

Evaluation of bone fracture risk in CKD

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Chronic kidney disease (CKD) patients commonly have impaired bone quality and strength secondary to the effects of metabolic and hormonal disturbances that occur with kidney failure, such as hyperphosphatemia, hypercalcemia, secondary hyperparathyroidism, vitamin D deficiency, chronic metabolic acidosis, chronic inflammation, and premature hypogonadism. These conditions hamper bone turnover and mineralization, leading to reduced bone mass and quality, ultimately increasing the risk of bone fractures. In late-stage CKD fracture risk is four times higher than in the general population and the most commonly affected bones are the femur (neck or intertrochanteric region), forearm, and humerus. Hip fractures are especially alarming as they are related to long hospital stays and high morbidity and mortality.

Current recommendations for the prevention and treatment of CKD-related mineral bone disease are still limited and understated. Namely, the [2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder](#) suggests bone mineral density testing to assess fracture risk only if results are expected to alter the therapy, thus leaving a large number of patients unaddressed.

CKD and the bones

The background of bone fragility in CKD is multi-dimensional. Besides the traditional risk factors, which include ageing and age-related osteoporosis, impaired muscle strength and function, malnutrition, and hypogonadism, these patients are also exposed to issues related to uremia, primary renal disease, comorbid conditions, and specific therapies. Jointly, these factors simultaneously cause disturbances in bone turnover, mineralization, and microarchitecture at the histological level.

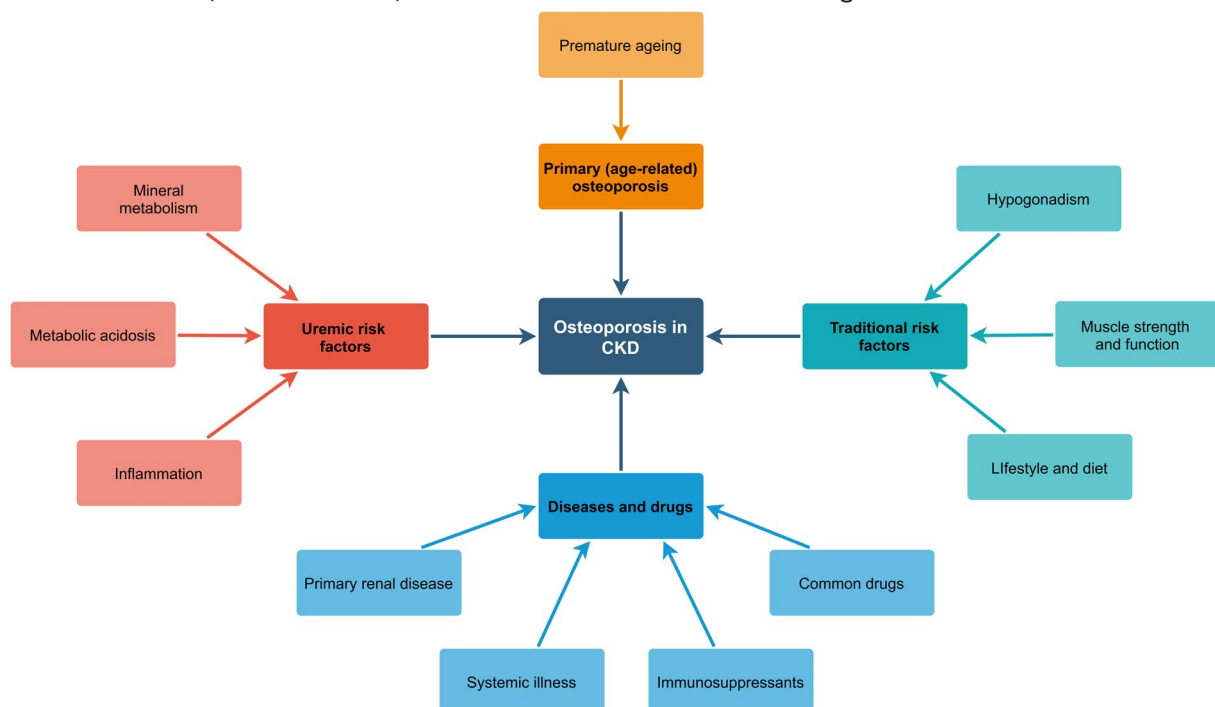


Figure 1. Traditional and non-traditional risk factors of bone fragility in CKD patients

One possible tool to estimate fracture risk is the [Fracture Risk Assessment Tool \(FRAX\)](#), which is supported by the greatest number of independent studies. It was developed in 2008 and used 12 personal, lifestyle, and medical factors to calculate a person's 10-year risk of major osteoporotic fracture. CKD is not a part of the FRAX score, but its applicability has been tested in this population in a study involving over 10,000 subjects in various stages of the disease. The results showed a similar relationship between FRAX and major osteoporotic fracture in CKD compared to individuals with preserved renal function, thus supporting the use of this score to stratify patients with non-dialysis-dependent CKD for major osteoporotic fractures and hip fractures.

