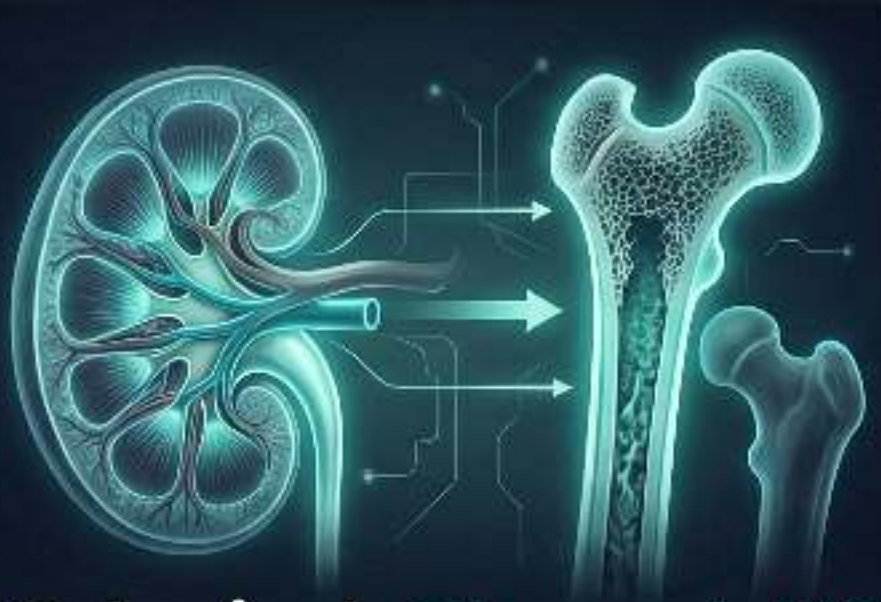
Management of Bone Disease After Kidney Transplantation

Evidence-Based Strategies for Pre-Transplant Assessment, PTH Monitoring, and Fracture Risk Evaluation



