Bone health in rheumatologic disease with kidney involvement

Dr Mehrdad Aghaei
Rheumatologist

- Renal impairment in rheumatic disease leads to a clinical syndrome termed CKD-MBD(chronic kidney disease-mineral and bone disorder)

CKD-MBD

- Is not a primary disease itself, but rather a systemic complication of chronic kidney disease (CKD) characterized by abnormalities in:

  Calcium, phosphate, parathyroid hormone (PTH), or vitamin D metabolism

  Bone turnover, mineralization, or volume

  Vascular or soft-tissue calcification.

Rheumatologic diseases that can lead to CKD (and thus CKD-MBD)

1. Systemic Lupus Erythematosus (SLE)
- Lupus nephritis can cause chronic kidney damage → CKD → CKD-MBD.
- One of the most common rheumatologic causes of CKD.

2. Rheumatoid Arthritis (RA)
- CKD may result from chronic inflammation, secondary amyloidosis, or nephrotoxic medications (e.g., NSAIDs, methotrexate, cyclosporine).
- Long-standing RA with CKD can develop CKD-MBD.

3. Systemic Sclerosis (Scleroderma)
- Scleroderma renal crisis or chronic vascular damage may lead to CKD → CKD-MBD.

4. Vasculitides (e.g., ANCA-associated vasculitis, polyarteritis nodosa)
- These can directly cause glomerulonephritis and kidney injury leading to CKD and subsequent CKD-MBD.

5. Chronic gout (less common mechanism)
- Uric acid nephropathy or nephrolithiasis may cause CKD, which can then progress to CKD-MBD.

Key Mechanisms

- CKD-MBD Axis:

Renal dysfunction leads to CKD-MBD, characterized by impaired phosphorus clearance, reduced vitamin D activation, hypocalcemia, and hyperphosphatemia.

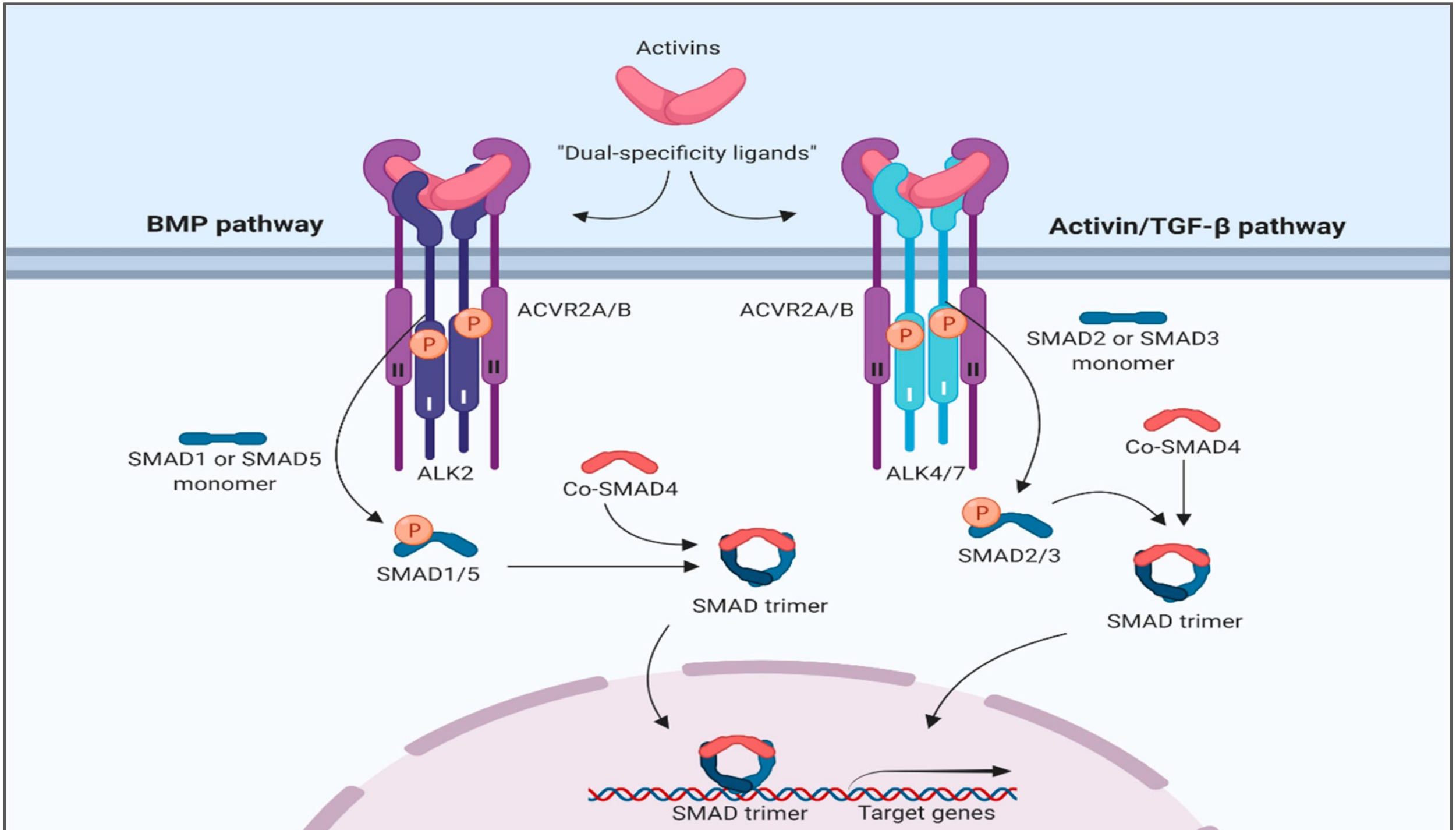
These changes induce secondary hyperparathyroidism and metabolic acidosis, which together promote bone mineral loss (renal osteodystrophy), extraosseous calcification, and defective bone remodeling.

