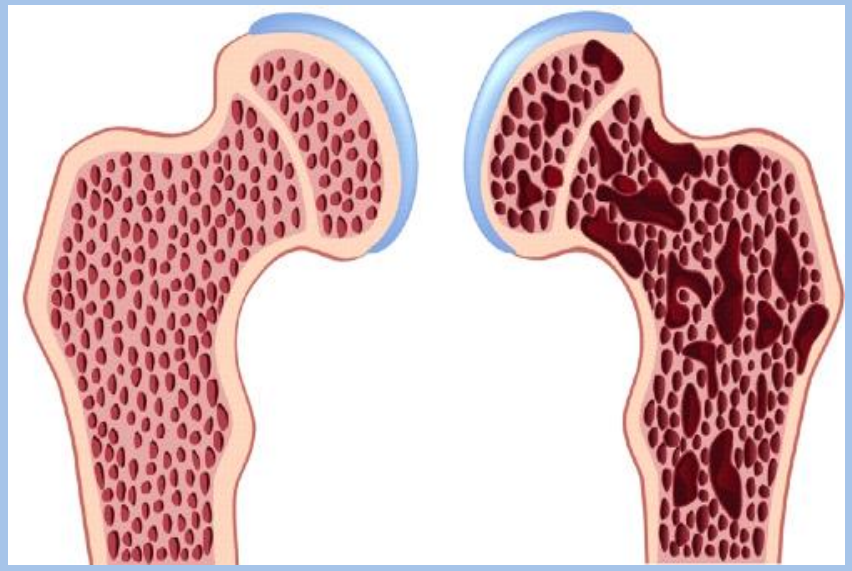

Osteoporosis in Renal Failure

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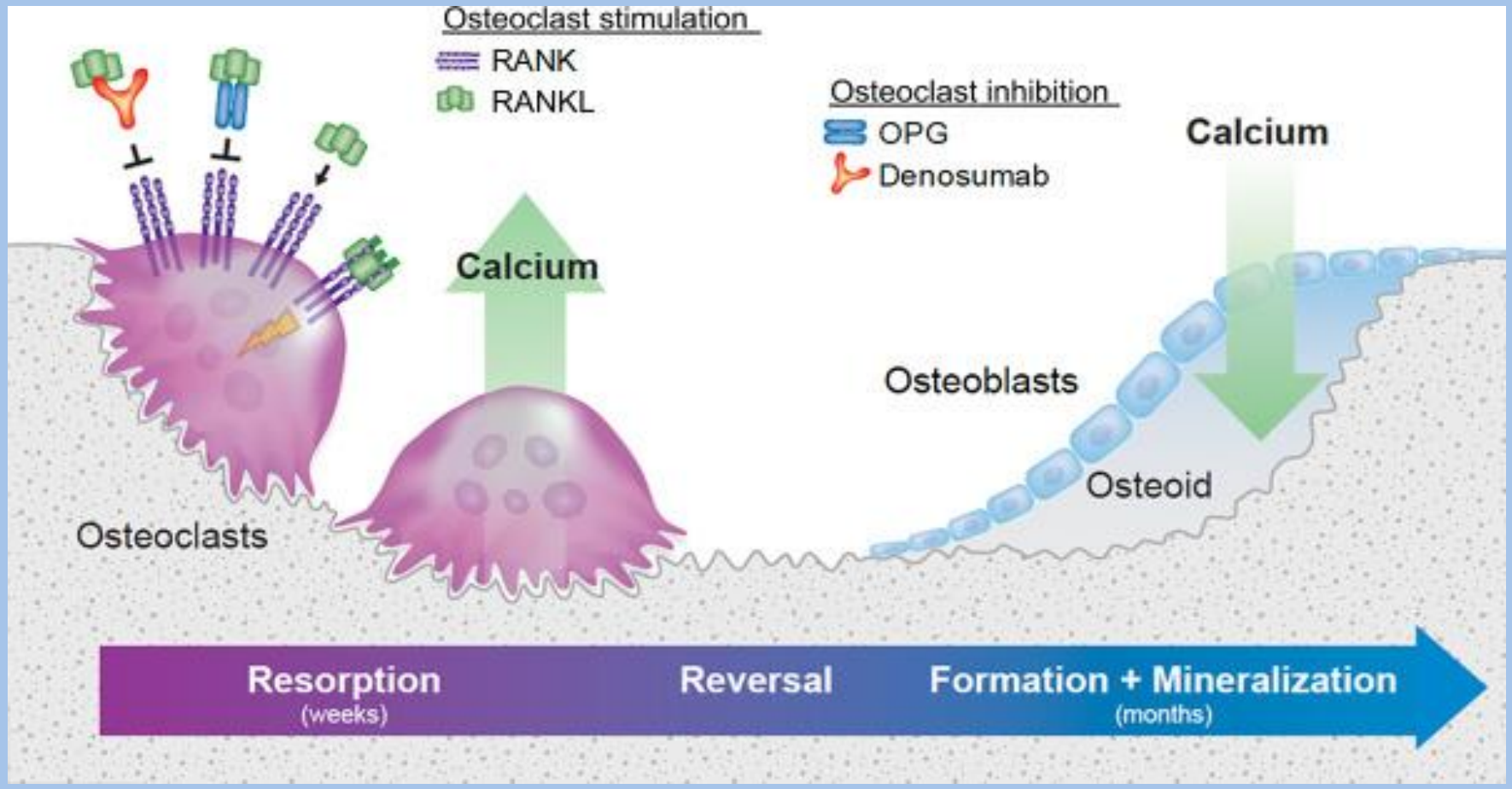
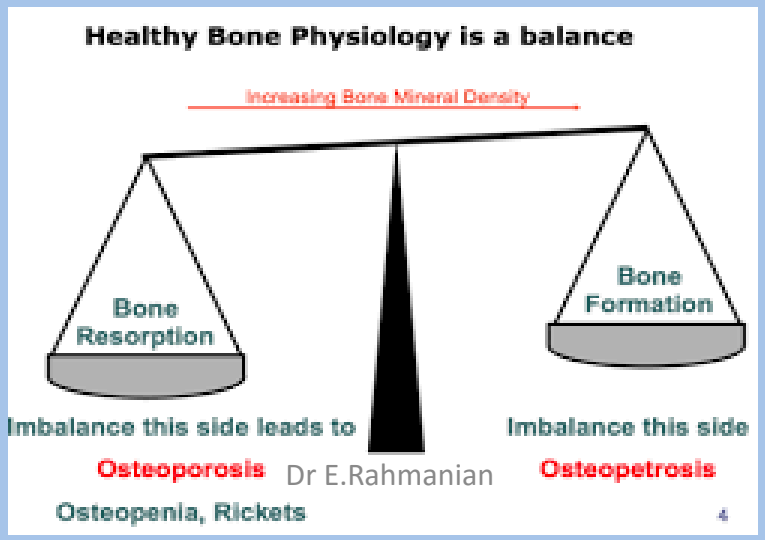


Osteoporosis

- Common disease that is characterized by low bone mass with micro-architectural disruption and skeletal fragility, resulting in an increased risk of fracture
- Hall mark of OP is decreases in both bone minerals and bone organic matrix