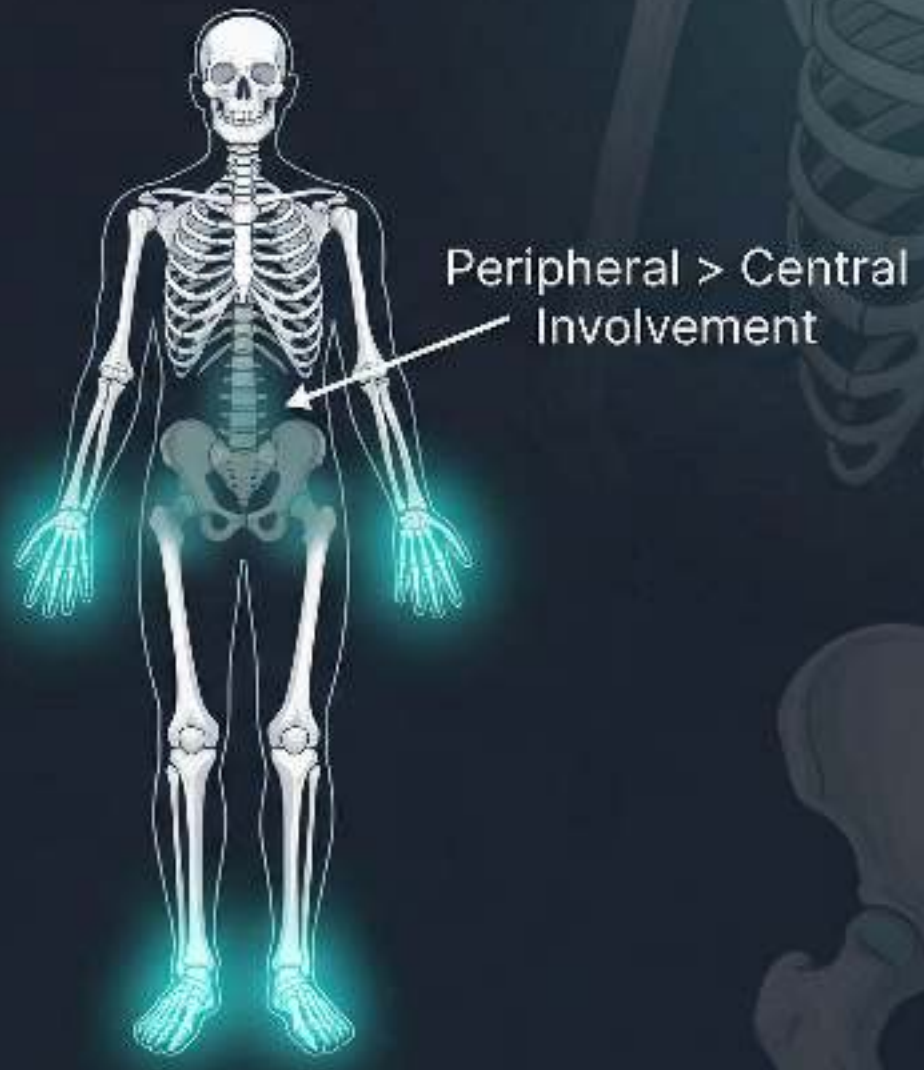
By Dr. Zakariyah ELsayed, MSc, MD

What You Will Learn Today

- Understand the pathophysiology of post-transplant bone disease
- Identify essential pre-transplant investigations and their clinical significance
- Recognize the critical role of PTH assay before and after transplantation
- Apply osteoporosis risk scoring systems (FRAX, TBS) in clinical practice
- Implement evidence-based treatment strategies to reduce fracture risk

Major Bone Diseases After Transplant

- Osteoporosis
- Osteonecrosis
- Dialysis-related Amyloidosis
- Renal Osteodystrophy



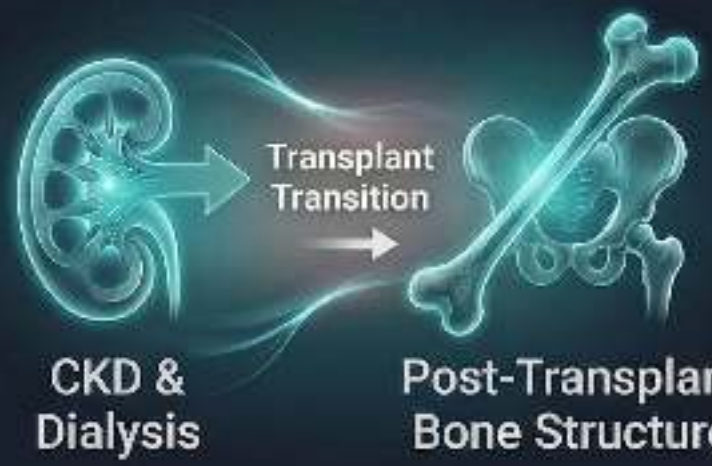
Fracture Risk is 4-Fold Higher in Kidney Transplant Recipients

- Post-transplant bone disease is a major clinical challenge.
- Annual fracture risk: **2-3% per year** in KTRs.
- Hip fracture rate: **3.3 per 1000** person-years.
- **34% higher** hip fracture risk vs. dialysis patients awaiting transplant.
- Fractures are associated with increased mortality, morbidity, and healthcare costs.

Post-Transplant Bone Disease Has Multiple Contributing Factors

Pre-Existing Factors

- Secondary hyperparathyroidism (CKD)
- Vitamin D deficiency/resistance
- Accumulated bone damage (dialysis)



Post-Transplant Factors

- Glucocorticoid-induced bone loss
- Calcineurin inhibitor effects
- Persistent hyperparathyroidism
- Hypophosphatemia

Bone Loss is Most Rapid in the First 6-12 Months Post-Transplant

Key Insight: Rapid early bone loss underscores the importance of pre-transplant assessment and early intervention.

SECTION 1

Pre-Transplant Evaluation

Establishing the Foundation for Post-Transplant Bone Health

Comprehensive Biochemical Panel is Essential Before Transplantation

KDIGO 2017 Recommendations for Baseline CKD-MBD Status

Key Investigation	Clinical Significance
Serum Calcium	Detect hyper/hypocalcemia
Serum Phosphate	Assess mineral metabolism
PTH	Severity of SHPT
25(OH) Vitamin D	Identify deficiency
Alkaline Phosphatase	Bone turnover marker
Serum Albumin	Calcium correction

Bone Turnover Markers in ESKD

Biochemical Marker	Mean ± SD
Bone-specific Alkaline Phosphatase (BALP)	3663.5 ± 806.7 ng/dl
Propeptides of Type I Procollagen (P1NP)	0.201 ± 0.069 µg/L
Tartrate-Resistant Acid Phosphatase (TRAP-5b)	2.58 ± 0.91 ng/ml

Interpretation: Markedly elevated markers indicate high bone remodeling activity.

