Osteoporosis In Patients With Chronic Kidney Disease Diagnosis And Evaluation

Dr Mansour Salesi

- It is ***difficult*** to diagnose osteoporosis in the setting of chronic kidney disease (CKD).
- ***Aging population***: *fragility fractures*, *reduced GFR*, and *low BMD* are more prevalent.

- ***CKD-MBD definition***
- Changes in ***mineral metabolism*** and bone structure develop early in the course of CKD and *worsen with progressive loss of kidney function*.
- ***CKD-MBD includes***:
- *Abnormalities of calcium, phosphorus, PTH, FGF23, and vit-D metabolism*
- *Abnormalities in bone turnover, mineralization, volume, linear growth, or strength and/or vascular or other soft tissue calcification*

- ***Renal osteodystrophy:***
  - *Hyperparathyroid-mediated high turnover bone disease*
  - *Osteitis fibrosa cystica*
  - *Adynamic bone disease*
  - *Osteomalacia*
  - *Mixed uremic osteodystrophy*

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

Fracture Risk In Chronic Kidney Disease

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

- *End-stage CKD is associated with an increased risk of fragility (low trauma) fractures.*
- *The risk of fracture-related mortality increases with the severity of CKD*

- In a systematic review and meta-analysis of studies evaluating fracture risk in adults with estimated *GFR <60*, there was a *significant increase in hip* and *nonvertebral* fractures compared with eGFR ≥60, and fracture risk increased with decreasing eGFR.
- The exact mechanism for this greater fracture risk in CKD is *not clearly established*, but there are biological changes in bone metabolism that render the skeleton in patients with progressive CKD *(GFR stages G3 to G5) more fragile*

Vilaca T, Salam S, Schini M, et al. Risks of Hip and Nonvertebral Fractures in Patients With CKD G3a-G5D: A Systematic Review and Meta-analysis. Am J Kidney Dis 2020; 76:521

CKD classification based upon GFR and Albuminuria

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

GFR stages	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60 to 89	Mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)
Albuminuria stages	AER(mg/day)	Terms
A1	<30	Normal to mildly increased (may be subdivided for risk prediction)
A2	30 to 300	Moderately increased
A3	>300	Severely increased (may be subdivided into nephrotic and nonnephrotic for differential diagnosis, management, and risk prediction)

- In addition, the *greater risk of falls* in this population with ***sarcopenia*** and *frailty* may also contribute to the greater fracture risk.
- ***Other risk factors:***
  - *Glucocorticoid, Hypogonadism, Hyperprolactinemia, Poor nutrition, Vitamin D deficiency, Inactivity*

Assessment of fracture risk

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

Clinical risk factors for fracture independent of bone mineral density

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption
Rheumatoid arthritis
Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Fracture risk assessment tool

- ***Fracture Risk Assessment Tool (FRAX):***
- 10-year probability of hip fracture (3%)
- Major osteoporotic fracture (***hip, clinical spine, proximal humerus, or forearm***) (20%)
- *FRAX does not include any adjustment of risk according to GFR*

Bone mineral density: DXA

- BMD testing is ***not routinely performed*** to assess fracture risk in patients with CKD and ***eGFR <30***
- It may be obtained in selected patients with eGFR <30 who have fragility fracture and no evidence of CKD-MBD including renal osteodystrophy.

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) http://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf (Accessed on November 08, 2017).

- Although BMD is also lower in patients with CKD and fracture, it is unclear if BMD by DXA can be used to predict fracture in patients with the most advanced CKD

Predialysis CKD

- *In cross-sectional studies, BMD by DXA has been shown to be lower in patients with predialysis CKD with fracture compared with those who do not had*

West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. J Bone Miner Res 2015; 30:913.

Dialysis dependent

- *BMD is also lower in dialysis-dependent patients with fracture.*
- *Compared with patients without fracture, patients with fracture had significantly lower BMD at the lumbar spine and radial sites, but not at the femoral neck*

- In a subsequent study of Japanese dialysis patients, *low hip BMD* (DXA) was predictive of any type of incident fracture when the PTH was *below the median value* (204 pg/mL).
- However, the relationship between hip BMD and fracture was *not significant if the PTH was above 204* pg/mL.

Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients--a single-center cohort study. Nephrol Dial Transplant 2012; 27:345.