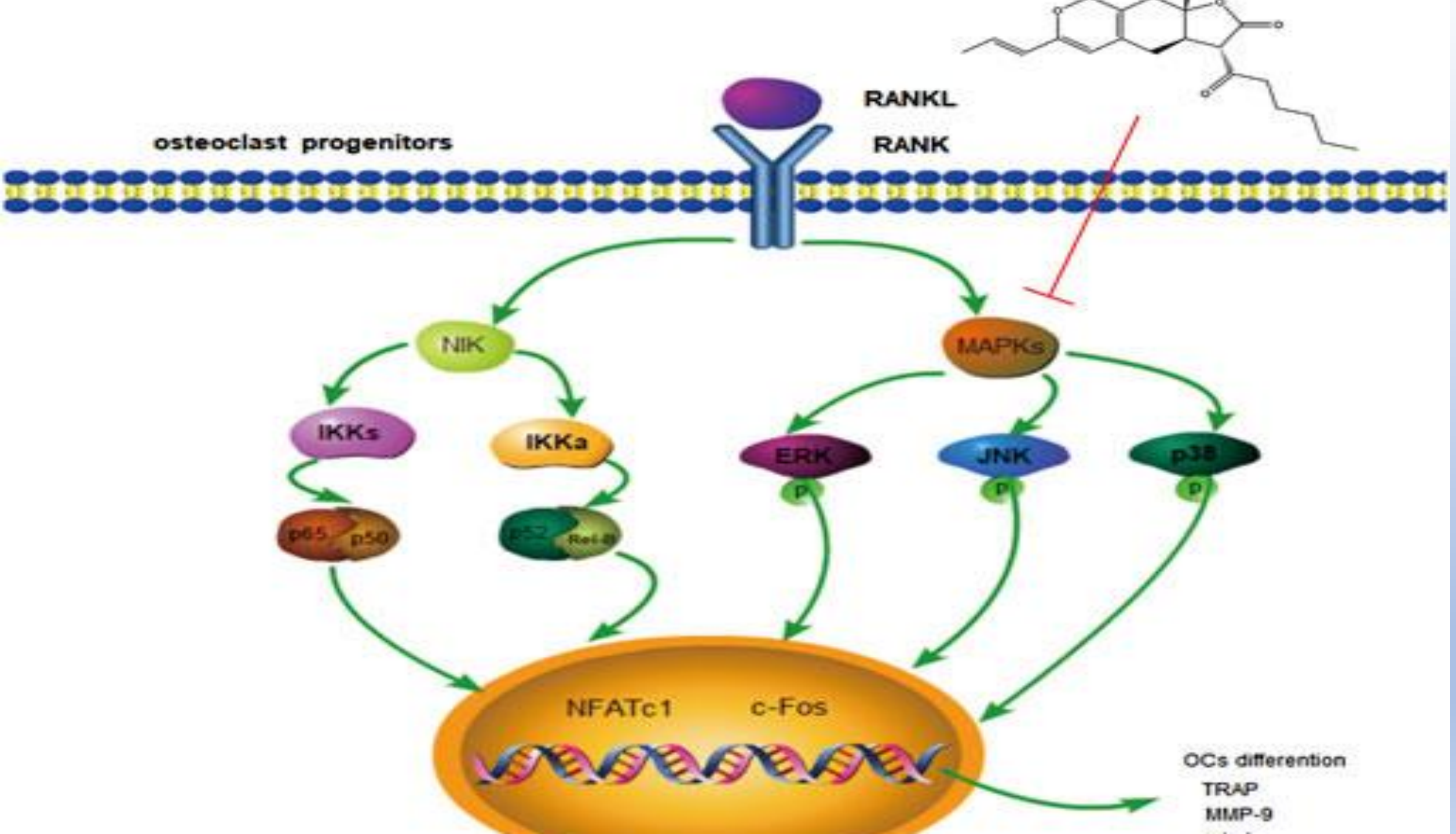
Inflammatory Cytokines and Immune Dysregulation:

