Management of CKD-MBD

Alimohammad Fatemi
Professor of Rheumatology

Introduction

- Patients with stage 4–5 CKD or on dialysis, excluded from RCTs in osteoporosis
  - (CKD-MBD) or renal osteodystrophy?
  - Renalism Discrimination based on kidney function
  - Therapeutic nihilism
- Lack of evidence on fracture prevention in this population

Screening(DXA, VFA)
Case Finding
Multidisciplinary Team

Identify and Treat Secondary Causes
Falls Prevention
Therapeutic Exercises

Optimize Calcium, Protein Intake, Vitamin D Status

Bone Targeted Therapies (Antiresorptive, Anabolic)

Screening(DXA, VFA)
Case Finding
Multidisciplinary Team

Identify and Treat Secondary Causes
Falls Prevention
Therapeutic Exercises

Optimize Calcium, Protein Intake, Vitamin D Status

Bone Targeted Therapies (Antiresorptive, Anabolic)

Screening(DXA, VFA)
Case Finding
Multidisciplinary
Team

Identify and Treat
Secondary Causes
Falls Prevention
Therapeutic Exercises

Optimize Calcium,
Protein Intake,
Vitamin D Status

Bone Targeted
Therapies
(Antiresorptive,
Anabolic)

Non-Pharmacological Management

- Identifying and addressing modifiable secondary causes:
  - Smoking
  - Alcohol abuse
  - Glucocorticoids
  - Malnutrition/Underweight
  - Falls risk
  - Lack of physical activity

Exercise

- Physical exercise improving BMD in CKD.

Cardoso et al. BMC Nephrol. 2020
de Araújo et al. Exp Gerontol.2023

- Supervised exercise > Home-based strategies

Hoffmann et al. J Bone Miner Res Off J Am Soc Bone Miner Res. 2022
Watanabe et al. BMC Nephrol. 2021

- Multimodal exercise strategy
  - Resistance
  - Endurance
  - Balance

Cejka et al. Wien Med Wochenschr. 2023

Screening(DXA, VFA)
Case Finding
Multidisciplinary
Team

Identify and Treat
Secondary Causes
Falls Prevention
Therapeutic Exercises

**Optimize Calcium,
Protein Intake,
Vitamin D Status**

Bone Targeted
Therapies
(Antiresorptive,
Anabolic)

Calcium
Vitamin D

Calcium/ Vitamin D

- BMD improvements with bisphosphonates in Vit D-replete subjects

+ Sufficient dietary calcium intake

No need for additional calcium supplements

Bourke et et al. Osteoporos In . 2013

Calcium/ Vitamin D

- Ca + Vit D supplements

  No longer universally recommended in osteoporosis patients

- Unless there is an underlying deficiency

Sanchez-Rodriguezet et al. Maturitas. 2020

Calcium

- Calcium alone has any effect on osteoporosis or fracture prevention

- Except in:
  - Frail older
  - Nursing home patients

Bolland et al. BMJ. 2015
Iuliano et al. BMJ. 2021

Calcium

- A recent European consensus recommends:
  - A minimal Ca intake from diet and supplements in CKD

800–1000 mg/day

Not exceeding 1500 mg/day

Evenepoel al. Nephrol Dial Transplant. 2024

Vitamin D

- Recent large population-based RCTs
  - No evidence of benefit of vitamin D on fracture outcomes

Jorgensen et al. Nephrol Dial Transplant. 2025

Vitamin D

- Recent large population-based RCTs
  - No evidence of benefit of vitamin D on fracture outcomes

Jorgensen et al. Nephrol Dial Transplant. 2025

- Correcting vitamin D deficiency prevents BMD loss in kidney transplant recipients

Tsujita et al. J Bone Miner Res. 2022

- No evidence in CKD or dialysis patients

Vitamin D

- KDIGO guidelines recommend:
  - Treating vitamin D deficiency based on 25-hydroxyvitamin D levels

< 15–20 ng/ml in CKD

Jorgensen et al. Nephrol Dial Transplant. 2025

Vitamin D

- European consensus statement:
  - Correcting vitamin D deficiency
  - Oral cholecalciferol with once-daily to monthly doses
  - 25-hydroxyvitamin D levels **> 30 ng/mL and < 60 ng/mL**

Jorgensen et al. Nephrol Dial Transplant. 2025

Calcium and CVD Risk?