- *In patients with advanced **CKD and elevated PTH** levels, the bone density is lost primarily from the **cortical bone (radius)**, and it may be increased in the **cancellous bone (spine)**.*
- *DXA is unable to predict the type of bone lesion in dialysis-dependent patients.*

Ott SM. Review article: Bone density in patients with chronic kidney disease stages 4-5. Nephrology (Carlton) 2009; 14:395.

- *Interpretation of DXA may be **confounded** by the presence of **extraosseous calcification** and focal areas of **osteosclerosis**, which may lead to artifactual increase in BMD.*

Limitations of DXA

- DXA measures areal BMD, rather than volumetric BMD.
- It cannot distinguish between cortical and cancellous bone
- It cannot assess bone microarchitecture or bone turnover
- New technologies (high resolution microCT and microMRI, hip structural analysis, finite element analysis) have been developed that allow noninvasive, three-dimensional evaluation of bone microarchitecture.

WHO Criteria

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

Category	BMD
Normal	A value for BMD within 1.0 SD of the young adult female reference mean (T-score greater than or equal to -1.0).
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (T-score less than -1.0 and greater than -2.5).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to -2.5).
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

- *In this setting, a diagnosis of osteoporosis can only be made by excluding CKD-MBD, including renal osteodystrophy*
- *Furthermore, osteoporosis frequently coexists with CKD-MBD.*

Differences between CKD-MBD and postmenopausal osteoporosis

Clinical factor	CKD-MBD	Postmenopausal osteoporosis
PTH levels	Increased	Usually normal*
Alkaline phosphatase	Increased	Usually normal*
Bone mineral density	Weakly related to fracture risk	Predicts risk of fracture
Bone loss	Mostly in cortical bone	Trabecular and cortical bone
Bone formation rate	Either very low (in adynamic bone disease) or very high	Generally normal or slightly increased
Vascular calcification	Strongly associated	Weakly associated
Laboratory findings¶	Abnormal	Normal or mildly abnormal

Diagnostic Evaluation

- ***Osteoporosis versus CKD-MBD***
- *The exclusion of renal adynamic bone disease is most important.*
- *Adynamic bone disease is characterized by low osteoblastic activity and bone formation rates*

- **eGFR 30 to 60 mL/min/1.73 m²**
- With a history of a *fragility fracture* and/or *low BMD* (DXA T-score ≤-2.5), we initially measure:
- *Calcium, Phosphorus, Parathyroid hormone (PTH), 25-hydroxyvitamin D, Alkaline phosphatase*
- Who have *normal* initial biochemical tests, indicating the absence of coexisting CKD-MBD, we make the *diagnosis of osteoporosis* as in patients without CKD.

- Who have *abnormalities* on initial testing suggestive of *CKD-MBD*

- ***eGFR ≥30 mL/min/1.73 m²***

- *In patients with CKD and eGFR ≥30, the WHO criteria for BMD or the presence of a fragility fracture may be used for the diagnosis of osteoporosis,* ***assuming that there are no accompanying biochemical abnormalities (CKD-MBD).***

- ***eGFR <30 mL/min/1.73 m²*** : With a history of a *fragility fracture* and/or *low BMD* (DXA T-score ≤-2.5), we measure:
- *Bone-specific alkaline phosphatase (BSAP), Calcium, Phosphorus, PTH, 25-hydroxyvitamin D*
- Measurement of PTH and BSAP can be helpful in excluding the presence of adynamic bone disease.

- However, ***bone biopsy is the gold standard*** for establishing the type of renal bone disease since no combination of biochemical parameters is sufficiently accurate.
- Measurement of *1,25-dihydroxyvitamin D* is *not recommended*, because the values are not stable, the assay is expensive, and the serum does not reflect tissue levels.

- ***Interpretation of lab tests***
- ***Calcium, phosphorus, vitamin D***:
- *In the majority of patients, serum calcium and phosphorus typically remain normal until GFR declines below 25 to 40 mL/min/1.73 m^2.*
- In patients with more severe CKD, *hypercalcemia* may signal the possibility of *adynamic* bone disease. (calcium carbonate to treat hyperphosphatemia)
- However, other causes of hypercalcemia (*hyperparathyroidism*, *multiple myeloma*) should be considered

- *25-hydroxyvitamin D deficiency* is a common finding in predialysis patients with CKD and is associated with elevated PTH levels
- Calcitriol (1,25-dihydroxyvitamin D) levels begin to fall when the GFR is less than 40.
- Calcitriol production is also reduced by *phosphate retention* and elevated levels of *FGF23*.