KDIGO 2017 Now Recommends BMD Testing in CKD Patients

2009 Guideline

BMD testing NOT routinely recommended (thought not to predict fractures).

2017 Guideline Update (Grade 2B)

In patients with CKD G3a-G5D... we suggest BMD testing to assess fracture risk if results will impact treatment decisions.

Recommended Sites

Hip (strongest value)

Lumbar Spine (L1-L4)

Distal Radius

Prevalent Vertebral Fractures Are Often Silent But Highly Predictive

- Vertebral fractures are common in CKD and often asymptomatic.
- Strong predictor of future fractures, independent of BMD.

Key Evidence (Velioglu et al. 2021):

- 43.4% prevalence in KTRs
- Many previously undiagnosed
- Steroid use: significant risk factor

Recommendation: Consider lateral spine imaging (VFA) in high-risk patients.

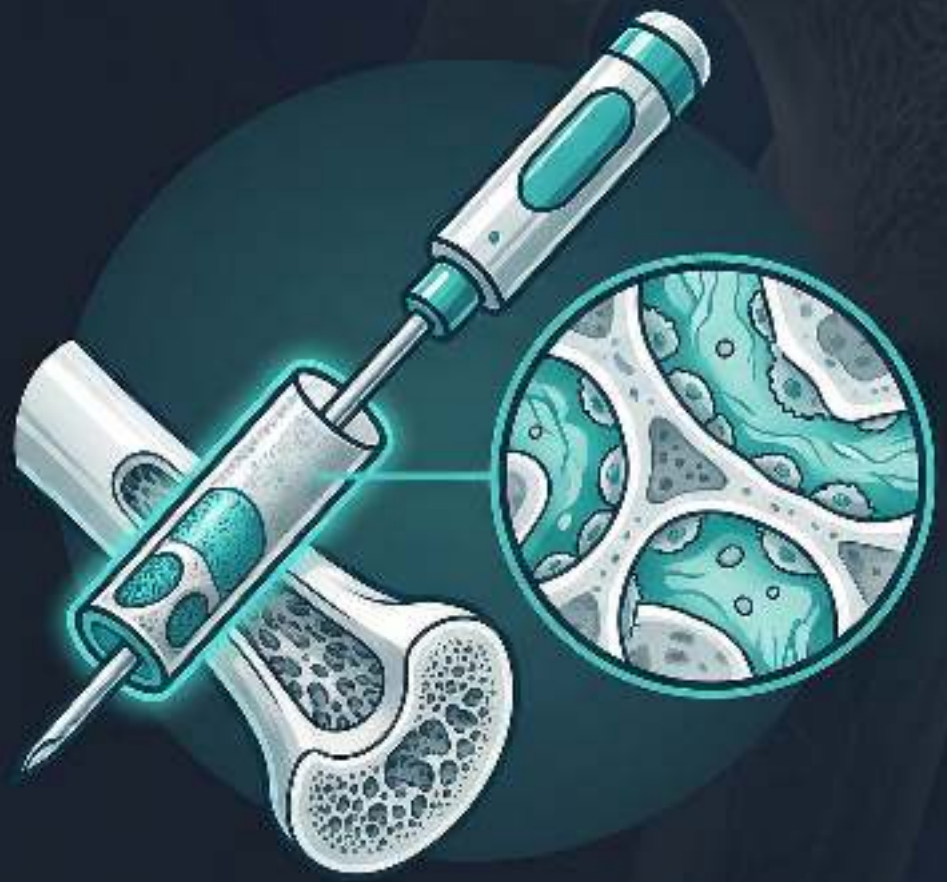
Bone Biopsy Remains the Gold Standard for Diagnosing Renal Osteodystrophy Type

Definitive Diagnosis:

- The only method to distinguish between:
  - High-turnover (osteitis fibrosa)
  - Low-turnover (adynamic bone disease)
  - Mixed uremic osteodystrophy
  - Osteomalacia

When to Consider Biopsy:

- Before initiating antiresorptive therapy (crucial to avoid worsening adynamic bone).
- Unexplained fractures despite normal BMD.
- Suspected adynamic bone disease.
- When histological findings will directly impact treatment decisions.



