

- ▶ There is some situations that treatment of osteoporosis differ from normal situations
- ▶ These difference result from limitation of drugs or inefficiency of drug on that situations
- ▶ Sometimes these situations became problematic even in expert of osteoporosis treatment
- ▶ The most important of these situations are renal failure and premenopausal osteoporosis



Treatment Of Osteoporosis In Special Situations

A person with long hair, seen from behind, stands in a stone archway. The archway is made of large, rough-hewn stones and is illuminated from within, casting a warm glow. The person is looking out at a bright, hazy landscape under a rising sun. The sky is dark with a crescent moon and stars. The overall mood is hopeful and contemplative.

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Premenopausal low BMD (Z score ≤ -2.0)

BMD recommended only :

1) secondary causes

2) fragility Fx

All should have lab exam for secondary causes

- ▶ In the case of premenopausal osteoporosis, secondary causes are responsible for at least half of case

Premenopausal low BMD (Z score ≤ -2.0)

Two type of low BMD :

- 1) Genetically or previous insult (stable BMD and BTM)
- 2) Ongoing insult (decreasing BMD and high BTM)

when interpreting a low BMD measurement in a premenopausal woman, the clinician must take into account the timing of recent pregnancy and lactation, as well as timing of peak bone mass.

Premenopausal low BMD (Z score ≤ -2.0)

In premenopausal women with low BMD alone,
without fractures, known secondary causes for low BMD, or evidence
of accelerated bone loss

**pharmacotherapy is almost never
indicated.**

Premenopausal low BMD (Z score ≤ -2.0)

In this situation it may be reasonable to treat with calcium and vitamin D and repeat a bone density study in **one year**

Premenopausal low BMD (Z score ≤ -2.0)

Treatment options

- ▶ Cad
- ▶ weightbearing exercise
- ▶ estrogen in hypogonadal premenopausal women
- ▶ Bisphosphonates?

Because bisphosphonates accumulate and persist in the maternal skeleton, cross the placenta, accumulate in the fetal skeleton, and cause toxic effects in pregnant rats, they should be used with caution in women who may become pregnant. Although several reports document normal pregnancies and fetal outcomes in women receiving bisphosphonates

- ▶ Teriparatide

Premenopausal low BMD (Z score ≤ -2.0)

Treatment options

- ▶ **Denosumab** have some advantages in premenopausal populations because of its **shorter half-life** relative to bisphosphonates and lack of skeletal accumulation, the efficacy and safety of this medication have not been defined in premenopausal women

Premenopausal low BMD (Z score ≤ -2.0)

Should not use :

- ▶ **Raloxifene and tamoxifen** should not be used to treat osteoporosis in menstruating women as they block estrogen action on bone, leading to further bone loss
- ▶ **Calcitonin** : no improvement in BMD or bone markers & concern about cancer in long term use



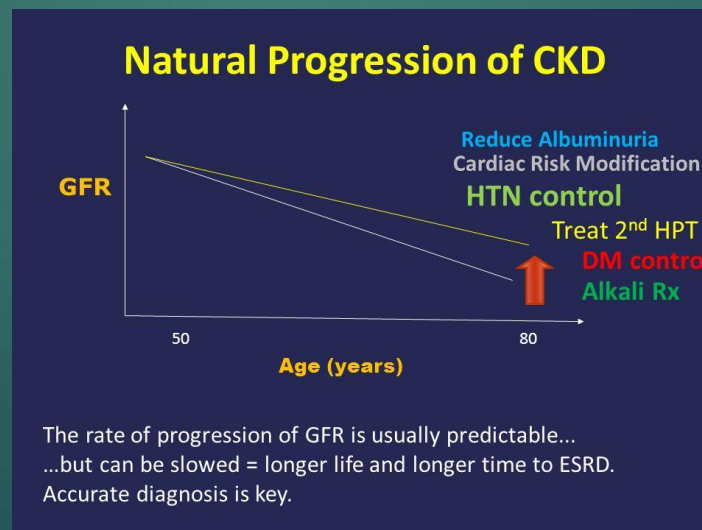
Osteoporosis in Chronic Kidney Disease (CKD)

Myth in CKD OP treatment

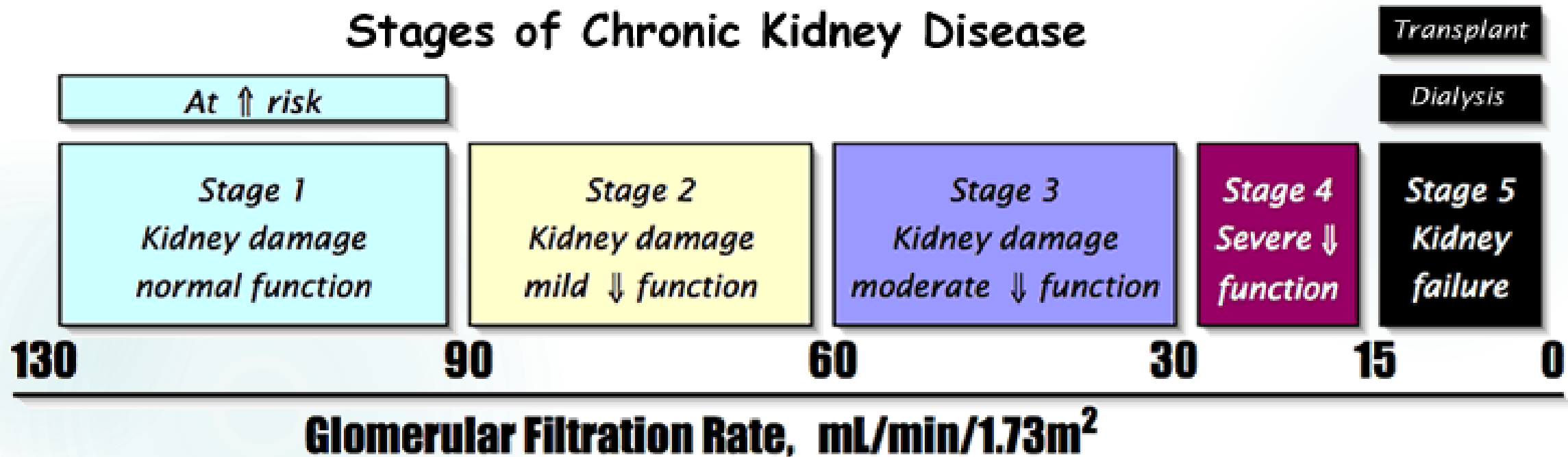
- ▶ Low BMD and Fragility fracture means osteoporosis
- ▶ Bisphosphonates contraindicated in CKD
- ▶ Denosumab only safe available treatment for OP in CKD
- ▶ Forteo and tymlos cannot be used in all CKD patients
- ▶ We cannot use 25(OH)vit.D3 in CKD and better to use 1-25 (OH)D