- ***Parathyroid hormone***
- A serum ***intact PTH*** (1-84) that is *nine times* (eg, 585 pg/mL) or more above the upper limit of the normal range is usually associated with histomorphometric features of *osteitis fibrosa cystica*.
- Very *low PTH* levels (<100 pg/mL) are usually associated with *adynamic bone disease*.
- If PTH levels are *modestly elevated* (eg, >150 pg/mL), they are not predictive of underlying bone disease.

- *In the absence of bone biopsy, PTH levels are the best available parameter to identify the extremes of bone turnover.*
- The ability of serum PTH to predict *adynamic bone disease* is predicated on the basis that the PTH synthesis is not being blunted by any pharmacologic agent (*vitamin D analogues*, or *cinacalcet*.)

Causes of secondary hyperparathyroidism

- ***Chronic kidney disease***
  - *Impaired calcitriol production*
  - *Hyperphosphatemia*
  - *Hypocalcemia*
- ***Calcium malabsorption***
  - *Vitamin D deficiency*
  - *Bariatric surgery*
  - *Celiac disease*
  - *Pancreatic disease (fat malabsorption)*
- ***Inhibition of bone resorption***
  - *Bisphosphonates*
  - *Denosumab*
- ***Hungry bone syndrome***
- ***Decreased calcium intake***
- ***Renal calcium loss***
  - *Idiopathic hypercalciuria*
  - *Loop diuretics*

Bone-specific alkaline phosphatase

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

- ***In clinical practice, the marker that has the most value in discriminating bone turnover in CKD is BSAP.***
- *In particular, a high BSAP may be helpful in excluding the presence of adynamic bone disease.*
- The combination of ***intact PTH*** and ***BSAP*** was slightly better able to discriminate bone turnover than BSAP alone.

Causes Of Elevated Bone-specific Alkaline Phosphatas

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

- Severe hyperparathyroidism
- Hyperthyroidism
- Paget disease of bone
- Metastatic carcinoma to bone
- Osteomalacia
- Severe 25-hydroxyvitamin D deficiency (<10 ng/mL)
- Recent large bone fracture
- Immobilization/space travel
- Treatment with teriparatide or 1-84 parathyroid hormone
- High bone turnover osteoporosis

- *Other markers of bone turnover used in the assessment and management of osteoporosis are not useful in the assessment and management of CKD-MBD.*
- Biochemical marker of bone resorption (***CTX***), and marker of bone formation, serum propeptide type I collagen (***PINP***), are both cleared by the kidney.
- The only available biochemical markers that are *not cleared* by the kidney are ***BSAP***, tartrate resistant acid phosphatase (***TRAP5b***), and the *trimer* form of ***PINP***.

Bone turnover markers

- ***Resorption markers***
  - *Type I collagen degradation products*
  - *Pyridinium crosslinks (PYD and DPD)*
  - *C- and N-telopeptides (CTX, ICTP, NTX)*
- ***Enzymes***
  - *Tartrate-resistant acid phosphatase (TRACP) 5b**
  - *Cathepsin K*
  - *Matrix metalloproteinases (MMPs)*
- ***Formation markers***
  - *Matrix proteins*
    - *Procollagen type I propeptides*
    - *C-terminal (PICP)*
    - *N-terminal (PINP)**
    - *Osteocalcin (OC)*
- ***Enzymes***
  - *Bone isoform of alkaline phosphatase (BALP)**

CKD-MBD
Chronic Kidney Disease Mineral and Bone Disorder

Bone biopsy

- Most clinicians ***do not perform*** bone biopsies outside *clinical research*.
- *Bone biopsy is particularly important in patients for whom a specific diagnosis of bone disease has significant management implications*
- ***The presence of renal osteodystrophy suggests more complex physiological abnormalities, and the traditional pharmacologic agents used in osteoporosis may not be effective or safe***

- *In particular, in clinical settings where a management decision must exclude adynamic bone disease and biochemical testing is not helpful in differentiating among the bone disorders, bone biopsy should be performed.*