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Original Research Paper

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FRACTURE PREVENTION IN KIDNEY DISEASE

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ABSTRACT The number of patients with chronic kidney disease (CKD) who are progressing to end-stage renal failure is growing at an alarming rate. Among this population, one of the significant morbidities is a marked increase in fracture risk, which can be as high as 46.3 per 1000 person-years. This elevated risk is primarily due to metabolic bone changes associated with CKD, which often result in weakened bones and an increased susceptibility to fractures. A key factor in preventing fractures in these patients is addressing mineral imbalances, particularly vitamin D deficiency, which is common in CKD. Ensuring that patients maintain adequate levels of vitamin D and other essential minerals is crucial for bone health. However, some patients do not respond adequately to traditional mineral supplementation. For these individuals, alternative therapies such as denosumab, a medication that helps to strengthen bone by inhibiting bone resorption, should be considered. This review investigates the specific fracture risks faced by dialysis patients and provides a comprehensive guide for effective fracture management in this vulnerable population. By implementing targeted strategies to address mineral imbalances and exploring viable alternative treatments, healthcare providers can significantly improve the quality of life and outcomes for patients with CKD.

KEYWORDS : Chronic Kidney Disease, Fracture Risk, Vitamin D Deficiency, Denosumab

INTRODUCTION

Chronic kidney disease (CKD) is a common and progressive condition affecting over 13% of the global population, exceeding 800 million individuals [1,2]. Estimates range from 4.902 to 7.083 million for those progressing to end-stage kidney disease (ESKD) necessitating renal replacement therapy [2]. Recognized for its impact on cardiovascular risk and ESKD, CKD stands as a substantial predictor of global morbidity and mortality, with an upward trajectory in figures.

Patients with CKD face an elevated risk of falls and fractures attributed to renal osteodystrophy and a heightened prevalence of fall-related risk factors. The fracture risk correlates with declining kidney function, with the highest risk observed in stage 5 CKD or dialysis patients [3]. Incidence rates vary across CKD stages: 15.0 to 20.5, 24.2, 31.2, and 46.3 per 1000 person-years for stages 1-2, 3a, 3b, and 4, respectively [4] . Notably, fractures are more frequent in dialysis females (13.63 per 1000 person-years) compared to males (7.45 per 1000 person-years) [5]. For a comprehensive overview, consult Table 1 summarizes available data on fracture incidence per 1000 person-years, emphasizing the heightened risk in the CKD population undergoing dialysis.

Fracture Incidence In Dialysis Patients

Understanding Fracture Risk

Accumulating evidence highlights the significant association between increased morbidity and mortality in chronic kidney disease (CKD) and underlying metabolic bone disease (MBD). Deteriorating kidney function disrupts bone and mineral homeostasis, leading to extraskeletal calcifications and altered bone turnover. These factors collectively predispose CKD patients to a heightened risk of fractures, with associated increases in morbidity and mortality [6]. Dialysis itself is an independent risk factor for fractures in CKD, with an age-adjusted incidence ratio for hip fractures of 9.83 for men and 8.10 for women after four years of dialysis [5]. Even in renal transplant recipients, a history of dialysis is linked to an elevated risk of hip fracture [7,8].

The fracture risk in CKD is particularly pronounced, reaching up to five times higher in patients with an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m2 compared to those with eGFR >60 ml/min/1.73m2 [4]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) further supports this, reporting a significantly greater incidence of skeletal fractures in dialysis patients versus the general population, coupled with a 3.7-fold increased unadjusted relative risk of death [9]. Comorbidities contributing to increased fracture risk in dialysis patients include age, sex, history of fractures, diabetes, and glucocorticoid use [10].

Hip fractures take the lead as the most prevalent type among dialysis patients, showcasing a four-fold higher incidence compared to the general population when adjusting for age, gender, and ethnicity [5,11]. Notably, Caucasian chronic kidney disease patients are three times more likely to experience hip fractures than their African-American counterparts [12]. In patients with CKD, fracture risk started to rise six months before initiation of dialysis and continued to rise, then stabilized after one year at a higher rate. This was different for hip fractures, which peaked at the initiation of dialysis and then declined [13].

Determinants Of Fracture Risk In Dialysis

Table 1: Relative Risk Of Fracture In Dialysis Patients

Female sex, higher age, previous history of major fractures, and cancer were found to be associated with increased fracture risk. Medications and other comorbidity conditions,

including diabetes mellitus, were not associated with an increased risk of major fractures.

Relative Risk of Any Fracture in Dialysis Patients [22].

