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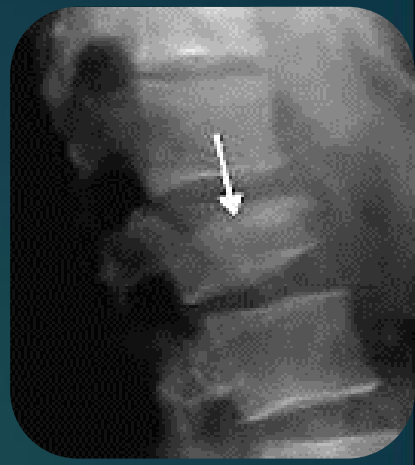

Osteoporosis treatment in CKD

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Case presentation

- A 54-year-old white man with ESRD on peritoneal dialysis therapy ,experienced a right hip fracture from a fall at home. After surgery and rehabilitation for hip surgery, he was referred for evaluation and management of metabolic bone disease.

- The patient's laboratory data showed a normal biochemical profile. total serum calcium level was 9.3 mg/dL; serum phosphorus, 4.5 mg/dL; total ALP, 85 (reference range, 10-120) IU/L; bone-specific ALP, 8 (reference range, 10-42) IU/L; and intact PTH, 154 (reference range, 15-65) pg/mL. Levels of biochemical markers of bone turnover, specifically serum CTX and PINP, were 186 (reference range, 150-650) ng/mL and 54 (reference range, 20- 108) mg/L, respectively.
- His 25-oh D level was 30 ng/mL. Femoral neck BMD T-score - 3.8, defined as osteoporosis.

Osteoporosis in CKD

- There is an **overlap in the age** of onset of chronic kidney disease (CKD) and osteoporosis.
- The elderly account for a large proportion of osteoporosis patients, many of whom also have CKD.
- In CKD patients, fracture rates are more than 10-fold higher compared with age- and sex-matched individuals without CKD.

GIOP in CKD

Major Recommendations

Initiate therapy in those with BMD T-scores ≤ -2.5 at :

- The femoral neck or spine(NOF guideline)
- The lumbar spine, femoral neck, total hip, or 33% radius (ACE guideline)

Initiate pharmacologic treatment in those with hip or vertebral (clinical or asymptomatic) fractures.

Initiate treatment in postmenopausal women and men age 50 and older low bone mass (-2.5< T-score < -1.0) :

- *10-yr hip fx probability ≥ 3% on FRAX.*
- *10-yr major osteoporosis-related fx probability ≥ 20% based on FRAX*

www.shef.ac.uk/FRAX

CaucasiaCaucasian woman, 58 years, smoker

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 58 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg) 65
4. Height (cm) 160
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2) T-Score -2.3