Osteoporosis in CKD

- ▶ There is an **overlap in the age** of onset of chronic kidney disease (CKD) and osteoporosis.
- ▶ The incidence of these diseases increases proportionally with age.
- ▶ The elderly account for a large proportion of osteoporosis patients, many of whom also have CKD



Stages of Chronic Kidney Disease



Osteoporosis in CKD

- ▶ Those with CKD stages 3a–5D have been shown to have low BMD and reduced mechanical strength, leading to a **strikingly elevated risk of fractures** (1.5- to twofold higher than in the general population)
- ▶ Risk **of hip fracture** in CKD patients is strikingly elevated while spinal compression fracture is not clearly elevated in CKD
- ▶ Patients' fractures tend to occur at a **younger age**, and there is an increase in associated morbidity and mortality (unadjusted **mortality is 3.7 times** higher in dialysis patients with fracture than in those without)
- ▶ phosphorus retention, secondary hyperparathyroidism, chronic acid loads, and elevated fibroblast growth factor 23 (FGF-23), sarcopenia contribute to the increased fracture risk

Tentori F et al (2014) High rates of death and hospitalization follow bone fracture among hemodialysis patients. *Kidney Int* 85(1):166–173. doi:10.1038/ki.2013.279

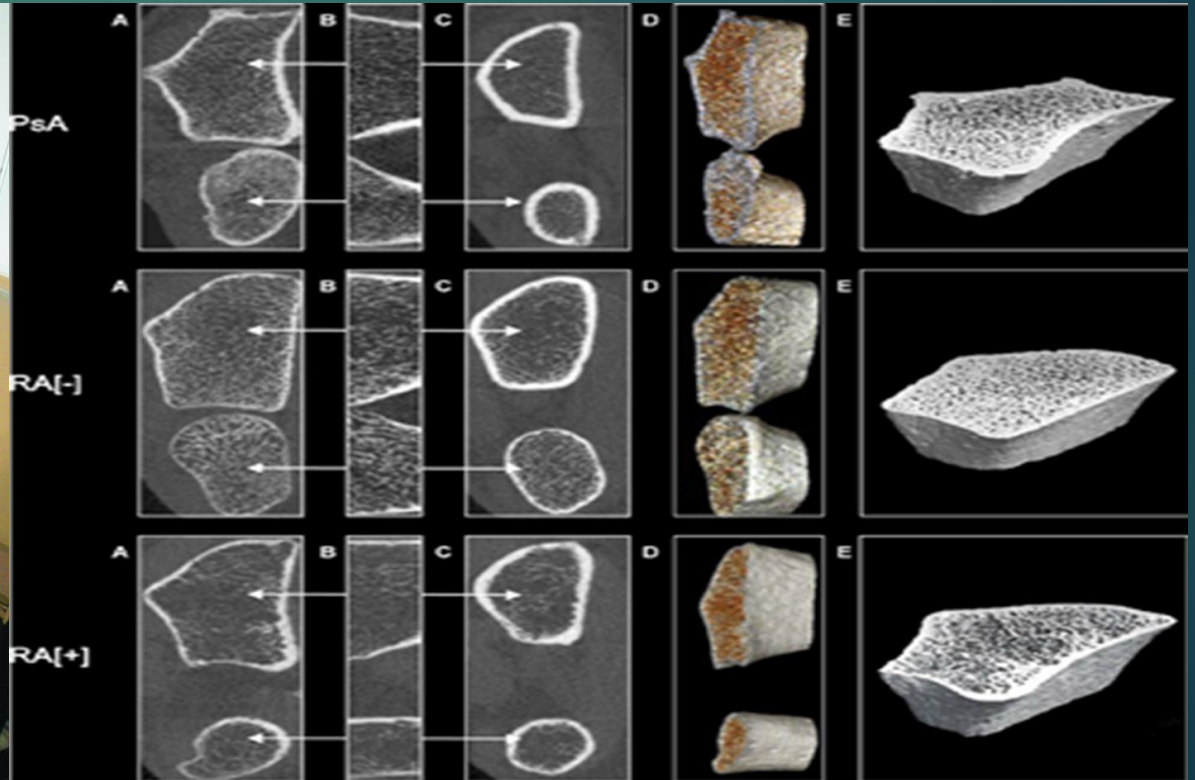
Diagnosis OP in CKD

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

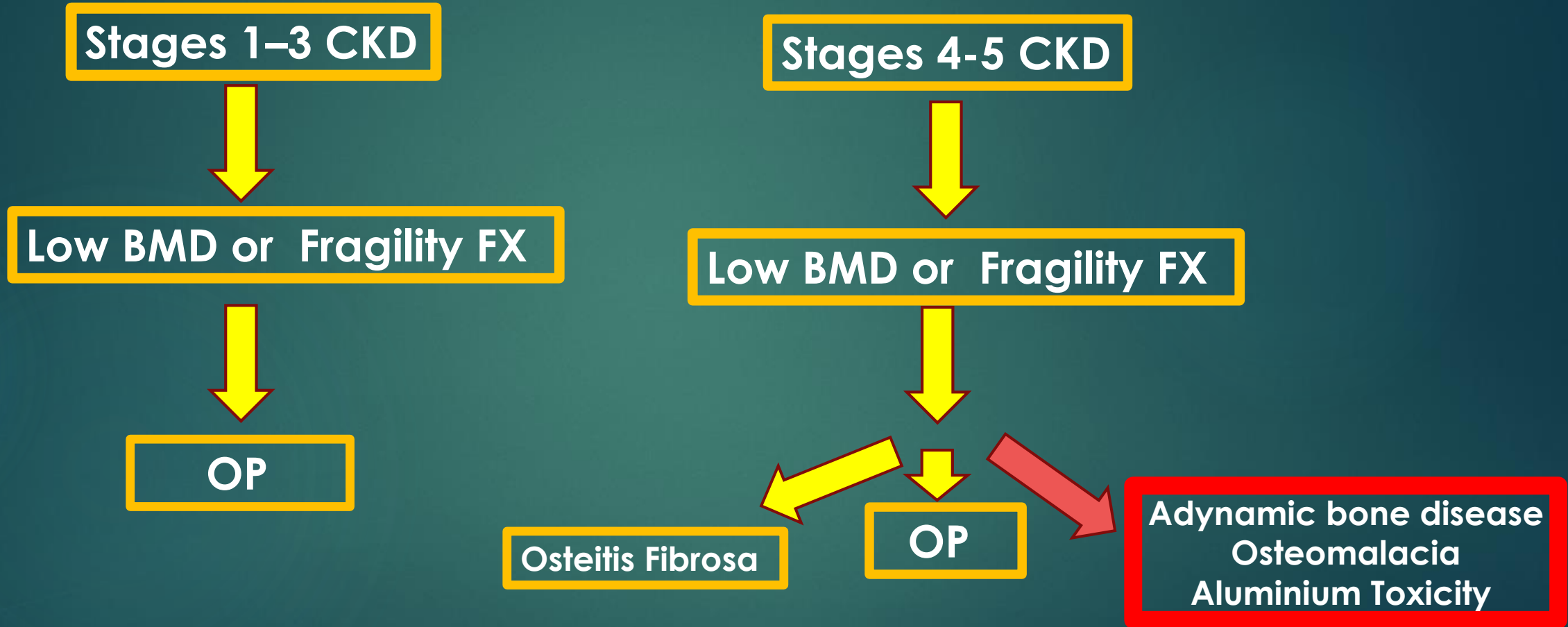
- ▶ High-resolution peripheral quantitative computerized tomography (**HRpQCT**) of the forearm or tibia has been shown to be a better predictor of fracture risk in stages 4 and 5CKD than DXA.



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.

Diagnosis OP in CKD



Low BMD and Fragility
fracture **don't** means
osteoporosis in CKD
stage 4-5



How diagnose Metabolic Bone Disease in CKD (MBD-CKD)

How diagnose Metabolic Bone Disease in CKD (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**

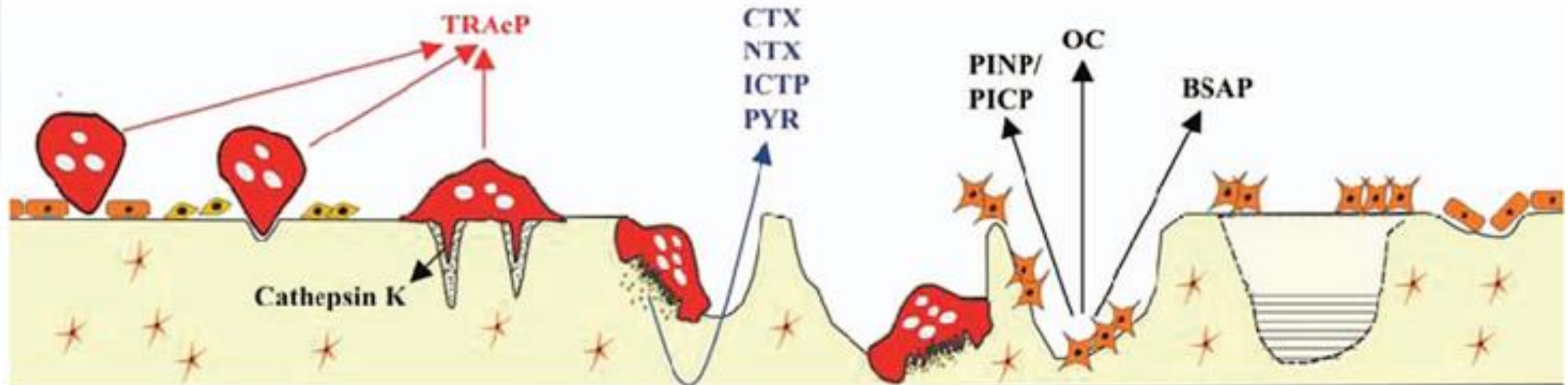
Bone Turnover Markers

Resorption Markers

- **Type I Collagen Degradation products**
 - Pyridinium Crosslinks (PYD and DPD)
 - C-and N-telopeptides (CTX, ICTP, NTX)
- **Enzymes**
 - Tartrate Resistant Acid Phosphatase (**TRACP**) 5b
 - Cathepsin K
 - MMPs

