, the improvement in BMD is small compared with fracture risk reduction, indicating that there is more to bone than BMD (5). In 2000, the National Institutes of Health defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to a higher risk of fracture. Bone strength reflects the integration of two main features: bone quantity and bone quality" (6). Thus, bone quantity (assessed by DXA to give two–dimensional areal bone density or with quantified computed tomography for area) is only one component. Bone quality is the second major component and includes bone remodeling abnormalities, collagen crosslinking, and mineralization properties. Remodeling abnormalities are generally evaluated with bone biopsy and dynamic histomorphometry (tetracycline labeling), and abnormalities are nearly universally abnormal in patients with CKD (7). Kidney Disease Improving Global Outcomes (KDIGO) recommended using the term "renal osteodystrophy" to define abnormalities in turnover, mineralization, and volume assessed by bone biopsy (8). Thus, renal osteodystrophy is one component of fracture risk, not the only cause of fractures. Treatments focused only on the abnormal bone remodeling of CKD are thus not likely to be efficacious in preventing fractures. Indeed, studies have shown that the incidence of age–adjusted hip fracture has actually increased over the past decades, despite an intensive focus on treatments for renal osteodystrophy, such as parathyroid hormone and phosphate-lowering therapies (9,10). Such treatments are clearly an important component of treating bone quality and may affect fracture (11), but they are almost certainly not enough to overcome the multitude of other risk factors, including muscle weakness and neuropathy, that predispose to falls, sex hormone abnormalities, diabetes, and aging.

In the general population, clinical risk factors have been combined into a fracture prediction algorithm called Fracture Risk Assessment Tool (FRAX) developed by the World Health Organization (WHO) (12). The goal of FRAX is to evaluate fracture risk of patients on the basis of individual patient models that integrate clinical factors with or without BMD assessment. The various FRAX tools have been refined in different countries to take into account the genetics of bone fracture. There are many risk factors for fractures used in FRAX, including age, sex, body mass index, family history, alcohol use, smoking, glucocorticoids, and rheumatoid arthritis. There is also an option to say yes or no to secondary osteoporosis, including diabetes, osteogenesis imperfecta, long-standing hyperthyroidism, hypogonadism, premature menopause, chronic malnutrition, or malabsorption and chronic liver disease. Noticeably absent in the list of secondary causes of osteoporosis is the presence of CKD! Studies have showed that the use of FRAX discriminates those with and without fracture in both patients with advanced CKD (13) and transplant recipients (14). The addition of BMD to the FRAX score improves the prediction of fracture risk.

In the study in this issue of the *Clinical Journal of the American Society of Nephrology*, Naylor *et al.* (15) used a new software analysis of spine BMD called trabecular bone score (TBS). TBS is a gray–scale textural analysis of the DXA image, and TBS measurements have been shown to correlate with direct measures of trabecular

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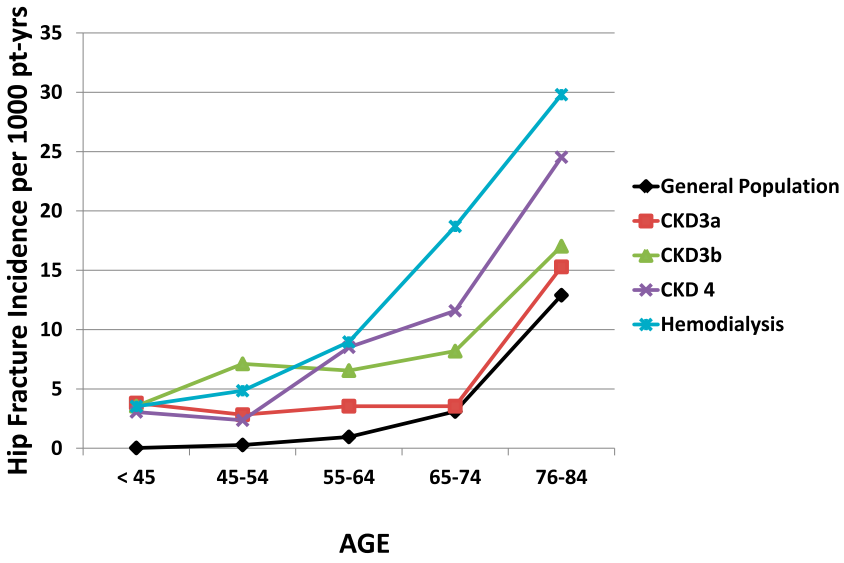