- Rheumatic diseases (e.g., RA, SLE, vasculitides) cause persistent elevation of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) that activate osteoclasts and inhibit osteoblasts, contributing to both localized and systemic bone loss.
- Chronic inflammation and immune cell activation increase RANKL production by osteoblasts and T cells, amplifying osteoclastogenesis and bone resorption.
- Autoantibodies (ACPAs, antiphospholipid) and microvascular damage contribute to bone fragility.

Hormonal and Molecular Pathways:

- CKD elevates sclerostin and FGF23, both of which suppress Wnt/β-catenin signaling and reduce osteoblast activity.
- Activin A/Smad and RANKL/c-Fos pathways promote osteoclast differentiation and function, further impairing bone formation and structure.


Activins
"Dual-specificity ligands"
BMP pathway
Activin/TGF-β pathway
ACVR2A/B
ACVR2A/B
P
P
P
P
II
II
II
II
ALK2
ALK4/7
SMAD1 or SMAD5
monomer
SMAD2 or SMAD3
monomer
Co-SMAD4
Co-SMAD4
P
P
SMAD1/5
SMAD2/3
SMAD trimer
SMAD trimer
SMAD trimer
Target genes


RANKL
RANK
osteoclast progenitors
NIK
IKKs
IKKa
MAPKs
ERK
JNK
p38
P
P
P
p65
p50
NFATc1
c-Fos
OCs differention
TRAP
MMP-9

Drug-Induced and Secondary Factors

- Glucocorticoids: ↓ osteoblasts, ↑ resorption; early bone loss within months.
- Calcineurin inhibitors (CyA, Tac): promote resorption via RANKL.
- Cyclophosphamide, Methotrexate: may impair osteoblast differentiation.
- Biologics: TNF and IL-6 blockade may partially reverse inflammatory bone loss.

Other contributors:

- Malnutrition, low Vitamin D due to photosensitivity in lupus.
- Sarcopenia, immobility, and frailty.
- Metabolic acidosis in CKD promoting bone buffering.

Osteoporosis

- Osteoporosis is a common disease that is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture, particularly at the spine, hip, wrist, humerus, and pelvis .

- It is difficult to diagnose osteoporosis in the setting of chronic kidney disease (CKD).