Calcium and CVD Risk?

- WHI Trial
  - Subgroup Analysis — CVD Endpoint
    - HR — 1.13 to 1.22

Vs.

    - HR — 0.83 to 1.08

Bolland et al. BMJ 2011

Calcium

- Calcium intake Food or Supplement
- At the levels 2000 to 2500 mg/d

  (The recommended tolerable upper intake range)

- Not associated with CVD risks in generally healthy adults

Chung et al. Ann Intern Med. 2016

Hyperphosphatemia

Hyperphosphatemia

- Hyperphosphatemia ≈ Fracture risk in HD patients

Barrera-Baena et al. Nephrol Dial Transplant. 2024

- KDIGO 2017 recommended to lower serum phosphate towards the normal range.

Hyperphosphatemia

- Dietary changes by limiting phosphorus intake to 800–1000 mg/day

Hyperphosphatemia

- Calcium-containing phosphate binders not recommended.
  - Hypercalcemia
  - Arterial calcification
  - Adynamic bone disease
  - Low PTH

KDIGO 2017. Kidney Int Suppl 2017

Hyperphosphatemia (Non calcium-binders)

- ↓ Serum Ca
- ↓ Coronary artery calcification
- ↓ All Cause mortality
- ↑ Bone Formation Rates

Jamal et al. Nephrol Dial Transplant 2009
Liu et al. Ren Fail 2014

Hyperphosphatemia (Non calcium-binders)

- ↓ Serum Ca
- ↓ Coronary artery calcification
- ↓ All Cause mortality
- ↑ Bone Formation Rates

- Any difference with calcium binders in:
  - Cardiovascular Calcifications
  - Cardiovascular mortality
  - BMD
  - Fracture Risk

Jamal et al. Nephrol Dial Transplant 2009
Liu et al. Ren Fail 2014

Ogata et al. JAMA. 2021
Phannajit et al. J Nephrol. 2022
Ruospo et al. CochraneDatabase Syst Rev.2018

Hyperphosphatemia (Non calcium-binders)

- A novel non-phosphate binder Tenapanor

- For constipation-predominant IBS

  - It inhibits the sodium hydrogen exchanger 3 (NHE3) in the bowel
  - Preventing paracellular absorption of phosphate (Pathway of phosphate absorption)

Markham et al. Drugs. 2019
King et al. Sci Transl Med 2018
Silva et al. Kidney360 2023

Protein Restriction?

- Sarcopenia is highly prevalent in CKD and especially dialysis patients

- Sarcopenia is associated with osteoporosis in CKD populations

  – Increased protein intake is recommended for sarcopenic older adults

Iuliano et al. BMJ. 2021
Dedeyne et al. Front Nutr. 2021
Paccou et al. J Endocrinol. 2024

Restriction of dietary protein and phosphate in CKD stage 4–5?

Obeid et al. Kidney360. 2022

Protein Restriction?

Higher protein intake

Benefits > Risks

In older adults with CKD and osteosarcopenia

Gielen et al. Metabolism. 2023

Screening(DXA, VFA)
Case Finding
Multidisciplinary
Team

Identify and Treat
Secondary Causes
Falls Prevention
Therapeutic Exercises

Optimize Calcium,
Protein Intake,
Vitamin D Status

Bone Targeted Therapies (Antiresorptive, Anabolic)

Bone Targeted Therapies

- Antiresorptive Agents
  - Bisphosphonates
  - Denosumab
  - SERMs
- Osteoanabolic agents
  - PTH Analogues
    - Teriparatide
    - Abaloparatide
  - Romosozumab

Bone Targeted Therapies

- Stages 1–3 — General population
- Stages 4–5D — Complex and challenging

Bisphosphonates

- For high bone turnover in patients with CKD
- Excretion is mainly through the kidneys
- They accumulate in the setting of CKD