Clear Calculate

BMI: 25.4
The ten year probability of fracture (%)
with BMD

Major osteoporotic	9.1
Hip Fracture	3.1

View NOGG Guidance

If you have a TBS value, click here: Adjust with TBS

Print tool and information

Weight Conversion

Pounds → kg Convert

Height Conversion

Inches → cm Convert

02765050
Individuals with fracture risk assessed since 1st June 2011

www.nos.org.uk

National Osteoporosis Society

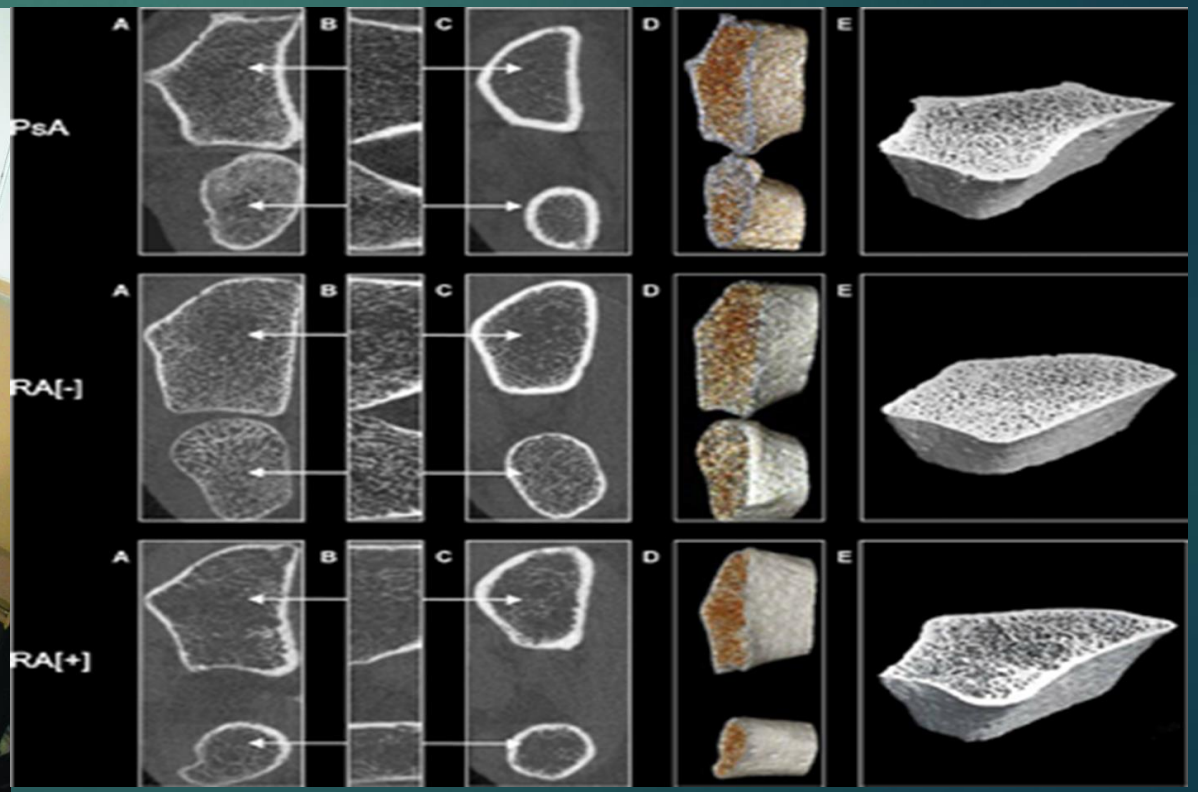
Diagnosis OP in CKD

Diagnosis OP in Stages 1–3 CKD

- WHO BMD (T-score) criteria for osteoporosis or a low trauma fracture can be used to establish a diagnosis of osteoporosis as long as there are no biochemical abnormalities suggesting CKD-MBD

Diagnosis OP in Stages 4, 5 CKD

- High-resolution peripheral quantitative computerized tomography (**HRpQCT**) of the forearm or tibia has been shown to be a better predictor of fracture risk in stages 4 and 5CKD than DXA.