- End-stage CKD is associated with higher risk of fragility fractures
- Fracture-related mortality risk increases with CKD severity

systematic review/meta-analysis of eGFR <60 vs ≥60

- Hip fractures: RR ≈ 2.36 (95% CI 1.64–3.39)
- Nonvertebral fractures: RR ≈ 1.47 (95% CI 1.15–1.88)

- Lower eGFR = higher risk Fx

In a Canadian healthcare database: decreasing eGFR linked to higher 3-year fracture incidence

- Females >65: fracture incidence by eGFR strata
  - G2 ≥60. : 4.3%
  - G3a 45–59 : 5.8%
  - G3b 30–44 : 6.5%
  - G4 15–29 : 7.8%
  - G5 <15. : 8.6%
- Males: corresponding incidences are lower but rise with CKD

Assessment of fracture risk

- The assessment of fracture risk includes evaluation of clinical risk factors for fracture , and, in most patients, measurement of bone mineral density (BMD) using dual-energy x-ray absorptiometry (DXA).

Clinical risk factors for fracture independent of bone mineral density

inical 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)

a from: Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005; 16:581.

phic 76445 Version 4.0

Fracture risk assessment tool

- FRAX estimates 10-year risk of hip and major osteoporotic fractures in adults 40-90 years.

- Utilizes clinical risk factors ± femoral neck BMD (DXA) for untreated patients.

- Validated in the general population; easy to apply in clinical settings

Questionnaire

1. Age (between 40 and 90 years) 57

2. Sex ○ Female ● Male

3. Weight kg 76 kg / cm

4. Height cm 180

5. Previous Fracture X

6. Parent Fractured Hip X

7. Current smoking X

8. Glucocorticoids X

9. Rheumatoid arthritis X

10. Secondary osteoporosis X

11. Alcohol 3 or more X

12. Femoral neck BMD Select BMD

Calculate Clear

FRAX

Home | Online Calculation | FRAXplus® | Paper Charts | About | FAQ | References | My FRAX®

English

Calculation Tool

Please answer the questions below to calculate the ten-year probability of fracture with or without BMD.

Continent Middle East & Africa **Country** Iran

Local Reference Reference (optional)

About the risk factors

Individuals with fracture risk assessed since 1st June 2011 : 233,489

Questionnaire

1. Age (between 40 and 90 years) 57

2. Sex Female Male

3. Weight kg 76 kg / cm

12. Femoral neck BMD Select BMD

Calculate Clear

FRAX Performance and Limitations in CKD

- FRAX does not directly adjust risk based on glomerular filtration rate (eGFR).
- Predicts fracture risk reliably in CKD stages G1–G3b, but underestimates risk in advanced CKD (G4–G5D).
- Does not capture CKD-specific factors (e.g., renal osteodystrophy, secondary hyperparathyroidism, falls).
- Interpretation requires clinical judgment—actual risk often exceeds FRAX estimate in advanced CKD.

Practical Application and Clinical Recommendations

- Use FRAX as a baseline tool for CKD patients, especially with added BMD data.
- For CKD G3b–G5, consider "up-adjusting" risk or combining with biochemical, clinical, and bone turnover data.
- Always integrate FRAX with clinical context (e.g., history of falls, fracture, bone quality abnormalities).

Bone Mineral Density (BMD) Assessment in Chronic Kidney Disease (CKD)

BMD Testing in CKD: Overview

- BMD measurement using DXA is standard for diagnosing osteoporosis and assessing fracture risk in the general population.

- In CKD, the predictive value of BMD varies depending on eGFR level and presence of CKD-MBD.

Indications for DXA in CKD

- For eGFR ≥30 mL/min/1.73 m² and clinical risk factors for fracture → DXA may be used to assess fracture risk.

- For eGFR <30 mL/min/1.73 m², BMD testing not routinely recommended, except in:

- Patients with fragility fracture

- No evidence of CKD-MBD or renal osteodystrophy

- When osteoporosis therapy is being considered

Monitoring Therapy

- In selected CKD patients (eGFR <30 mL/min/1.73 m^2) on osteoporosis therapy:

- Baseline and 2-year BMD (hip and lumbar spine) assessment may guide response.