Bisphosphonates

- In GFR < 30 ?
  - Excessive accumulation in the skeleton
  - Over suppression of bone remodeling

Khairallah. Curr Opin Nephrol Hypertens. 2025

Bisphosphonates

- In mild and moderate CKD:
  - Effective
  - Well tolerated
  - Increase in BMD at the hip and lumbar spine
  - Reduction in fractures

Miller et al. J Bone Miner Res 2005
Shigematsu et al. BMC Nephrol. 2017
Whitlock et al. Can J Kidney Health Dis 2024

Bisphosphonates

- IV bisphosphates Acute kidney injury

- Infusion of 5 mg over at least 15 min prevents this complication

Fixen et al. Osteoporos Int. 2022
Miller et al. J Bone Miner Res. 2013

- Slower infusion rates of 30 min in patients with GFR < 50

or

- 60 min < 30 have been recommended

Schini et al. Osteoporos Int. 2022
Sahota et al. Osteoporos Int. 2022

Bisphosphonates

- Off-label use (with proper informed consent):
  - In a personalized approach in patients with stage 4–5 CKD and osteoporosis
  - Consider risks and benefits

Evenepoel et al. Nephrol Dial Transplant. 2021

Denosumab

- Drug metabolism is unaffected by CKD

Denosumab

- In women 60-69 y CKD stages 2 and 3

  -2.5 <T< -4

- In all GFR subgroups showed:
  - Similar, persistent BMD gains
  - Low incidence of fractures

Broadwell et al. J Clin Endocrinol Metab. 2021

Denosumab

- In 324 patients with dialysis and non dialysis-dependent kidney disease:
  - Similar efficacy of denosumab in BMD gain regardless of kidney function

Kunizawa et al. Sci Rep 2020

Denosumab

- The most important adverse effect in CKD patients

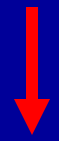
Hypocalcemia

- 24% GFR< 15
- 14% In HD

Cowan et al. J Bone Miner Res 2023

Selective Estrogen Receptor Modulators

Selective Estrogen Receptor Modulators

- In a RCT:
- Raloxifene Postmenopausal women
  - With normal kidney function / Stage 1–3 CKD
  - Vertebral fractures 

Ishaniet al. J Am Soc Nephrol JASN. 2008

Selective Estrogen Receptor Modulators

- Two small RCTs
  - Raloxifene — Postmenopausal women (Stage 5 CKD)
  - Lower bone turnover
  - Lumbar spine BMD gains

Hernández et al. Kidney Int. 2003
Haghverdi et al. Iran J Kidney Dis. 2014

PTH Analogues

- Teriparatide
- Abaloparatide

PTH Analogues

- Equally effective in patients with stage 3 CKD compared to those with normal kidney function

Laurent et al. Curr Osteoporos Rep. 2025

PTH Analogues

- Adverse events:
  - Transient hypotension
  - Hypercalcemia
  - Hyperuricemia

More common in patients with the lowest levels of GFR

Laurent et al. Curr Osteoporos Rep. 2025

Romosozumab

- Humanized monoclonal antibody
- Against sclerostin (Inhibitor of bone formation)
  - Bone Formation ↑
  - Bone Resorption ↓

Romosozumab

- Similar efficacy and safety in stage 3 CKD patients compared to those without CKD

Miller et al. J Bone Miner Res. 2022
Miyauchi et al. J Bone Miner Res. 2022

Romosozumab

- In RCTs:
  - More MI and strokes

    Romosozumab-treated patients than alendronate users

Laurent et al. Curr Osteoporos Rep. 2025

Romosozumab

- Sclerostin suppressed vascular calcifications in CKD?

Brandenburg et al. Nephrol Dial Tranplant. 2019
De Maré et al. J Bone Miner Res. 2022

Osteoanabolic Agents

- Limited evidence to support the efficacy and safety of bone anabolic drugs in CKD stage 4–5 patients.

Thanks For Your Kind Attention