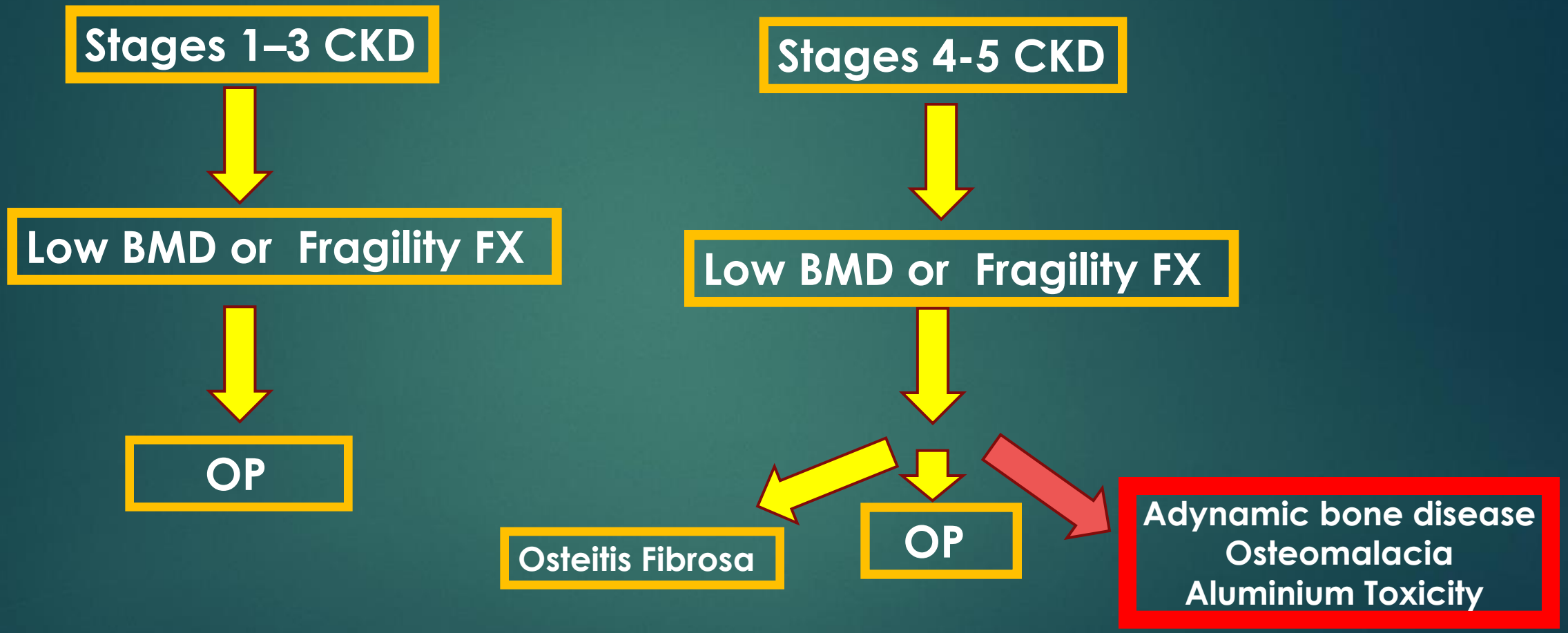
Diagnosis OP in Stages 4, 5 CKD

The diagnosis of osteoporosis in stages 4 and 5 CKD is one of the exclusion

excluding either renal osteodystrophy or CKD–MBD as the cause of low BMD or fragility fractures.

(KDIGO2017)

Diagnosis OP in CKD



How diagnose MBD-CKD

- Best accomplished by measuring specific biochemical tests & markers of bone turnover (BTM) and/or quantitative bone histomorphometry
- In patients with CKD G3a–G5D, it is reasonable to perform a **bone biopsy if** knowledge of the type of renal osteodystrophy will **impact treatment decisions**

KDIGO 2017

Box 4. Bone Turnover Markers

Anabolic Markers

- ★ Bone-specific alkaline phosphatase (bone ALP)
- Serum osteocalcin
- ★ Serum or plasma procollagen type I amino-terminal propeptide (PINP)

Resorption markers

- ★ Serum carboxy-terminal crosslinking telopeptides of type I collagen (CTX)
- Urinary amino-terminal crosslinking telopeptides of type I collage (NTX)
- Tartrate resistant acid phosphatase (TRAP5b)

In GFR between 30 - 60 mL/min

- with a history of a fragility fracture and/or BMD (T-score ≤ -2.5), initially measure serum calcium, phosphorus, (PTH), and 25-OH D.
- By normal biochemical tests, indicating the absence of co-existing CKD-MBD, we make the diagnosis of osteoporosis as in patients without CKD.

In patients with an eGFR <30 mL/min

- with a history of a fragility fracture and/or low (BMD) (T-score ≤ -2.5), measure bone specific alkaline phosphatase in addition to serum calcium, phosphorous, PTH, and 25-OH D.
- Measurement of bone specific alkaline phosphatase may be helpful in excluding the presence of ABD.

Without measurements of serum PTH or bone-specific alkaline phosphatase never treat OP in CKD stage 4-5 & when PTH and BSAP low never treat with antiresorptive

Treatment of OP in CKD

Supplementation with calcium and vitamin D

- Recommended calcium intakes around 1000 mg/day .
- Assessment of patients' dietary calcium intake could further equip clinicians to make individualized recommendations for meeting recommended intakes.
- Repletion of nonactivated vitamin D stores is accomplished using cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) and should target a serum 25-hydroxy vitamin D level >30 ng/mL.