Determinants of bone quantity and bone quality

Bone strength is determined by bone quantity and bone quality. In clinical practice, bone is most commonly assessed by bone mineral density (BMD), which is measured using dual-energy x-ray absorptiometry (DXA). BMD reflects the composite of bone volume and mineralization and is a key determinant of osteoporosis. In the CKD population, BMD correlates inversely with bone turnover and predicts incident bone fractures, thus supporting a more liberal use of DXA in this population as suggested in the 2017 KDIGO recommendations. DXA scan results are presented as a T-score which represents the difference between individual bone density and the average bone density of healthy young adults. A T-score of -2.5 or less is indicative of increased susceptibility to fracture.

Bone quality is related to bone microarchitecture, mineralization, turnover, matrix and mineral composition, and microdamage. A non-invasive tool to estimate bone microarchitecture that can complement lumbar spine BMD information in the prediction of fracture risk is the trabecular bone score. This recently developed tool captures information related to trabecular microarchitecture based on a textural index that evaluates pixel grey-level variations in the lumbar spine DXA.

The gold standard for quantifying bone turnover and mineralization is the histomorphometric analysis of the tetracycline double-labelled bone biopsy. Typical findings in CKD patients include variable bone turnover disturbances, while mineralization defects are more rare. Bone microarchitectural findings include lower cortical area, lower matrix mineral density, lower trabecular bone mineral density, and spatially disrupted trabeculae. However, this procedure is not readily feasible, and bone turnover markers have been suggested as a surrogate of or adjuvant to bone biopsy to assess bone turnover.

Screening for bone fracture risk in CKD patients

CKD-related osteoporosis can progress subclinically over the years, gradually impairing bone quantity and quality and enhancing the risk for fracture. There is still a paucity of systematic reviews, meta-analyses, and randomized controlled trials specifically dealing with the topic of osteoporosis in advanced CKD. Therefore, there is still no universally endorsed policy for patient screening to identify those at high risk of fracture. The European Renal Osteodystrophy (EUROD) workgroup, the Committee of Scientific Advisors, and the Committee of National Societies of the International Osteoporosis Foundation (IOF) have recently issued a [consensus statement on the diagnosis and management of osteoporosis in CKD stages G4-G5D](#). They suggest considering biennial hip and lumbar spine DXA in men over 50 years of age and postmenopausal women. FRAX can be added to this assessment. CKD patients older than 50 and with a prior major osteoporotic fracture should be considered for pharmacological treatment without the need for BMD assessment. Otherwise, a DXA T-score threshold ≤ -2.5 at the lumbar spine or hip is recommended to initiate pharmacological intervention.

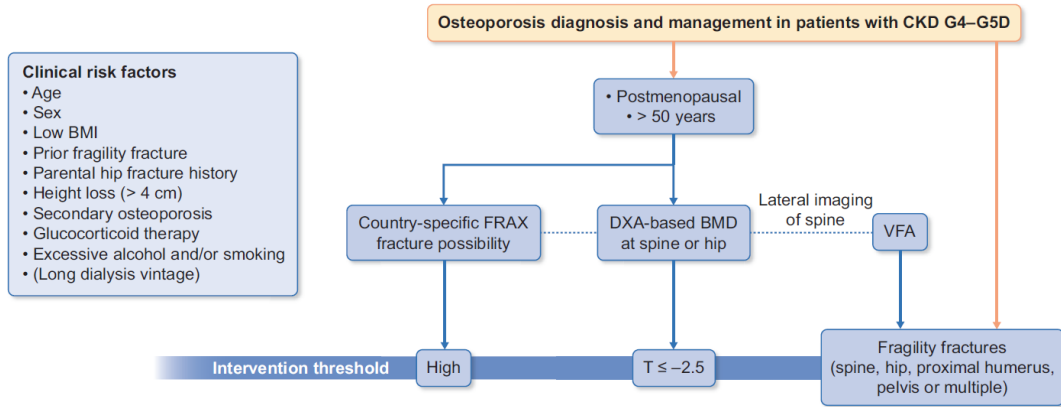


Figure 2. Approach to fracture risk assessment in patients with CKD stage 4-5D and osteoporosis

Given the substantial limitations of bone biopsy as the gold standard to assess bone turnover, a recent study by Joergensen et al. evaluated the diagnostic performance of certain biochemical biomarkers in this area: full-length (amino acids 1-84) "biointact" parathyroid hormone (PTH), bone-specific alkaline phosphatase (BsAP), intact procollagen type I N-terminal propeptide (PINP), and tartrate-resistant acid phosphatase isoform 5b (TRAP5b). The suggested cut-off values for high turnover were >97U/L for total AP, >33.7ug/L for BsAP, >120.7ng/mL for PINP, and >5.05 U/L for TRAP5b, whereas cut-off values for low bone turnover were <87U/L, <24.2ug/L, <49.8ng/mL and <3.44 U/L for total AP, BsAP, PINP, and TRAP5b respectively. The highest diagnostic performances were seen with combinations of biomarkers. The overall diagnostic accuracy for high turnover was 90% and for low turnover 78%, suggesting an acceptable diagnostic performance in excluding both high and low-turnover bone disease. Another indirect biomarker and predictor of bone status is PTH which exhibits a U-shape relationship with vertebral fracture risk, where both high and low-normal levels are associated with an increased risk of fracture. Thus, defining the optimal PTH level in CKD patients remains a challenge.