Formation Markers

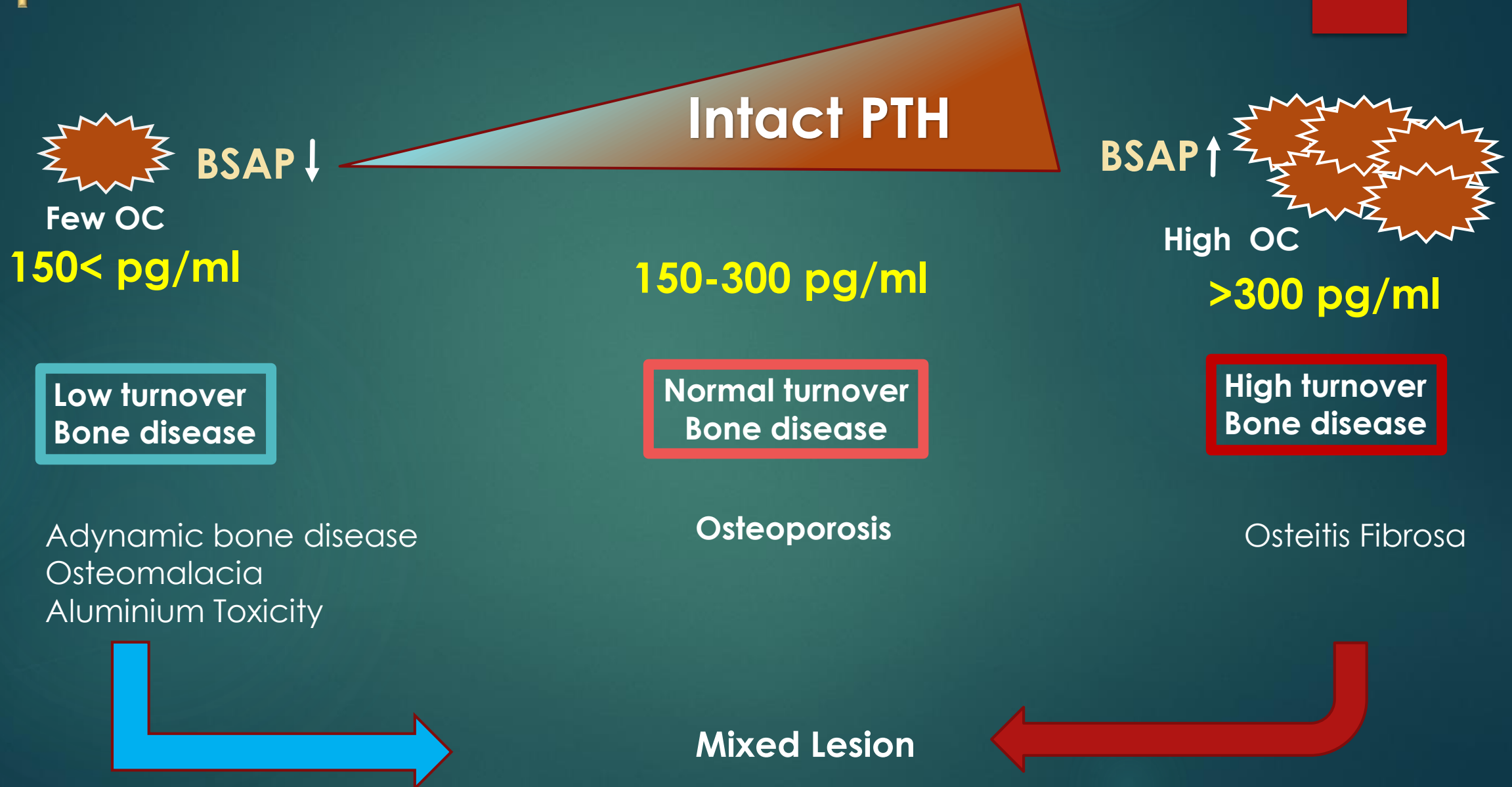
- Matrix proteins
 - Procollagen type I propeptides
 - C-terminal (PICP)
 - N-terminal (PINP)
 - **Osteocalcin (OC)**
- Enzyme
 - bone isoform of alkaline phosphatase (**bone ALP**)



How diagnose Metabolic Bone Disease in CKD (MBD-CKD)

- ▶ In patients with CKD G3a–G5D, we suggest that **measurements of serum PTH or bone-specific alkaline phosphatase** can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover

Spectrum Of Renal Bone Disease



Take home message

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 in CKD

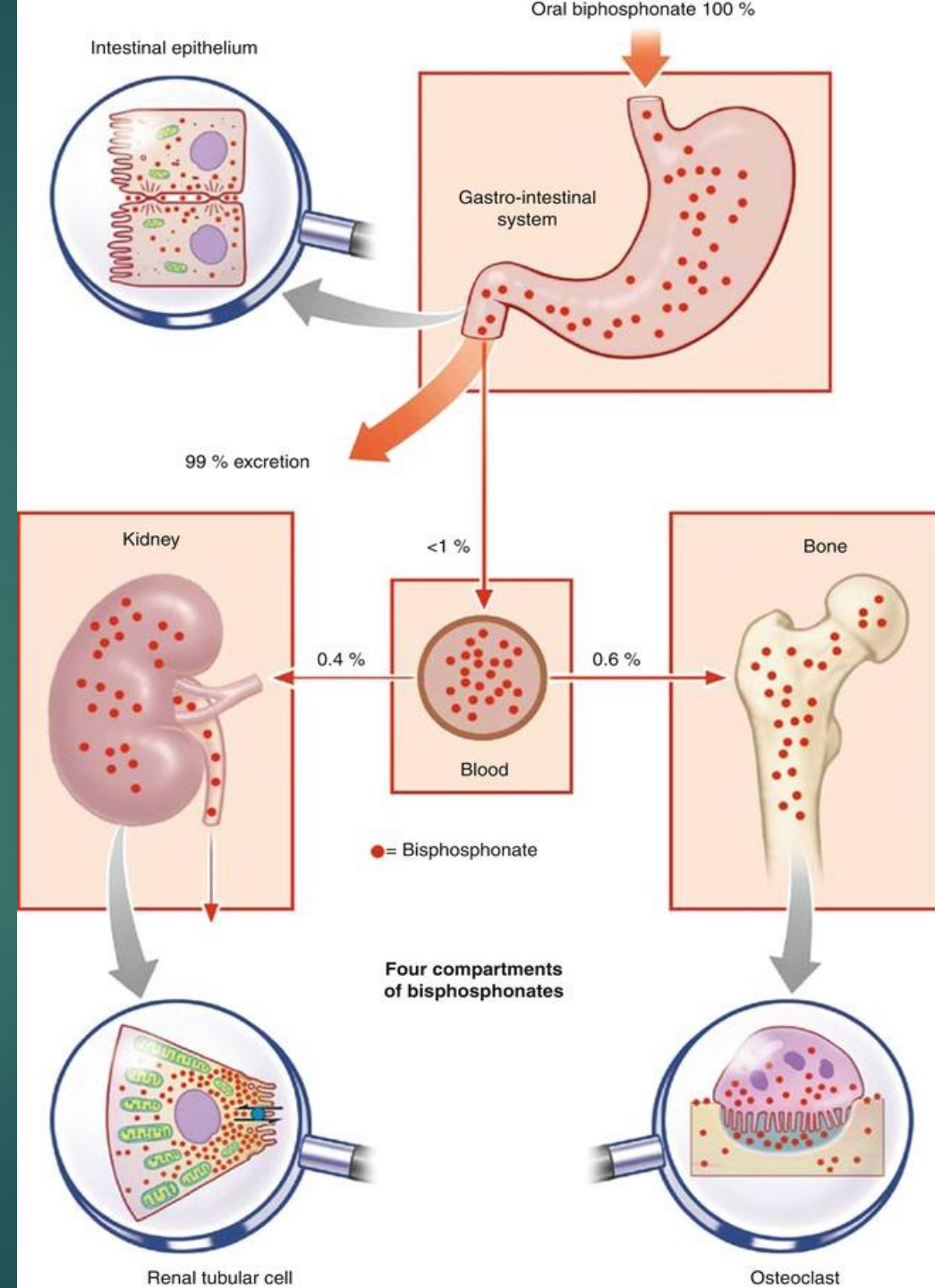
- ▶ As a matter of fact, recent data have shown that excessive **exogenous calcium** in adults may be **harmful** at all stages of CKD
- ▶ This is particularly clear if hypercalcemia, low PTH levels, ABD, and/or arterial calciication are present
- ▶ Repletion of **nonactivated vitamin D** stores is accomplished using cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) and should target a serum 25-hydroxy vitamin D level >30 ng/mL.
- ▶ Treatment with an **activated vitamin D** agent should target a PTH level <70 pg/mL for stage III CKD patients or <110 for stage IV CKD patients, and requires monitoring of serum calcium and phosphate levels

Management of OP in Stages 4 and 5 CKD

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**'

Bisphosphonates in CKD

- ▶ Bisphosphonates are cleared by the kidney both by filtration and active proximal tubular secretion.
- ▶ About 50% of that excreted by the kidney



Bisphosphonates in CKD

- ▶ Bisphosphonates can safely be used at stage to 1 - 3 CKD stages, hemodialysis and after the kidney transplant.
- ▶ When bisphosphonates are given stage 4 CKD patients it seems reasonable to **reduce the dose to 50%**.
- ▶ Rheumatologist and metabolic disease physicians tend to use **ibandronate** and **pamidronate** & **risedronate** especially for patients with CKD, dialysis and myeloma

Bisphosphonates renal toxicity

- ▶ Oral bisphosphonates have never been shown to have any renal toxicity while intravenous bisphosphonates may have
- ▶ Intravenous ibandronate, has not been shown in either clinical trials nor post marketing reports to have a negative effect on the kidney
- ▶ There have never been any head-to-head studies in normal, healthy subjects or in subjects with impaired GFR on renal effects between these two bisphosphonates.
- ▶ Even zoledronic acid, when administered slower (60 min) than the registered label (15min) seems safe in clinical experience even in those patients with impaired GFR.

3 new interesting study on efficacy and safety of bisphosphonates in CKD

AMERICAN SOCIETY OF BONE AND MINERAL RESEARCH 2017 ANNUAL MEETING.

SEPTEMBER 8–11, 2017, DENVER, COLORADO

Are BPs effective for improving BMD in CKD?

- ▶ The **efficacy of bisphosphonate** in patients with moderate or severe CKD [estimated glomerular filtration rate [eGFR] of <45 mL/min), looking at bone-mineral density **(BMD) changes** in a Danish population between 1999 and 2016. The study excluded patients who had previously used oral bisphosphonates
- ▶ The review included data from a regional database of all DXA-based routine measurements in Funen, Denmark, in which the use of **oral bisphosphonates** in moderate to severe CKD was expectedly rare, with only **81 patients** identified.
- ▶ 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.
- ▶ After adjustment for factors including age, sex, body mass index (BMI), baseline eGFR, fracture history, and other comorbidities, the mean difference was +1.81% and, in the propensity score-adjusted analysis, the difference was +2.44% in favor of oral bisphosphonate use.
- ▶ The finding of an improved BMD is good news, as this suggests these drugs could be **effective at improving bone BMD**

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 Cockcroft-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.

The second study evaluated all-cause mortality rates among a population of patients in UK primary-care records with eGFR <45 (CKD 3B), aged 40 and older.