Curr Osteoporos Rep. 2017; 15(3): 214–221

Pharmacological Agents Approved for the Treatment of Osteoporosis

Evidence-based clinical efficacy of medications

Medication	Fracture risk reduction			Route of administration
	Hip	Spine	Non-vertebral	
Bisphosphonates				
[redacted]				
[redacted]				

Table 3 Dose Recommendations for Bisphosphonates[42,43,45,56,48,49]

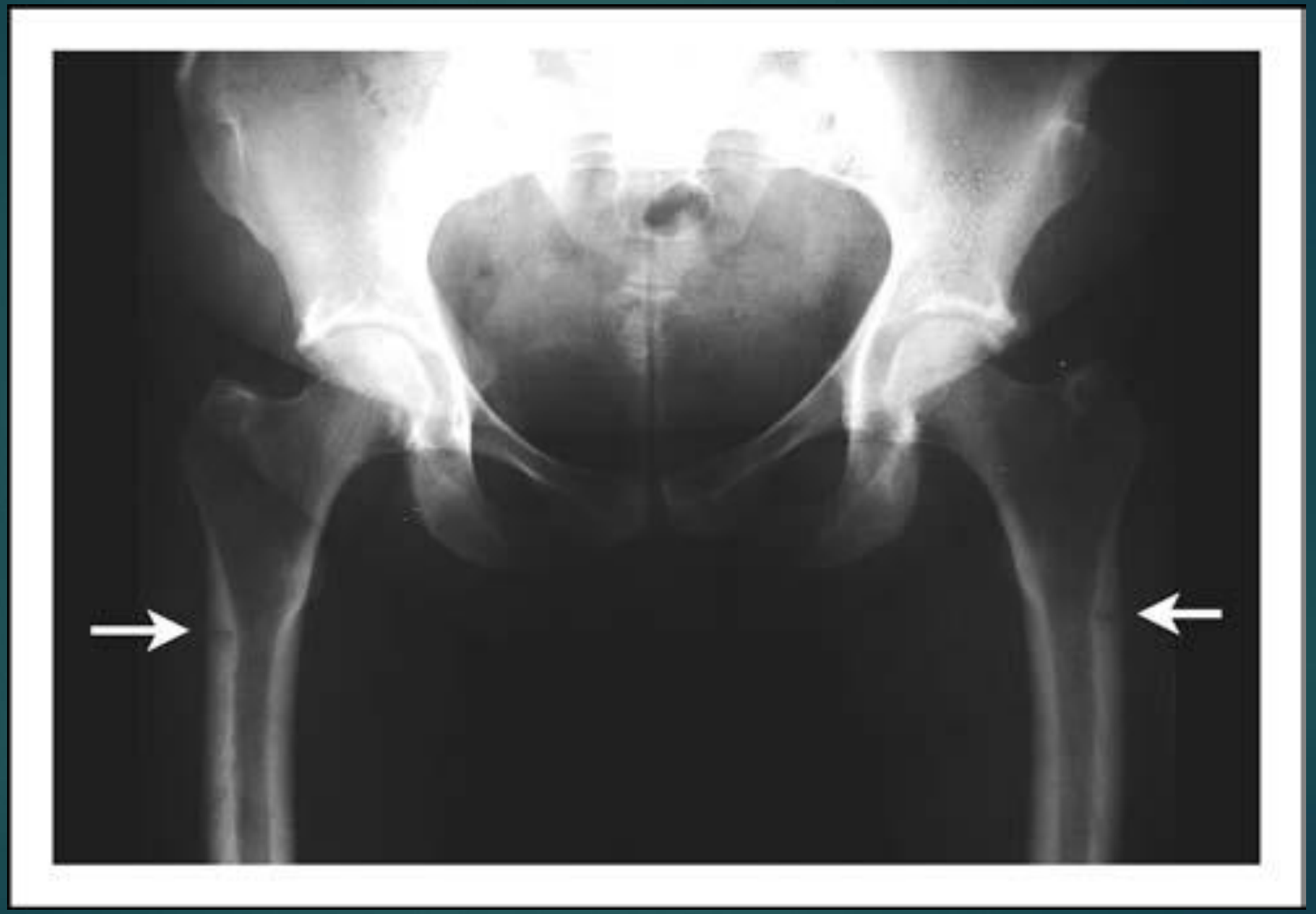
Bisphosphonate	Prophylactic Dose	Treatment Dose	CrCl Recommendation
Alendronate	5 mg PO once daily or 35 mg PO once weekly	10 mg PO once daily or 70 mg PO once weekly	≥ 35 mL/min
Risedronate (IR)	5 mg PO once daily or 35 mg once weekly	5 mg PO once daily or 35 mg PO once weekly or 150 mg PO once monthly	≥ 30 mL/min
Zoledronic acid	5 mg IV every 2 years	5 mg IV once yearly	≥ 35 mL/min
Ibandronate	2.5 mg PO once daily or 150 mg PO once monthly	2.5 mg PO once daily or 150 mg PO once monthly or 3 mg IV every 3 months	≥ 30 mL/min