Figure 1. | **Hip fracture incidence increases with progressive CKD**. As patients age in the general population, there is a higher incidence of hip fracture. This incidence increases with progression of CKD. Data from Alem *et al.* (25) for patients on dialysis and the general population from Olmstead, Minnesota and Naylor *et al.* (24) for CKD stages 3 and 4 courtesy of the Canadian Institute for Clinical Evaluative Sciences. Pt-yrs, patient years.

microarchitecture both *ex vivo* as assessed by microcomputed tomography (16) and *in vivo* from iliac crest bone biopsy (17). TBS has also been shown to predict fractures independent of major clinical risk factors or areal BMD measured by DXA at the spine and hip, and it has been reported to increase the accuracy of fracture prediction in patients with BMD above the osteoporotic threshold (18,19). TBS is widely available, and its results are now incorporated into international fracture risk prediction guidelines as well as the WHO FRAX Tool (20). Naylor *et al.* (15) found that TBS alone from BMD was more predictive of future fracture than FRAX alone in Canadian women with eGFR<60 ml/min per 1.73 m^2 when followed for an average of 4.7 years. Because of this study's small sample size of patients with advanced disease (only four patients with CKD stage 4 and 50 patients with CKD stage 3b), validation is needed in other cohorts before wide-scale implementation in patients with CKD and especially those with concomitant remodeling abnormalities of renal osteodystrophy. If validated in other cohorts, this may offer yet another tool for clinicians to classify fracture risk more accurately.

So why do we not routinely measure BMD in patients with CKD? In the 2003 Kidney Disease Outcomes Quality Initiative guidelines, BMD testing was only recommended in post-transplant patients because there were no studies in patients with CKD that showed that a low DXA predicted subsequent fracture. In other words, its utility as a screening tool to identify those patients at risk was not proven (21). In the 2009 KDIGO CKD-Mineral Bone Disorder (CKD-MBD) guidelines, BMD was not recommended for routine use. At that time, there were studies showing that low BMD (or quantified computed tomography) predicted fractures in patients with all stages of CKD. However, the consensus was that the risk of treating patients with drugs, such as bisphosphonates, was high and that the benefit was uncertain, despite secondary analyses of common antiosteoporosis treatments. Unfortunately, these secondary analyses included generally normal creatinine and normal parathyroid hormone levels, and it was felt that the results were not generalizable to more advanced CKD. Therefore, the guideline did not recommend screening, because there was no treatment (22). In the 2016 KDIGO guideline update (currently out for public comment at www.kdigo.org), BMD is now recommended "if the results will change clinical management." Why and what does this mean? More studies have shown high fracture risk and utility of BMD, and a new treatment, denosumab, has actually been studied in advanced CKD (23). Thus, it was felt that, although treatment options remain ill defined, in some patients, the treatment outweighs risk. Thus, the guideline statement in the recent KDIGO CKD-MBD guideline update is more open ended and recommended that clinicians weigh the individual's risk of more fractures versus consequences of treatment.

We have both seen patients with CKD who are debilitated from their fractures to the point of immobility. These patients are often denied interventions proven effective in the general population, simply because they have CKD. This presents the common quagmire in the care of patients with CKD. We lack prospective clinical trials that help guide appropriate interventions in the management of cardiovascular disease, diabetes, and even hypertension. In patients with CKD and low bone density or mass, the bone is almost certainly more fragile than in patients without CKD with the same BMD because of the CKD–induced abnormal bone quality. What we do not know is if treatments that have been shown to improve bone quantity and reduce fractures in the non-CKD populations work in patients with CKD. Is it not about time that we find out? Should manufacturers and funding agents not care about the one in 10 individuals with kidney disease worldwide? Strategies in the recent cardiovascular Systolic Blood Pressure Intervention Trial (SPRINT) of stratifying by CKD should similarly be used in studies to improve bone health in patients with CKD. Such studies are long overdue.

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Disclosures

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