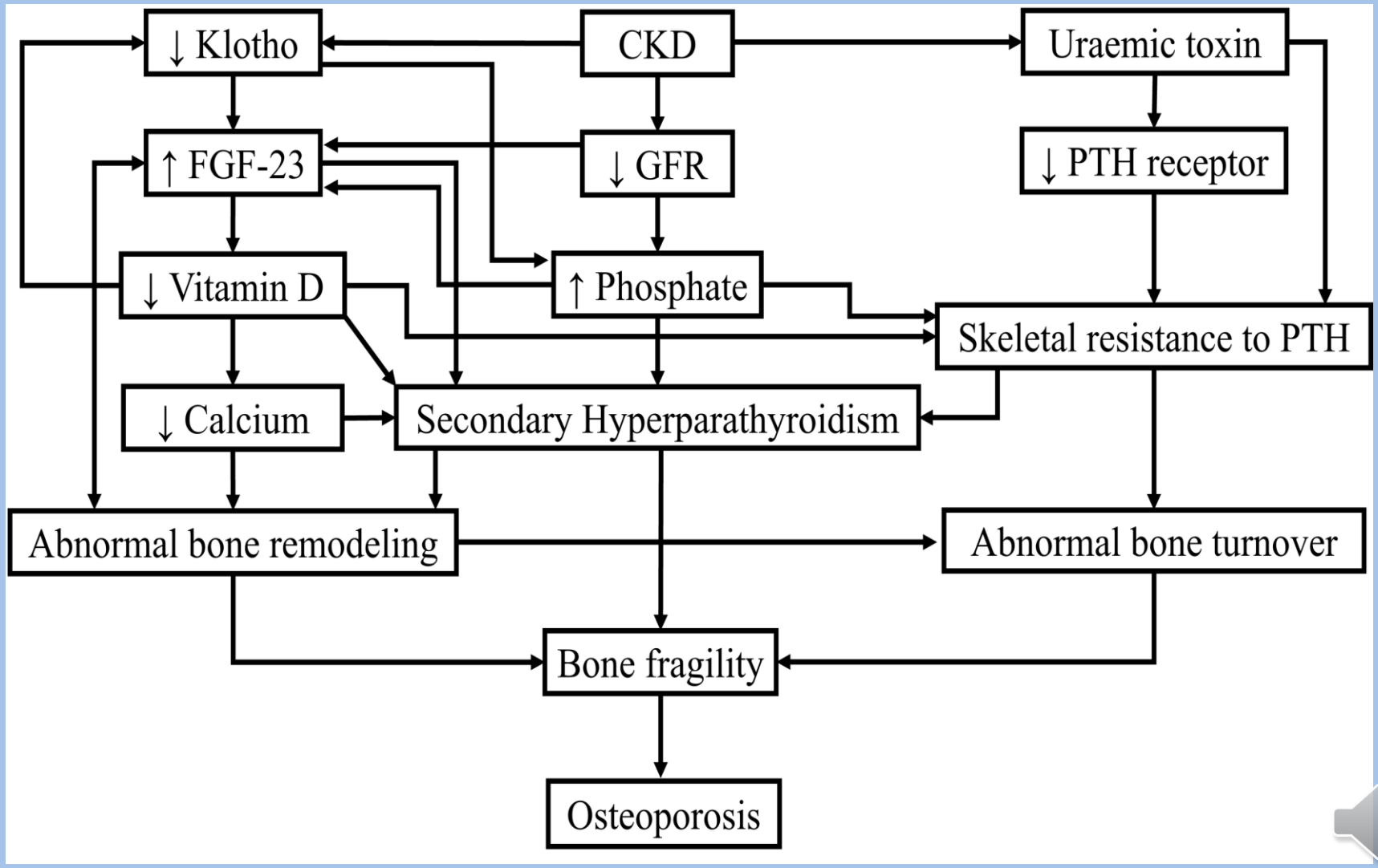
Prevalence

- 200 milion people all over the world
- >50% of women & 30-40% of men over 50 years
- >1.5 milion Fx/year in US
- Leading cause of morbidity and mortality in older people
- Number of patients with osteoporosis has been increasing due to aging population
- Postmenopausal women are particularly prone to bone fractures

Osteoporosis in CKD

- **First,** CKD is a state of accelerated/premature ageing.
- **Second,** multitude drugs with proven or putative detrimental bone effects include corticosteroids, loop diuretics, heparin, PPi and vitamin K antagonists .
- **Third,** the uraemic environment, characterized by (micro)inflammation, metabolic acidosis, accumulation of uraemic toxins and disturbances in calcium, phosphate, parathyroid hormone (PTH) and vitamin D metabolism, causes renal bone disease, commonly referred to as renal osteodystrophy (ROD).

Pathogenesis of CKD-MBD



Renal osteodystrophy

- A term confined to the spectrum of bone histomorphometry in CKD.