CrCl = creatinine clearance; IR = immediate release; IV = intravenous; PO = orally.

The limitations in use of approved pharmacologic choices for osteoporosis is the lack of evidence for fracture risk reduction in patients with severe CKD

so all OP drugs are ‘**off-label**”

Agent	Dose	Dose Adjustment in CKD	Use in CKD4-5	Mechanism	Notes
Injectable calcitonin (Calcimar)	0.5 mL/d SC	None	No adjustment	Inhibits bone resorption	No data for efficacy in CKD4-5
Nasal calcitonin (Miacalcin)	200 μg spray/d	None	No adjustment	Inhibits bone resorption	No data for efficacy in CKD4-5
Alendronate (Fosamax)	70 mg/wk	No adjustment for eGFR ≥ 30 mL/min; avoid for eGFR < 30 mL/min	Off-label use[a]	Bisphosphonate; inhibits bone resorption	Consider limiting exposure to <3 y in CKD
Ibandronate (Boniva)	150 mg/mo	No adjustment for eGFR ≥ 30 mL/min; avoid for eGFR < 30 mL/min	Off-label use[a]	Bisphosphonate; inhibits bone resorption	Consider limiting exposure to <3 y in CKD
Risedronate (Actonel or Atelvia)	150 mg/mo or 35 mg/wk	No adjustment for eGFR ≥ 35 mL/min; avoid for eGFR < 35 mL/min	Off-label use[a]	Bisphosphonate; inhibits bone resorption	Consider limiting exposure to <3 y in CKD
Zoledronic acid (Reclast)	5 mg/y IV over 15 min	Contraindicated for eGFR < 35 mL/min	Off-label use[a]; only consider in very high-risk patients; reduce infusion rate to 30 min	Bisphosphonate; inhibits bone resorption	Slow infusion rate down to 30-60 min in advanced CKD
Denosumab (Prolia)	60 mg SC every 6 mo	None	Insufficent safety and efficacy data	Monoclonal antibody with affinity for RANKL; reduces osteoclast activity	Ensure normal vitamin D levels and calcium intake
Teriparatide (Forteo)	20 μg/d SC	None	Insufficient data on efficacy or safety in CKD4-5	Recombinant human PTH; stimulates osteoblast activity	Uncertain efficacy in advanced CKD; patients should have normal or explained bone ALP and not be hypercalcemic
Raloxifene (Evista)	60 mg/d	None	Use with caution	Selective estrogen receptor modulator; inhibits osteoclast activity	Safety and efficacy not established in patients with moderate or severe decreased kidney function



M. Zabihi

Drug holiday

- Patients at **moderate to lower fracture risk**, drug holiday for 2-3 years can be considered after:
  - 3-5 years of oral bisphosphonate use
  - 3 annual doses of IV Zoledronic acid
- Patients at **higher fracture risk**, drug holidays can be considered:
  - after 6-10 years of oral bisphosphonate use
  - after 6 annual doses of IV Zoledronic acid

clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2016. *Endocr Pract* 2016;22:S1–S42.

Denosumab

- Not cleared by the kidney, but there is limited clinical experience in patients with severe CKD.
- Denosumab administration in hemodialysis patients has been associated with clinically significant hypocalcemia.
- Patients who have hypocalcemia should not receive bisphosphonates or denosumab until hypocalcemia is corrected.