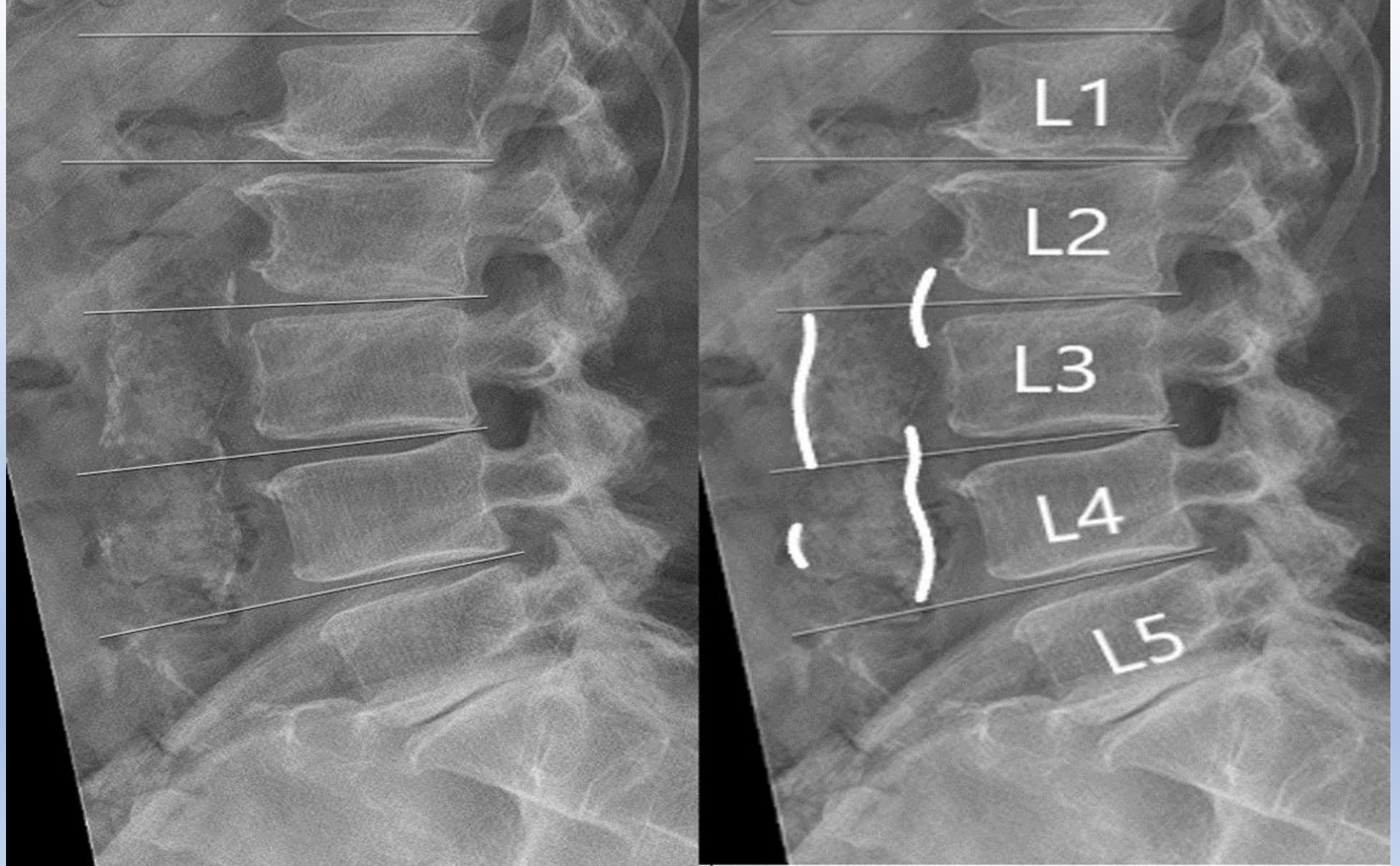
- Monitoring consistent with KDIGO and 2021 ERA-EDTA CKD-MBD consensus.