❖Renal osteodystrophy includes:

1. Hyperparathyroid-mediated, high-turnover bone disease or "***osteitis fibrosa cystica***"
2. Adynamic bone disease
3. Osteomalacia
4. Mixed uremic osteodystrophy

Candidates for BMD testing

National Osteoporosis Foundation (NOF) recommendation:

1. Women 65 years and older and men 70 years and older, regardless of clinical risk factors.
2. Adults who have a fracture after age 50 years
3. Younger postmenopausal women, women in the menopausal transition, and men age 50 to 69 years with clinical risk factors for fracture.
4. Adults with a condition (eg, Rheumatoid arthritis) or taking a medication (eg, glucocorticoids in a daily dose ≥5 mg prednisone or equivalent for ≥3 months)

Clinical risk factors of fracture in CKD

Traditional risk factors

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

CKD-specific risk factors

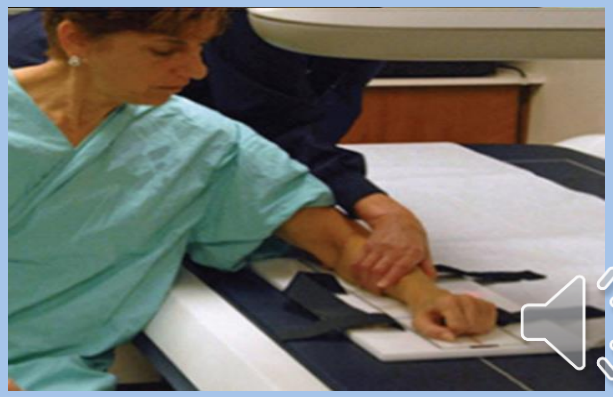
- Long dialysis duration
- Glucocorticoid use
- Sarcopenia
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Chronic illness
- Poor nutrition
- Vitamin D deficiency
- Immobilization
- Hypogonadism

BMD technique

1. Spine

2. Hip

3. Forearm



Diagnostic categories for osteoporosis and low bone mass by DXA

Category	Bone mass
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 SD).
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 and greater than -2.5 SD).
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 SD).
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.

Laboratory assessment

GFR 30 to 60 mL/minute

- Calcium
- Phosphorus
- Parathyroid hormone (PTH)
- 25-hydroxyvitamin D
- Alkaline phosphatase

GFR <30 mL/min

- Calcium
- Phosphorus
- PTH
- 25-hydroxyvitamin D
- Bone-specific alkaline phosphatase (BSAP)
- Measurement of **1,25-dihydroxyvitaminD** is not recommended

Osteoporosis in CKD and GFR ≥30 mL/minute

- T-score< -2.5 SD
- Presence of a fragility fracture

❖ There are no accompanying biochemical abnormalities (eg, hyperparathyroidism, hyperphosphatemia) that indicate the possible coexistence of renal osteodystrophy or CKD-MBD (mineral bone disorder).

Osteoporosis in CKD and GFR <30 mL/minute

- Can be challenging
- Bone physiology is more complex and features of CKD-MBD may predominate.
- WHO BMD criteria can not be used for the diagnosis of osteoporosis.
- Diagnosis of osteoporosis can only be made by excluding CKD-MBD, including renal osteodystrophy.

Interpretation in GFR <30 mL/min

- There are few data to support a specific approach to the diagnosis of osteoporosis in G4-G5 CKD.
- **PTH** and **BSAP** use to predict underlying bone turnover and can be helpful in excluding the presence of adynamic bone disease
- **Bone biopsy** is the gold standard for establishing the type of renal bone disease

Management

Non-pharmacological

Lifestyle Modification:

- Regular weight-bearing exercise
- Fall prevention
- Cessation of smoking
- Avoiding alcohol intake
- Exercise and Physical Therapy

Non-pharmacological

Ca supplementation

- Excessive exogenous calcium in adults may be harmful at all stages of CKD
- KDIGO guidelines for CKD-MBD suggest limiting calcium-based phosphate binders for all patients with CKD G3a–5D
- Daily dietary calcium intake with 1000 mg/day is recommended for achieving neutral calcium balance
- Additional calcium supplements or calcium-containing medications should be avoided for patients with adequate daily calcium intakes of 800–1000 mg/day
- Dairy products also contain phosphorus, nondairy sources of calcium (calcium-fortified orange juice, soy products, vegetables) may be preferred in some patients.