SECTION 2

The Role of PTH Assay

A Critical Biomarker Before and After Transplantation

Pre-Transplant PTH Establishes Baseline SHPT Severity

- **Clinical Utility:**
  - Document baseline SHPT severity
  - Guide medical therapy decisions
  - Inform parathyroidectomy considerations
  - Predict post-transplant PTH trajectory

- **KDIGO Target (CKD G5D):**

🎯 PTH levels should be maintained at **2-9 times** the upper limit of normal for the assay.

Severe Pre-Transplant Hyperparathyroidism Does NOT Preclude Successful Transplantation

Evidence from Rodrigues et al. 2024 (n=1,576)

Traditional Belief

✕ Severe SHPT is a barrier to transplantation.

New Evidence

✓ Severe pre-transplant hyperparathyroidism (PTH ≥771 pg/mL) was **NOT associated with:**

- Delayed graft function (HR 0.56)
- Death-censored graft failure (HR 1.01)
- All-cause mortality (HR 0.56)

Clinical Implication: A deceased donor allograft should not be refused solely due to uncontrolled hyperparathyroidism.

PTH at 3 Months Post-Transplant is the Critical Fracture Risk Predictor

Contrast

- Unlike pre-transplant levels, post-transplant PTH is a powerful predictor of outcomes.

Natural History

- PTH typically decreases significantly in the first 3 months.
- However, hyperparathyroidism persists in 20-50% at 1 year.

The Critical Window

- The 3-month time point is essential for risk stratification.

Key Insight

- PTH levels at this time strongly predict long-term fracture risk.

PTH >130 ng/L at 3 Months Carries 7.5-Fold Increased Fracture Risk

Landmark Evidence: Perrin et al. (Am J Transplant 2013)

Study Design

- Longitudinal study of 143 KTRs with 5-year follow-up.

Key Finding

- PTH >130 ng/L at 3 months identified as optimal threshold (ROC AUC 0.711).

7.5x

HR 7.5

Adjusted Hazard Ratio

Structured PTH Monitoring Enables Timely Intervention

2-4 Weeks:
- PTH, Ca, PO4 (Assess initial response)

3 Months (CRITICAL):
- PTH >130 ng/L indicates High Risk. Trigger for management decisions.

6 Months:
- PTH, Ca, PO4, 25(OH)D (Evaluate persistence)

12 Months:
- Full panel + DXA (Determine intervention need)

Annually:
- Surveillance based on CKD stage

SECTION 3

Osteoporosis Risk Scoring Systems

FRAX, TBS, and Integrated Risk Assessment

FRAX Calculates 10-Year Fracture Probability Using Clinical Risk Factors

Purpose: Estimates **10-year probability** of **Major Osteoporotic Fracture (MOF)** and **Hip Fracture.**

****Key Clinical Risk Factors:****

- Age, Sex, BMI
- Previous Fracture
- Parental Hip Fracture
- Current Smoking
- Glucocorticoid Use
- Rheumatoid Arthritis
- Secondary Osteoporosis
- Alcohol Intake (≥3 units/day)
- BMD (Optional)

Note: Country-specific algorithms available.

FRAX Identifies High-Risk Patients Not Detected by T-Score Alone

Naylor et al. 2014

- 19.0% of KTRs met treatment criteria.
- **Crucial Finding:** High-risk patients identified by FRAX were often missed by T-scores alone.