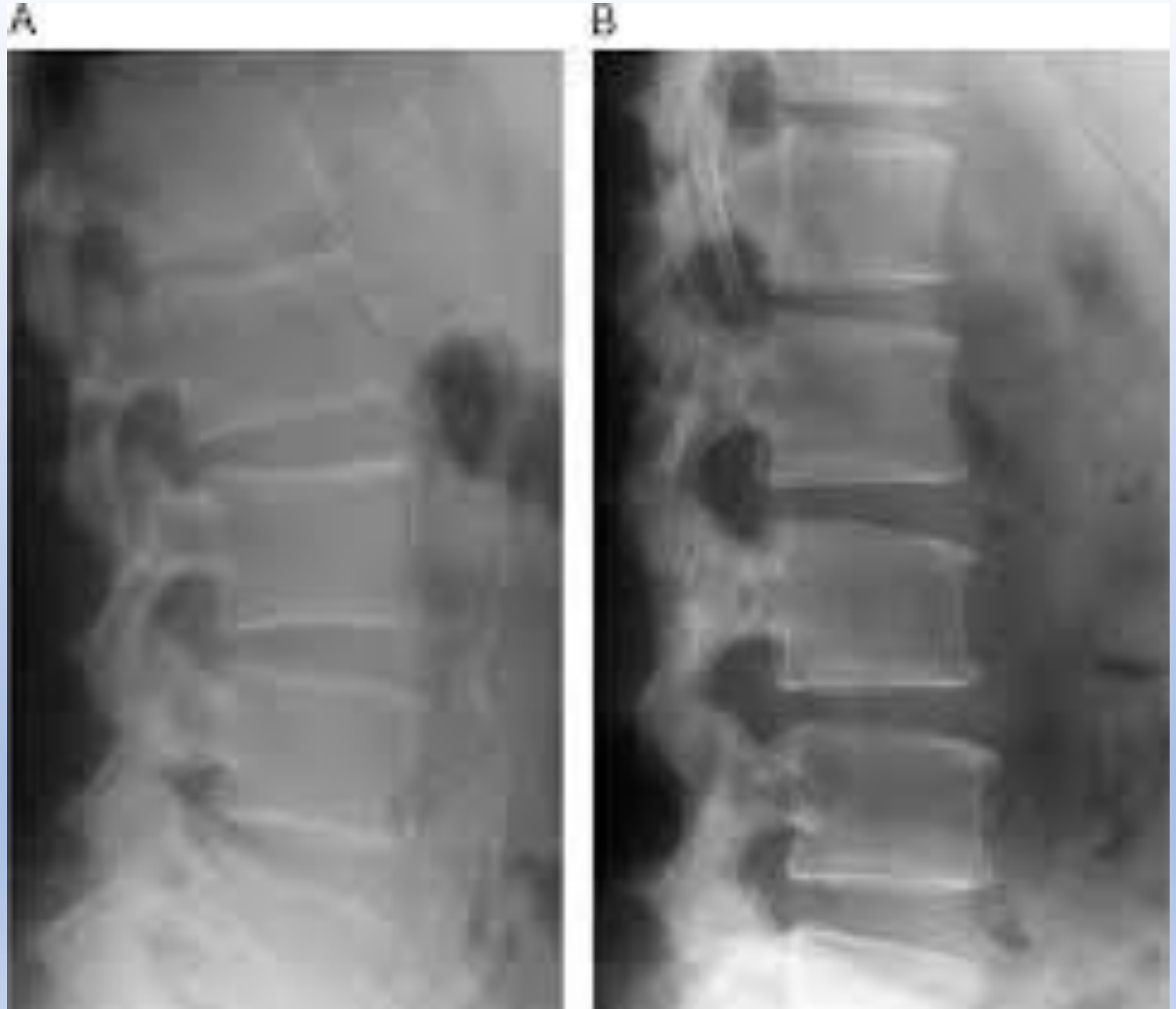
Limitations of DXA in CKD

- **In dialysis-dependent CKD:**
- DXA cannot distinguish bone lesion types (e.g., renal osteodystrophy).

- Bone diseases may share similar T-scores despite distinct histomorphologic patterns.

- Artifacts and confounders:
- Extraosseous calcifications and osteosclerosis may falsely increase measured BMD.


L1
L2
L3
L4
L5


A
B

Diagnostic categories for osteoporosis and low bone mass based upon BMD measurement by DXA

Diagnostic categories for osteoporosis and low bone mass based upon BMD measurement by DXA

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.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.

Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007.

Graphic 74190 Version 10.0

When eGFR <30 mL/min/1.73 m2 and history of fragility fracture or DXA T-score ≤ -2.5:

- Measure: BSAP, Calcium, Phosphorus, PTH, 25-hydroxyvitamin D
- PTH and BSAP help characterize bone turnover and help exclude adynamic bone disease
- Bone biopsy remains the gold standard for definitive renal osteodystrophy typing

What not to measure (and why)

- Do not rely on 1,25-dihydroxyvitamin D for routine assessment:
  - Not stable, expensive, serum does not reflect tissue levels
  - Focus on 25-hydroxyvitamin D status and PTH trends instead

Interpreting calcium, phosphorus, and vitamin D

- Calcium and phosphorus:
  - Serum calcium and phosphorus often normal until GFR falls below 25–40 mL/min/1.73 m2
  - Hypercalcemia in CKD may indicate adynamic bone disease or other causes (hyperparathyroidism, myeloma)

25-hydroxyvitamin D:

- Deficiency common in predialysis CKD and can worsen secondary hyperparathyroidism

- Calcitriol (1,25-dihydroxyvitamin D):
  - Levels fall with GFR <40 mL/min/1.73 m2 and are markedly reduced in end-stage CKD
  - Reduced by phosphate retention and high FGF23

Interpreting PTH (parathyroid hormone)

- PTH as a surrogate for bone turnover extremes:
  - Very high PTH (e.g., >9x ULN, ~585 pg/mL) suggests osteitis fibrosa cystica
  - Very low PTH (<100 pg/mL) suggests adynamic bone disease
  - Modestly elevated PTH (>150 pg/mL) alone is not predictive of bone type
-

- PTH alone has suboptimal discrimination for turnover when used in isolation (AUROC < 0.8)
- KDIGO approach: use PTH trends over absolute targets to guide treatment
- Important caveat: elevated PTH in CKD is not automatically due to CKD; assess for other causes of secondary hyperparathyroidism
-

Role of bone turnover markers

- PTH and BSAP can help infer turnover and screen for adynamic bone disease
- If bone biopsy is not feasible, use PTH trends and BSAP to stratify turnover risk
- Interpretation should consider potential pharmacologic effects (vitamin D analogues, cinacalcet) that blunt PTH synthesis

Practical workflow in CKD patients with fracture risk

- Step 1: Confirm CKD stage and retrieve bone health history (fragility fracture, DXA)
- Step 2: Order BSAP, calcium, phosphorus, PTH, 25-hydroxyvitamin D
- Step 3: Assess PTH trends over time rather than single value
- Step 4: Evaluate for secondary causes of elevated PTH (multifactorial osteoporosis in CKD)
- Step 5: If uncertainty remains about turnover type, consider bone biopsy
- Step 6: Tailor osteoporosis treatment to turnover phenotype and CKD stage
-

Important considerations for treatment planning

- Be cautious with treatments that affect bone turnover in CKD (e.g., CKD-MBD therapies)
- Address vitamin D deficiency or insufficiency to help modulate PTH and bone health
- Manage phosphate levels to reduce secondary hyperparathyroidism
- Consider non-pharmacologic measures: fall prevention, nutrition, exercise as CKD and fracture risk co-manage

Quick reference (lab interpretation cheat sheet)

- High PTH (very high): common in high bone turnover (osteitis fibrosa); consider turnover-directed therapy
- Very low PTH: suggestive of adynamic bone disease
- Modest PTH elevation: not definitive for turnover type; rely on trends and BSAP
- BSAP elevated: higher bone formation activity; supports high turnover in the right context
- 25(OH)D low: treat deficiency to help secondary hyperparathyroidism
- 1,25(OH)2D low: expected with CKD; focus on 25(OH)D and PTH management
-

Key Takeaways

- DXA is useful in early to moderate CKD (eGFR ≥30).
- Selective use in advanced CKD without CKD-MBD and with clinical fracture evidence.
- Interpretation requires caution due to renal bone disease heterogeneity and imaging artifacts.
- Further studies needed to refine fracture prediction in end-stage CKD.