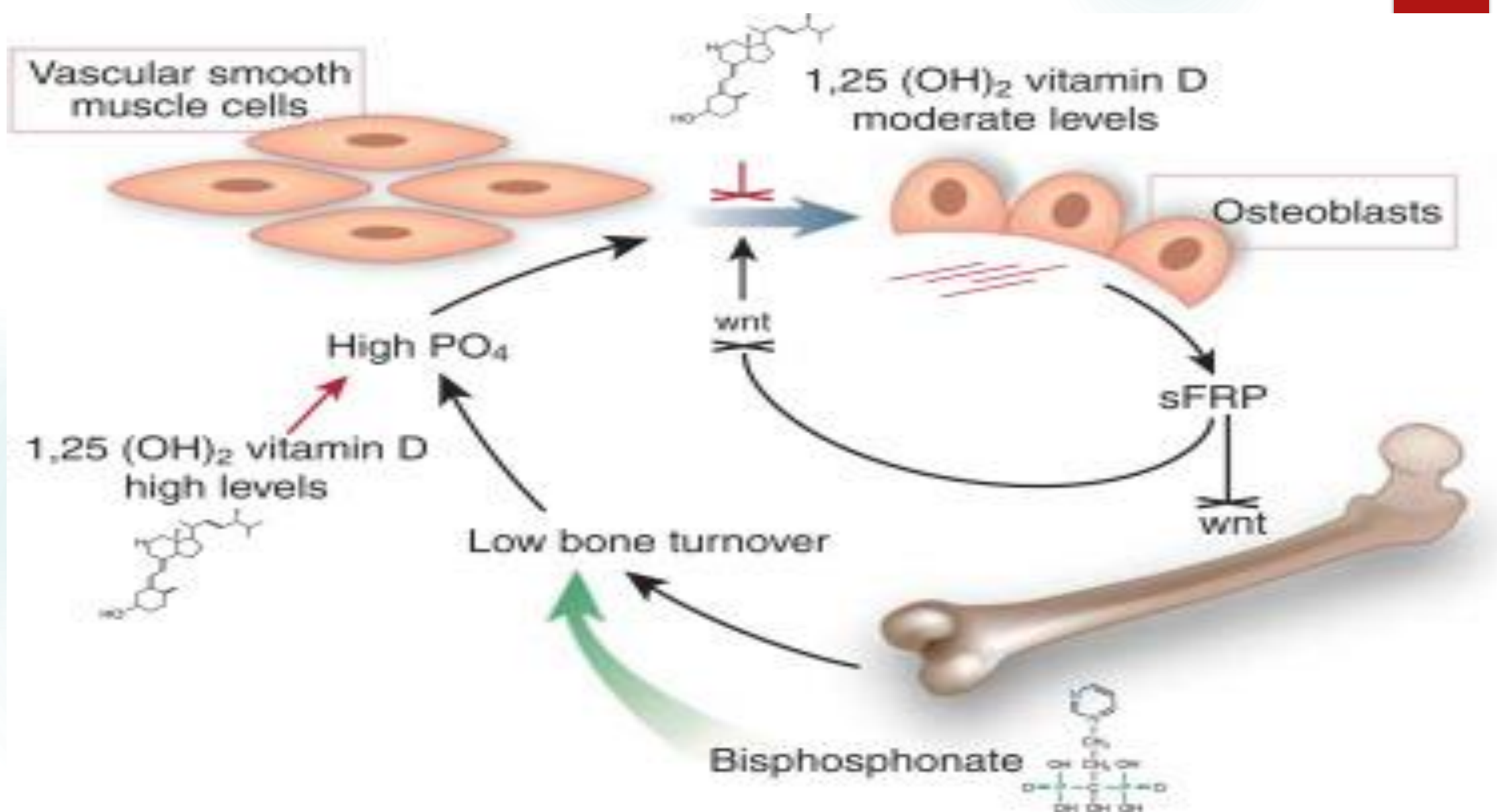
- ▶ They found that among 18,904 oral bisphosphonate users with CKD 3B, compared with 190,850 nonusers also with CKD 3B, the **bisphosphonate users had significantly lower all-cause mortality**, with an adjusted HR of 0.85 (95% CI 0.82–0.88).
- ▶ **Greater reductions** in mortality linked to bisphosphonate use were seen in **women** (HR, 0.82) ,than men (HR, 0.96); in those with **previous fracture** (HR, 0.78) compared with no previous fracture (HR, 0.90); and in those with more **severe CKD** (stage 4 or higher; HR, 0.71) compared with stage 3B (HR, 0.88; all $P < .0001$).
- ▶ Reassuring that bisphosphonates are, despite being contraindicated in some of these patients, not associated with increased mortality in actual users of the drug

Third analysis evaluated the risk of acute kidney injury (AKI), gastrointestinal events, and hypocalcemia leading to hospital admission in the same UK population of patients with stage 3B or higher CKD, with an eGFR < 45 mL/min, but at age 50 or older

- ▶ Among those patients, 19,315 were oral bisphosphonate users who were compared with 210,568 bisphosphonate nonusers.
- ▶ Overall, 8846 patients developed acute kidney injury, 499 had gastrointestinal events, and 682 developed hypocalcemia.
- ▶ In comparing the incidence rates of events between oral bisphosphonate users and nonusers, the hazard ratios (HR) were not significant for acute kidney injury (HR, 0.95; 95% CI, 0.8–1.07), gastrointestinal events (HR, 0.85; 95% CI, 0.48–1.52) or hypocalcemia (HR, 1.11; 95% CI, 0.77–1.62).
- ▶ "Bisphosphonate use is not associated with acute kidney injury, gastrointestinal events, or hypocalcemia among patients with moderate to severe (stage 3B+) CKD

Bisphosphonates toxicity in CKD

A theoretical concern about bisphosphonate toxicity in CKD is a correlation between low bone turnover and **vascular calcification**. It is postulated that the mineralizing bone surface buffers the extracellular phosphate concentration. With a low mineralizing surface, phosphate loads cannot be deposited into the bone and instead increase the serum concentrations



Duration of Bisphosphonates in CKD

While there are no data on duration of bisphosphonate use in more advanced CKD, it seems logical that because bone retention may be greater in CKD, that duration of use could be shorter than 3–5 years.