Characte Rristic	Relative Risk (95% CI)
Female, Age 75+	3.43 (2.33, 5.06)
Prior Hip Fracture	3.17 (2.13, 4.70)
Female, Age 65-74	2.58 (1.79, 3.63)
Female, Age 55-64	2.36 (1.56, 3.54)
Albumin ≤ 3.30 g/dL	1.91 (1.39, 2.66)
Male, Age 75+	1.86 (1.24, 2.77)
Non-Black Race vs. Black Race	1.79 (1.14, 2.78)
Prior Transplant	1.76 (1.16, 2.66)
PTH > 900 pg./mL	1.72 (1.02, 2.90)
Male, Age 65-74	1.65 (1.10, 2.48)
Female vs. Male	1.59 (1.32, 1.92)
Albumin 3.31-3.60 g/dL	1.59 (1.16, 2.21)
Albumin 3.61-3.80 g/dL	1.55 (1.08, 2.24)
Albumin, per 1 g/dL Lower	1.45 (1.25, 1.72)
Phosphorus < 3.5 mg/dL	1.29 (0.93, 1.77)
Male, Age 55-64	1.25 (0.84, 1.85)
Needs Assistance to Walk	1.18 (0.95, 1.46)

Relative Risk of Hip Fracture in Dialysis Patients [22].

Characteristic	Relative Risk (95% CI)
Female, Age 75+	7.79 (3.69, 16.43)
Male, Age 75+	5.05 (2.36, 10.82)
Female, Age 65-74	4.67 (2.22, 9.83)
Prior Hip Fracture	4.52 (2.57, 7.97)
Albumin ≤ 3.30 g/dL	3.59 (1.77, 7.25)
Albumin 3.61-3.80 g/dL	3.06 (1.44, 6.54)
Albumin 3.31-3.60 g/dL	2.81 (1.39, 5.69)
Male, Age 65-74	2.38 (1.07, 5.26)
Prior Transplant	2.35 (1.03, 5.36)
Male, Age 55-64	2.15 (1.01, 4.57)
Non-Black Race vs. Black Race	2.02 (0.93, 4.34)
Albumin, per 1 g/dL Lower	1.85 (1.41, 2.44)
Phosphorus < 3.5 mg/dL	1.62 (0.94, 2.81)
Female vs. Male	1.41 (1.04, 1.89)
Needs Assistance to Walk	1.39 (0.97, 1.99)
PTH > 900 pg/mL	1.14 (0.34, 3.80)

Treating And Managing Fractures

Chronic kidney disease (CKD) is associated with a decline in bone quality and quantity. Understanding the mechanisms underlying bone loss in CKD is crucial for guiding appropriate pharmacological interventions [14]. Patients with CKD who present with fractures pose a unique management challenge for healthcare providers. However, the 2017 update of the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines provides a comprehensive framework for the diagnosis, evaluation, prevention, and treatment of CKD-mineral and bone disorders (MBD) [15]. The primary strategies outlined in these guidelines include lifestyle modification, phosphate management, calcium maintenance, addressing parathyroid hormone (PTH) abnormalities, and employing antiresorptive and other osteoporosis therapies, such as denosumab. Lowering elevated PTH levels in affected patients can significantly improve bone health and reduce the risk of subsequent fractures.

Fractures in this patient population often arise from imbalances in circulating bone biomarkers. Therefore, correcting mineral disturbances, such as through vitamin D supplementation, should be considered a first-line approach in the therapeutic decision-making process [16]. Figure 1 illustrates the recommended management of vertebra, femur, humerus, or pelvis fractures in CKD patients, considering their clinical presentation and PTH levels.

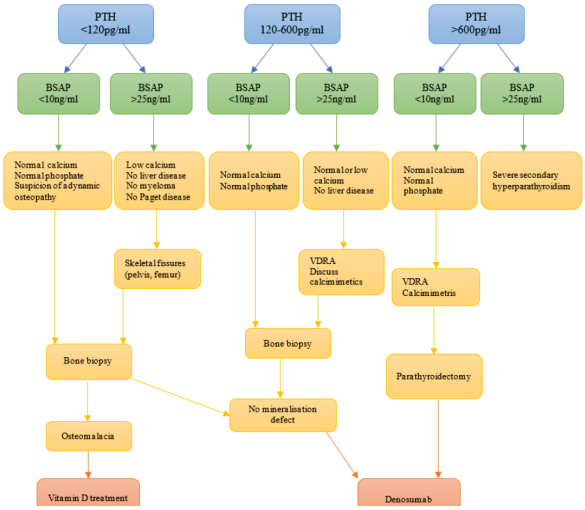

Figure 1—Guidelines for managing fractures in patients with chronic kidney disease.
BSAP: Bone-Specific Alkaline Phosphatase; PTH: Parathyroid Hormone; and VDRA: Vitamin D Receptor Activators [25].