Non-pharmacological

Vitamin D supplementation

- Recommend cut-off value : 30 ng/mL
- Treatment and prevention of vitamin D deficiency in CKD and dialysis patients : 800 IU/daily
- Vitamin D provided during dialysis is more effective than home prescriptions
- Calcitriol decreased bone turnover leading to the notion about decreasing active vitamin D therapy in adynamic bone disorder.

Intervention thresholds for pharmacological therapy

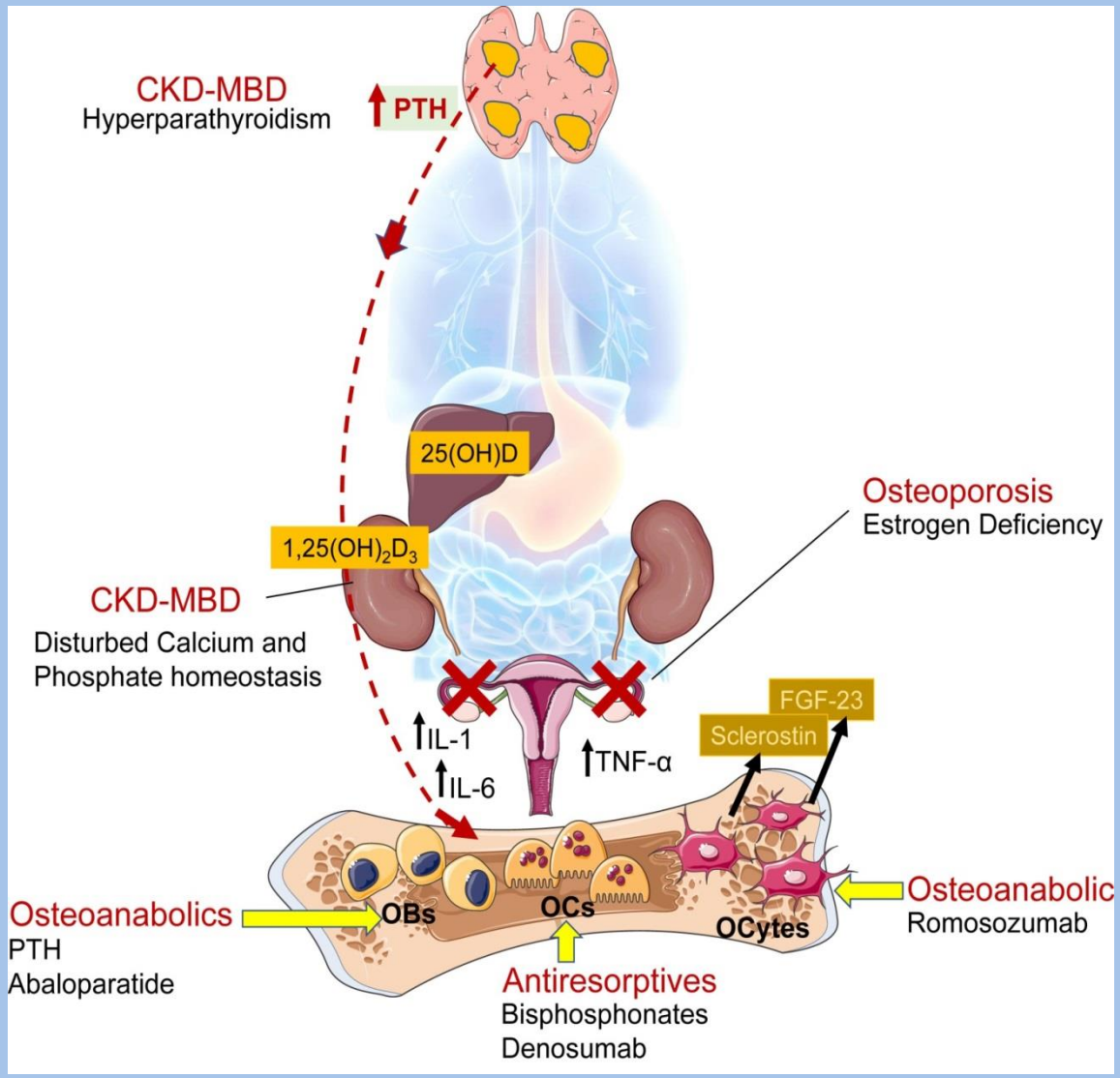
- CKD patients >50 years with:

1. Prior fragility fracture
2. In the absence of Fx, T-score <-2.5 at the lumbar spine or hip

A higher threshold of -2.0 or -1.5 may be more appropriate(???)

- Control of CKD-MBD & Managing hyperphosphatemia and SHPT
- Control of uraemia

Pharmacological intervention



Bisphosphonates

- Anti-resorptive agent, induce osteoclast apoptosis
- All bisphosphonates are excreted via kidney
- In patients with CKD G1–3
- FDA contraindicated bisphosphonates exposure in CrCl <35 mL/min

- Bisphosphonates results in the suppression of arterial thickening , in addition reducing the incidence of myocardial infarction.

Denosumab

- Anti-resorptive agent, RANK-L inhibitor, inhibits osteoclast proliferation
- Efficacy is not influenced by the kidney function
- Cleared by the reticuloendothelial system
- There is no restriction of its use in patients with eGFR <35 mL/min
- should not be discontinued post KT
- Risk of severe hypocalcaemia increased in CKD(nadir 7 days after administration)
- CKD G4–5 and male sex are associated with denosumab-induced hypocalcemia
- Needs to precaution and administering active vitamin D & calcium supplement before starting.

Teriparatide

- Anabolic agents
- Best choice in Adynamic bone diseases but Larger studies are needed
- Daily injection for 18-24 months
- Not improve BMD early after KT

[Cejka, D.; Benesch, T.; Krestan, C.; Roschger, P.; Klaushofer, K.; Pietschmann, P.; Haas, M. Efect of teriparatide on early bone loss after kidney transplantation. Am. J. Transplant. 2008, 8, 1864–1870.]

- Careful administration for parenteral teriparatide due to the potential for Hypercalcemia & Hypercalciurea
- PTH efects are not persistent after discontinuation of therapy, unless anti-resorptive agents are given.

Selective estrogen receptor modulators (SERMs)

❖ ***Raloxifene***

- FDA approved for prevention & treatment of OP
- In postmenopausal women, must be administered with caution

- We no longer consider ***estrogen(ERT)*** a first-line therapy for osteoporosis in postmenopausal women because increases in the incidence of breast cancer, coronary heart disease, stroke, and venous thromboembolism

Romosozumab

- Monoclonal Ab that inhibits Sclerostin
- S.c injection monthly for 1 year
- No dosage adjustment needed in CKD
- Risk of Hypocalcemia
- In GFR < 30 greater risk of hypocalcemia

Approach to OP in CKD

1- correct CKD-MBD, uremia according nephrology guidelines

2-Life style modification(weight bearing ex., smoke/alcohol cessation, fall prevention)

3-Consider GFR

4-Consider Bone turn over(PTH, BSALK, Bone biopsy)

5-BMD(DXA)

Dr E.Rahmanian

T-score<-2.5

Or Fragility Fx

T-score>-2.5

& No Fx

High turn over

Low turn over

Supportive care,

Consider FRAX

Monitoring

DXA Repeat

- The optimal interval for repeating DXA scans is uncertain
- In general population frequent testing (<2 years) is unnecessary.
- In ***high-risk patients*** receiving drug therapy, BMD changes are small compared to measurement error, and changes may take 2 years to be significant.
- DXA should only be repeated if the result will influence clinical management or rapid changes in BMD are expected.

Thanks for your attention