Velioglu et al. 2021

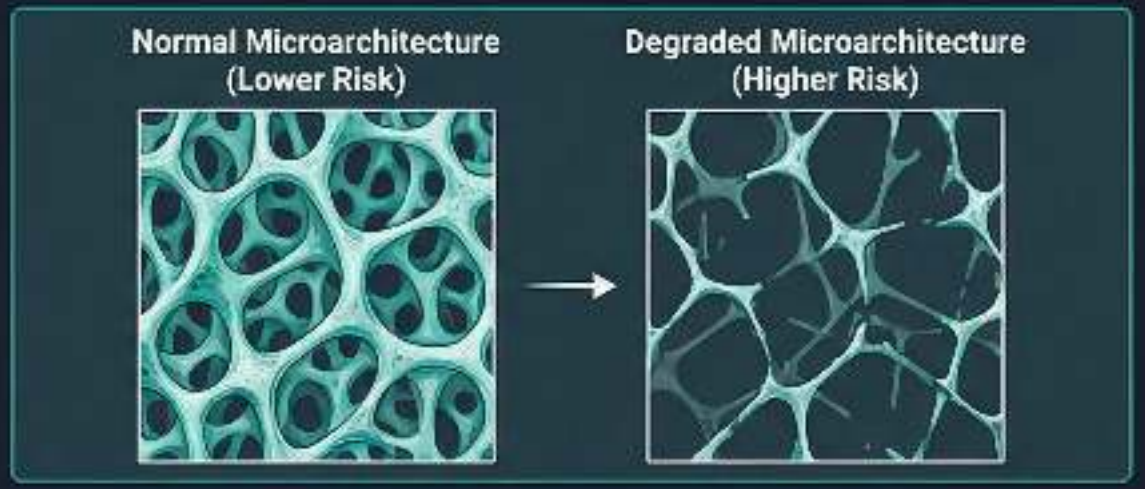
- 23.5% of KTRs had high hip fracture probability (≥3%).

Durak et al. 2024 (Proposed KTR Thresholds)

- MOF **≥3.4%** = **High Risk**
- Hip Fracture **≥0.4%** = **High Risk**

Trabecular Bone Score (TBS) Measures Bone Quality Independent of BMD

- **Definition:** TBS is a textural analysis of lumbar spine DXA images that assesses bone microarchitecture.
- **Key Distinction:** Measures bone **quality** (microarchitecture) vs. BMD which measures bone **quantity**.
- **Advantage:** Provides independent fracture risk prediction.



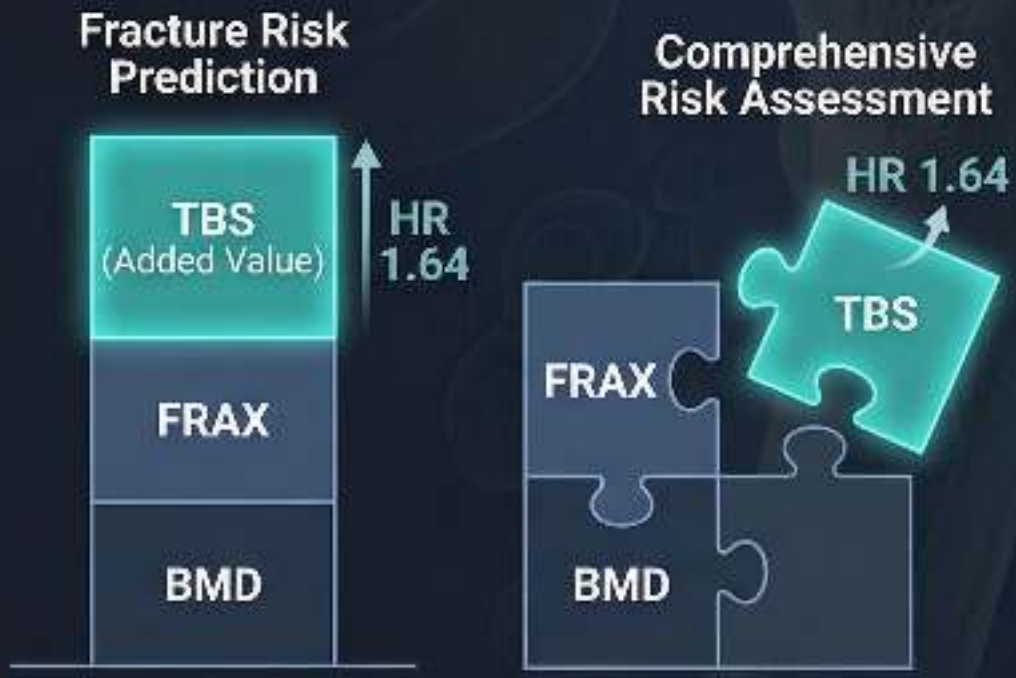
TBS Interpretation		
TBS Value	**Microarchitecture**	**Fracture Risk**
>1.350	Normal	Lower Risk
1.200 - 1.350	Partially Degraded	Intermediate Risk
<1.200	Degraded	Higher Risk