Denosumab

Denosumab

- ▶ Denosumab is cleared by the reticuloendothelial system and not the kidney, which forms the basis of the lack of a lower GFR limit with denosumab use.
- ▶ Efficacy of denosumab, which increases BMD and suppresses fractures, did not differ depending on kidney function
- ▶ Denosumab significantly increased BMD of the lumbar spine and femoral neck in hemodialysis patients, although the sample size was small

S. A. Jamal," et al., "Effects of denosumab on fracture and bone mineral density by level of kidney function," Journal of Bone and Mineral Research,vol.26,no. 8, pp. 1829–1835, 2011

Denosumab

For the renal population, there are additional considerations to entertain with denosumab use

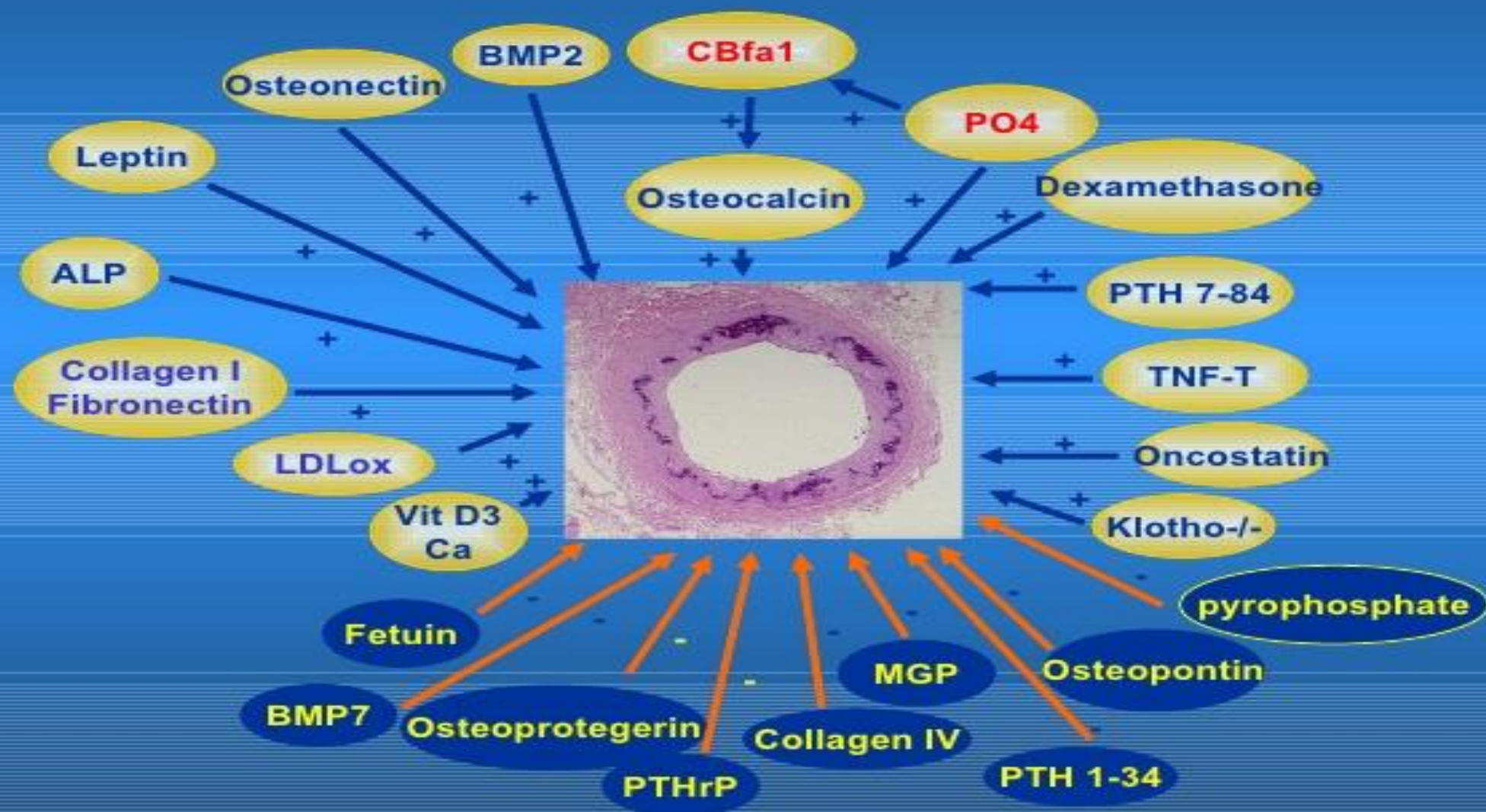
Denosumab Hypocalcemia

- ▶ Denosumab may induce **hypocalcemia** through strong suppression of bone resorption, which tends to be amplified in CKD patients
- ▶ It may be especially important if they are **concomitantly** receiving calcium-sensing receptor agonists such as **cinacalcet**
- ▶ This hypocalcemic effect may be mitigated by ensuring adequate 25 hydroxy-vitamin D levels and calcium intake.

Denosumab vascular calcification?

- ▶ Vascular calcification is the major cause of death in the CKD population.
- ▶ This is an important issue as serum OPG levels rise with denosumab administration as a regulatory response once RANK pathways are inhibited.
- ▶ There is conflicting and opposing data with regard to the influence of OPG on vascular calcification

Inductors (+) and inhibitors (-) of vascular calcifications



Denosumab and mineralization defect

- ▶ On quantitative bone histomorphometry in the original registration trials, there were significantly more subjects on denosumab that had no single tetracycline labels as opposed to the placebo groups that had tetracycline labels.
- ▶ While absent single tetracycline labels may be seen in 0.5% of healthy normal subjects, the preponderance of absent labels with denosumab suggests the absence of bone mineralization during the administration in a subset of the clinical trial subjects

Raloxifene in CKD

- ▶ Raloxifene, a selective estrogen receptor modulator **improved BMD** in postmenopausal women with CKD
- ▶ **Greater increases** in BMD were associated with lower creatinine clearance
- ▶ Patients on raloxifene showed **slower progression of kidney disorders** and significantly fewer kidney-related adverse events compared to the placebo group.
- ▶ **Reduced** serum **calcium** concentration and increased **PTH** secretion were reported.

Morello KC, Wurz GT, DeGregorio MW. Pharmacokinetics of selective oestrogen receptor modulators. Clin Pharmacokinet.2003;42:361-72.