Raloxifene and Calcitonin

- Not considered in G4 CKD due to lack of data showing a benefit for reducing non-vertebral fracture risk.
- Raloxifene increases the risk of thromboembolism.

Intravenous Bisphosphonate

- If an oral bisphosphonate or denosumab is not tolerated, Zoledronic acid could be considered in lieu of no treatment, particularly in patients at high risk for recurrent fracture and mortality.

- In patients with an GFR<35 mL/min, using a slower infusion rate (60 minutes) may lower the risk of renal damage. Treatment should be limited to less than 3 years.

Teriparatide

- MAY be beneficial in patients with ABD.
- Teriparatide-induced improvement in parameters of bone formation may be mediated by its effect on sclerostin.

Teriparatide concern in CKD

- Because teriparatide can increase urinary calcium there was no greater risk of clinical nephrolithiasis, though preexisting kidney stones were an exclusionary criteria for trial randomization.
- Serum uric acid did rise significantly more than placebo.

Are BPs effective for improving BMD in CKD?

- The **efficacy of bisphosphonate** in patients with [eGFR] of <45 mL/min), looking at **(BMD) changes** in a Danish population between 1999 and 2016.
- However, compared with 282 bisphosphonate nonusers, also with stage 3B CKD, the bisphosphonate **users** showed gains of an average of **0.59% total hip** BMD per year, whereas the **nonusers** lost an average of **1.98%** annually.
- The finding of an improved BMD is good news, as this suggests these drugs could be **effective at improving bone BMD**

American Society of Bone and Mineral Research 2017 Annual Meeting. September 8–11, 2017, Denver, Colorado

Are BPs effective for preventing fracture in CKD?

- In two post-hoc analyses from the pooled risedronate registration studies and the alendronate fracture intervention trials, both of these oral bisphosphonates in their original registration formulations (5 mg/day of risedronate and 10 mg/day of alendronate) were used in approximately 600 patients per trial (300 treated and 300 placebo)to treat subjects with PMO with eGFR by Cockgroft-Gault equations between 15 and 30 mL/min .
- In both trials the two bisphosphonates reduced the incidence of either morphometric vertebral fractures or all clinical fractures significantly as compared to placebo over an average of 2.6 years duration without any change in renal function.