Lower TBS Predicts Fractures Independent of BMD and FRAX

Evidence from Naylor et al. 2016 (n=327 KTRs)

Key Findings:

- KTRs had significantly lower TBS vs. controls (1.365 vs. 1.406, $p<0.001$).
- TBS predicted fractures **independent** of FRAX score and BMD.
- **Adjusted HR per SD decrease in TBS: 1.64** (95% CI 1.15-2.36)



Clinical Implication:

TBS adds prognostic value beyond BMD and should be considered in comprehensive risk assessment.

Combining Multiple Tools Provides the Most Comprehensive Risk Assessment

Tool	Measures	Strength	Limitation
DXA BMD	Quantity	Gold Standard	No quality info
FRAX	10-yr Probability	Clinical Factors	Not KTR-validated
TBS	Microarchitecture	Independent of BMD	Requires software
PTH	Turnover	Strong Predictor	Single marker

Recommended Approach: Combine DXA BMD + FRAX + TBS + PTH for comprehensive fracture risk stratification.

SECTION 4

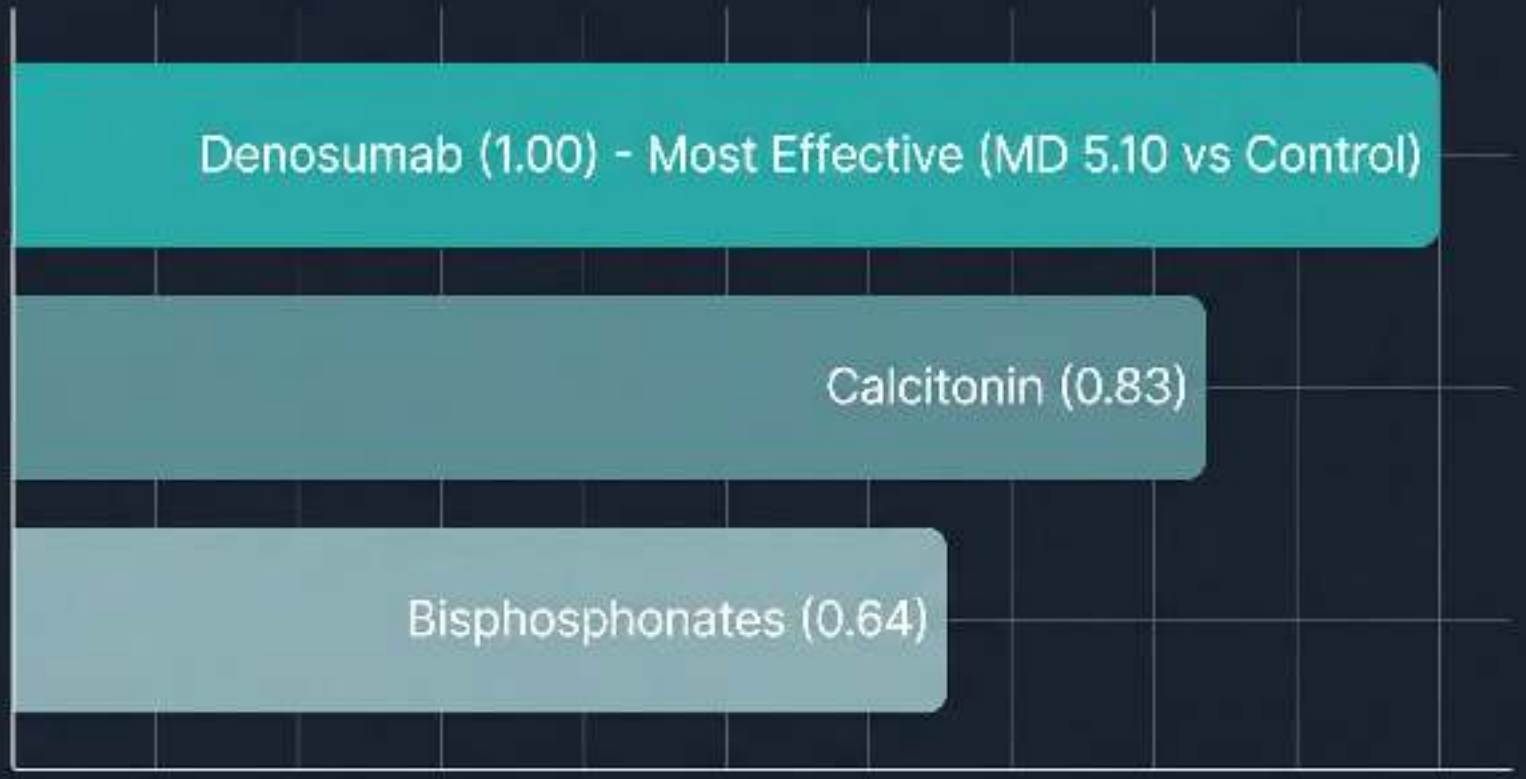
Evidence-Based Treatment Strategies

Pharmacological and
Non-Pharmacological Interventions

Denosumab is Most Effective for Lumbar Spine BMD in KTRs

2025 Network Meta-Analysis (Liu et al.) - 21 RCTs, 1,066 Participants

Lumbar Spine BMD Efficacy (P-Score Ranking)



Femoral Neck BMD

- Calcitonin ranked highest (P-Score 0.89)
- Bisphosphonates showed significant benefit vs control

Safety

No significant differences in adverse events between interventions.

Indications for Parathyroidectomy in Kidney Transplant Recipients

Primary Indications:

- **Persistent Hypercalcemia:** Serum Calcium >11.5 mg/dL (>2.9 mmol/L) or symptomatic hypercalcemia.
- **Progressive Bone Loss:** Significant decline in BMD despite medical therapy.
- **Symptomatic Disease:** Bone pain, pruritus, or unexplained fractures.
- **Calciphylaxis:** Rare but urgent indication.
- **Refractory Hyperparathyroidism:** Persistently elevated PTH (>800 pg/mL) unresponsive to calcimimetics/Vitamin D after >12 months.