Bazedoxifene in CKD

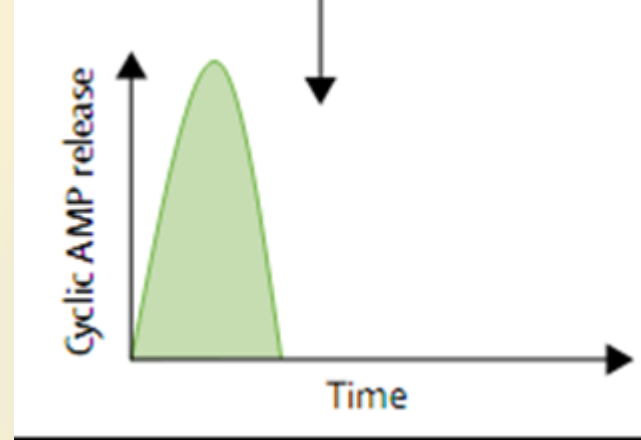
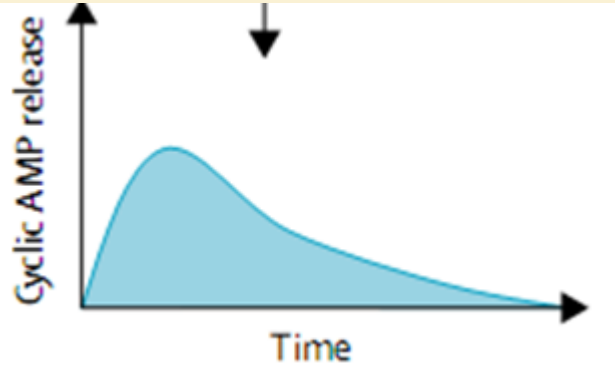
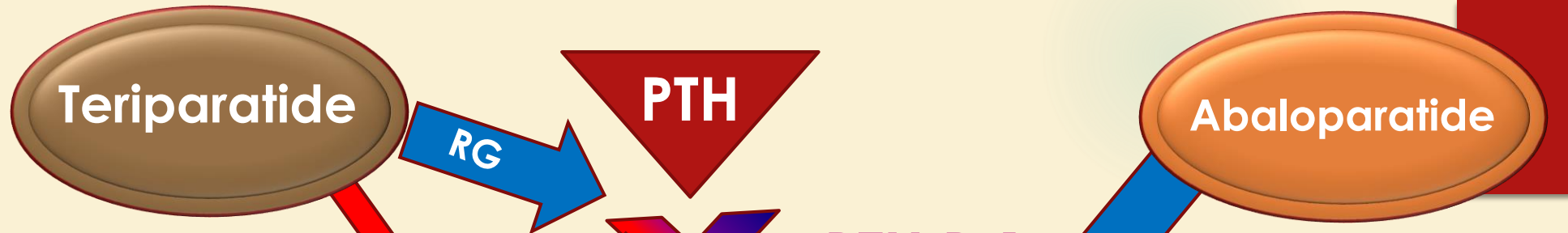
- ▶ Bazedoxifene, another SERM approved for osteoporosis treatment, has also been evaluated in patients with mild to moderate renal impairment.
- ▶ It reduced the risk of fractures and was safe, but the majority of patients included had a **GFR 60-90 mL**

Adami S, et al. The efficacy and safety of bazedoxifene in postmenopausal women by baseline kidney function status. *Climateric*. 2014 Jun;17(3):273-84

Teriparatide in CKD

- ▶ It is unknown if sustained and uncorrected elevated PTH levels could mitigate the anabolic effect of teriparatide
- ▶ PTH inhibits sclerostin binding to osteoblasts, thereby promoting bone formation which is elevated in CKD

Cejka D, et al. Sclerostin serum levels correlate positively with bone mineral density and microarchitecture in haemodialysis patients. Nephrol Dial Transplant 2012; 27:226.



Long duration
Response
Osteocatabolic

↑ RANK L
↓ OPG

Short duration
response
Osteoanabolic

↑ Osteoblast differen
↓ OB Apoptosis

Teriparatide in CKD

- ▶ In teriparatide trials had small sub-sets that had eGFR down to 30 mL/min.
- ▶ In these subsets, there were similar increases in BMD and PINP
- ▶ Fracture numbers were too small to have power for statistical analysis
- ▶ There were no changes in renal function as assessed by changes in serum creatinine

Is teriparatide effective for increasing BMD in CKD?

A recent post-hoc analysis of a post marketing surveillance study that included elderly female Japanese patients with OP who were at high risk of fracture (82% had a previous fracture) and stage 4 or 5 CKD and had been receiving subcutaneous teriparatide 20 µg daily for up to 24 months revealed that teriparatide appeared to be effective by increasing BMD and procollagen type 1 N-terminal propeptide

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, though the clinical consequences of this change in serum uric acid over the trial duration are unknown

Abaloparatide (TYMLOS)

- ▶ Theoretically Tymlos had better effect in CKD but till this time there is 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

Anti-sclerostin antibody in CKD

- ▶ In addition to the apparent relationship between sclerostin and bone strength, blood level of sclerostin has been shown to be associated with aorta valve **calcification** and cardiovascular mortality in CKD patients
- ▶ Further studies are needed to investigate the efficacy of sclerostin antibody treatment not only for fracture prevention but also for reducing cardiovascular mortality in CKD patients

Cinacalcet

- ▶ Control of hyperphosphatemia is important for CKD patients to prevent cardiovascular events and reduce the risk of death.
- ▶ The BONAFIDE trial demonstrated that long-term treatment with cinacalcet substantially reduced PTH and diminished elevated bone turnover as well as several biomarkers
- ▶ From a secondary analysis of the EVOLVE trial, cinacalcet reduced the rate of clinical fractures by 16–29%

Angiotensin-Converting Enzyme inhibitors

- ▶ Yamamoto et al reported that dialysis patients who received angiotensin-converting enzyme inhibitors or angiotensin II type I receptor blockers had an approximately 30% lower risk of hospitalization for any fracture

Thank You