Table 4. Diagnostic Performance of Biochemical Markers for a Diagnosis of High or Low Bone Turnover

	Exploration Cohort (n = 100)		Validation Cohort (n = 99)				
	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
High Turnover							
Biointact PTH, pg/mL	0.78 (0.67, 0.86)	>143.5	70%	74%	57%	84%	73%
Total AP, U/L	0.77 (0.65, 0.86)	>97	76%	77%	61%	87%	77%
BsAP, µg/L	0.83 (0.73, 0.91)	>33.7	73%	86%	71%	88%	82%
Intact PINP, ng/mL	0.85 (0.74, 0.93)	>120.7	73%	94%	85%	89%	88%
TRAP5b, U/L	0.78 (0.66, 0.86)	>5.05	77%	76%	59%	88%	76%
BsAP + intact PINP	0.84 (0.74, 0.94)	As above	63%	97%	90%	85%	86%
BsAP + TRAP5b	0.79 (0.70, 0.88)	As above	63%	91%	76%	85%	82%
PINP + TRAP5b	0.84 (0.74, 0.94)	As above	82%	94%	88%	91%	90%
Low Turnover							
Biointact PTH, pg/mL	0.77 (0.65, 0.86)	<90.5	69%	52%	19%	91%	54%
Total AP, U/L	0.76 (0.63, 0.85)	<87	64%	57%	21%	90%	58%
BsAP, µg/L	0.82 (0.72, 0.90)	<24.2	87%	58%	28%	96%	63%
Intact PINP, ng/mL	0.83 (0.72, 0.91)	<49.8	80%	70%	33%	95%	72%
TRAP5b, U/L	0.84 (0.74, 0.91)	<3.44	73%	74%	34%	94%	74%
BsAP + intact PINP	0.84 (0.75, 0.93)	As above	73%	74%	34%	94%	74%
BsAP + TRAP5b	0.86 (0.79, 0.94)	As above	60%	81%	38%	92%	78%
PINP + TRAP5b	0.85 (0.77, 0.93)	As above	67%	77%	34%	93%	72%

AUC and cutoffs as determined by Liu's method¹¹ were calculated using the exploration cohort only. Sensitivity, specificity, NPV, and PPV were calculated for the validation cohort only, using the specified cutoffs. For combined biochemical markers, both markers were above/below the cutoff for a positive test result, while either above/below were counted as a negative test result. Abbreviations: AP, alkaline phosphatase; AUC, area under the receiver operator characteristics curve; BsAP, bone-specific alkaline phosphatase; NPV, negative predictive value; PINP, procollagen type I N-terminal propeptide; PPV, positive predictive value; PTH, parathyroid hormone; TRAP5b, tartrate-resistant acid phosphatase isoform 5b.

Figure 3. Biomarkers for high and low bone turnover in CKD patients

There is mounting evidence that bone turnover markers may also be useful in guiding mineral metabolism and osteoporosis therapy. Current interventions for high bone turnover include anti-

resorptive agents (bisphosphonates and denosumab) and measures to suppress PTH secretion (phosphate control, active vitamin D, calcimimetics, and parathyroidectomy). Options for a low bone turnover state comprise anabolic therapy (teriparatide and romosozumab) and measures to increase PTH secretion (decrease calcium load and reduce PTH targeting therapy). Besides pharmacological treatment, patients at risk should also be advised to consider lifestyle modification including adequate intake of key bone nutrients, weight-bearing exercises, multimodal exercise programs, moderation of alcohol consumption, and cessation of smoking.

Key points

1. Patients with advanced CKD have several times higher risk for bone fractures than the general population.
2. DXA is a non-invasive and reliable method to assess bone mineral density and bone quantity. Trabecular bone score complements DXA findings.
3. Bone histomorphometry is the gold standard for quantifying bone turnover and assessing bone quality. However, in practice, this invasive method is replaced by bone turnover biomarkers.
4. FRAX is an easy-to-use and well-evaluated tool to assess bone fracture risk and can be used to risk-stratify patients with non-dialysis CKD for major osteoporotic fractures and hip fractures.
5. Although the ability to predict the risk for bone fractures in CKD patients has improved over the last decades, more specific guidelines on screening and risk prevention are needed.

Further reading

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