Timing Consideration:

Preferably performed **>12 months post-transplant** to allow for spontaneous resolution, unless severe hypercalcemia necessitates earlier intervention.

Key Takeaways for Clinical Practice

PRE-TRANSPLANT

- Comprehensive biochemical panel (PTH, Ca, PO4, 25(OH)D, ALP).
- DXA BMD if results will impact treatment.
- **Severe pre-transplant hyperparathyroidism should NOT preclude transplantation.**

POST-TRANSPLANT

Measure PTH at 3 months – critical for risk stratification.

- PTH >130 ng/L indicates high fracture risk.
- Use FRAX + TBS as adjuncts to BMD.
- Consider denosumab or bisphosphonates for low BMD (eGFR >30).

OVERALL

- **Individualize treatment based on CKD-MBD parameters and underlying bone turnover state.**

Clinical Case Scenario

Patient Profile

- 36-year-old Female
- Unknown original kidney disease
- Hemodialysis since 2022
- Live Unrelated Renal Transplant (Oct 2022)
- Meds: Prednisolone, Cyclosporine, Mycophenolate

Key Labs

- Creatinine: 128 umol/L
- Calcium: 2.3 mmol/L
- Alk Phos: 90 IU/L
- **Cyclosporine Level: 200 ng/mL** ← Highlight
- BMD: Normal

Presenting Complaint: Severe generalized bony aches, no systemic symptoms.

Diagnostic Challenge

What is the most likely diagnosis for this patient's severe generalized bone pain?

A Rhabdomyolysis

B Osteoporosis

C Drug Induced (CNEI Pain Syndrome)

D Vitamin D Deficiency

Hint: Consider the medication history and normal BMD.

Diagnosis & Management

Correct Diagnosis: Drug Induced (Calcineurin Inhibitor-Induced Pain Syndrome - CIPS)

Pathophysiology

- Intraosseous Vasoconstriction
- Intraosseous Hypertension
- Marrow Edema

Management

Diagnosis:
MRI is Gold Standard (shows edema)

Treatment:
Calcium Channel Blockers (Nifedipine)
+ Reduce Cyclosporine dose

Key References

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