Lifestyle Modification: Non-pharmacologic interventions include modifying dietary calcium and nutritional vitamin D, increased physical activity, smoking cessation, weight-bearing exercise, fall prevention, and mitigating factors in the home such as shower rales, removing throw rugs, handrails on steps and single-level homes, and avoidance of excessive alcohol and sedative intake.

Exercise and Physical Therapy: Exercise improves muscle impairment, physical function, and physical performance across the spectrum of CKD. Exercise training prescriptions should be individualized to one's physical function. The duration of exercise depends on the patient's health and physical condition. Types of exercise include aerobic, resistance, and flexibility exercise.

Correction of Biochemical Abnormalities of CKD-MBD

Phosphate: In patients with CKD, hyperphosphatemia levels should be lowered towards the normal range. Phosphate load from phosphate-rich sources should be avoided. Non-calcium-based phosphate binders, such as sevelamer, have advantages over calcium-based binders in increasing the bone formation rate and improving trabecular architecture.

Calcium: Excessive exogenous calcium in adults may be harmful at all stages of CKD. Daily dietary calcium intake of 1000 mg/day is recommended for achieving neutral calcium balance. Additional calcium supplements or calcium-containing medications should be avoided for patients with adequate daily calcium intakes of 800–1000mg per day. Administration of a calcimimetic agent increases the sensitivity of the calcium-sensing receptor (CaSR) and vitamin D receptor (VDR) expression and decreases PTH gene expression and PTH secretion of the parathyroid gland.

Vitamin D and Fracture Risk in Chronic Kidney Disease:
Vitamin D dysregulation and imbalance are integral to Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). With the complex interplay of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D levels becoming dysregulated. These affect bone turnover mineralization and contribute to the development of extraskeletal calcifications. Renal osteodystrophy, the skeletal manifestation of CKD-MBD, is histologically classified into high, low, and mixed bone turnover states [17].

80% of patients with chronic kidney disease (CKD) and fractures have vitamin D deficiency and relative

hypoparathyroidism [18,19]. Vitamin D, primarily synthesized through sun exposure, is crucial in maintaining serum calcium homeostasis [18]. Low vitamin D levels, defined as <20 to 30 ng/mL, can trigger secondary hyperparathyroidism, leading to bone loss, osteoporosis, fractures, and mineralization defects. If left untreated, this deficiency may progress to osteomalacia and muscle weakness, increasing the risk of falls and fractures [21]. In addition to treating vitamin D deficiency, the addition of calcimimetics reduced fracture incidence compared to placebo or conventional treatment.

Bisphosphonates

Bisphosphonates are contra-indicated in patients with GFR lower than 35 mL/min. Osteoclasts ingest them and induce decreased osteoclast activity, and in etidronate and clodronate, the drugs cause apoptosis. Decreasing osteoclast activity leads to a reduction in bone absorption. Gastrointestinal absorption of bisphosphonates is poor, and their excretion relies solely on the kidneys. Consequently, patients with CKD tend to accumulate a higher percentage of bisphosphonates. These medications can bind to bone mineral for 10 to 12 years in individuals with CKD. While their primary function is inhibiting bone resorption, they also secondarily suppress bone formation, often resulting in adynamic bone in CKD patients [22].

Denosumab

Denosumab, an FDA-approved human monoclonal antibody targeting the receptor activator of nuclear factor kappa B ligand (RANKL), is indicated for treating osteoporosis and CKD-associated osteoporosis [15]. By inhibiting osteoclast formation, function, and survival, denosumab effectively reduces bone resorption. Observational studies and small clinical trials have proved denosumab's efficacy in improving bone mineral density and reducing bone turnover in CKD patients [23]. Furthermore, a 24-month study in osteoporotic dialysis patients demonstrated that denosumab administration not only enhanced bone metabolism but also did so without significant adverse effects [24]. In patients with CKD stages 4-5D with severe secondary hyperparathyroidism (SHPT), denosumab administration led to significant hypocalcemia and a rise in PTH levels within the first 15 days, often necessitating calcium supplementation. [25]. Therefore, close monitoring is recommended during those first weeks, and correction of vitamin D deficiency before treatment decreases this tendency.

CONCLUSION

The increasing prevalence of fractures and associated mortality in dialysis-dependent CKD patients underscores the need for effective therapeutic strategies and interventions. Current literature emphasises the importance of addressing mineral and bone disorders (MBD), particularly vitamin D deficiency. Denosumab may be a promising option, especially in dialysis patients with low bone mineral density. However, the utility of these interventions in the treatment of established fractures, as opposed to their preventative role, warrants further investigation.

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