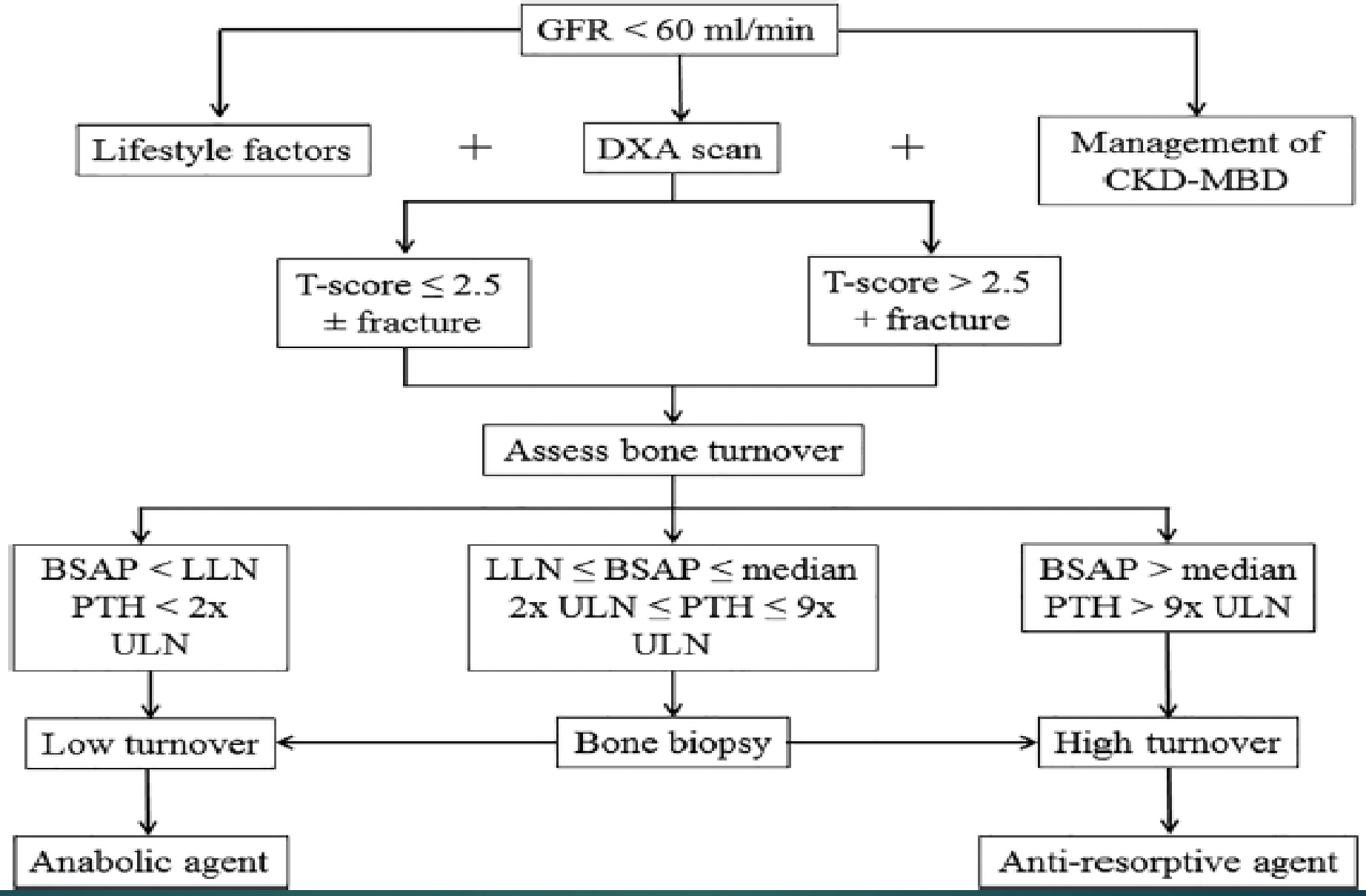
Abaloparatide (TYMLOS)

- Theorically Tymlos had better effect in CKD but till this time there in no clinical trial on this drug in CKD
- No dosage adjustment is required for patients with mild, moderate, or severe renal impairment

Anti-sclerostin antibody in CKD

- Although elevated levels of sclerostin have been reported in CKD stages 3 to 5D patients there are no clinical data on anti-sclerostin antibody treatment in CKD patients.
- In phase 2 in clinical trial of romosozumab, subjects who had estimated creatinine clearance as low as 30mL/min were included
- Since romosozumab was associated with favorable effects on bone turnover in that study population, its efficacy in improving bone fragility in CKD patients may be anticipated

Moe SM, Chen NX, Newman CL et al (2015) Anti—sclerostin antibody treatment in a rat model of progressive renal osteodystrophy. J Bone Miner Res 30(3):499–509.



Rethinking Bone Disease in Kidney Disease,JMBR plus 2017

Case

Our patient had levels of bone turnover markers that were not discriminatory enough to distinguish the cause of bone turnover, so a transiliac biopsy was performed and adynamic renal bone disease was diagnosed.

Our patient, with biopsy-proven idiopathic renal ABD, was administered teriparatide, 20 mg/d.

There have been no additional fractures over the 2-year period, his PINP level

increased 60 mg/L from baseline and his bone ALP level doubled from baseline 4 months after teriparatide therapy initiation, suggesting an anabolic response.

In the PMO registration trials for teriparatide, lumbar spine BMD returned to baseline 12 months after discontinuation of teriparatide therapy unless the patients were using a bisphosphonate,though there seemed to be maintenance in fracture risk reduction.

Our patient was started on treatment with low-dose risedronate (35 mg every other week) due to his low GFR and due to evidence in prior clinical trials that the 2.5-mg/d risedronate dosage reduced vertebralor hip fractures to the same degree as the registered 5.0-mg/d dosage.


Our vision is a world without fragility fracture
in which healthy mobility is a reality for all.