Chronic kidney disease (CKD)-associated osteoporosis

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AZAR 1404

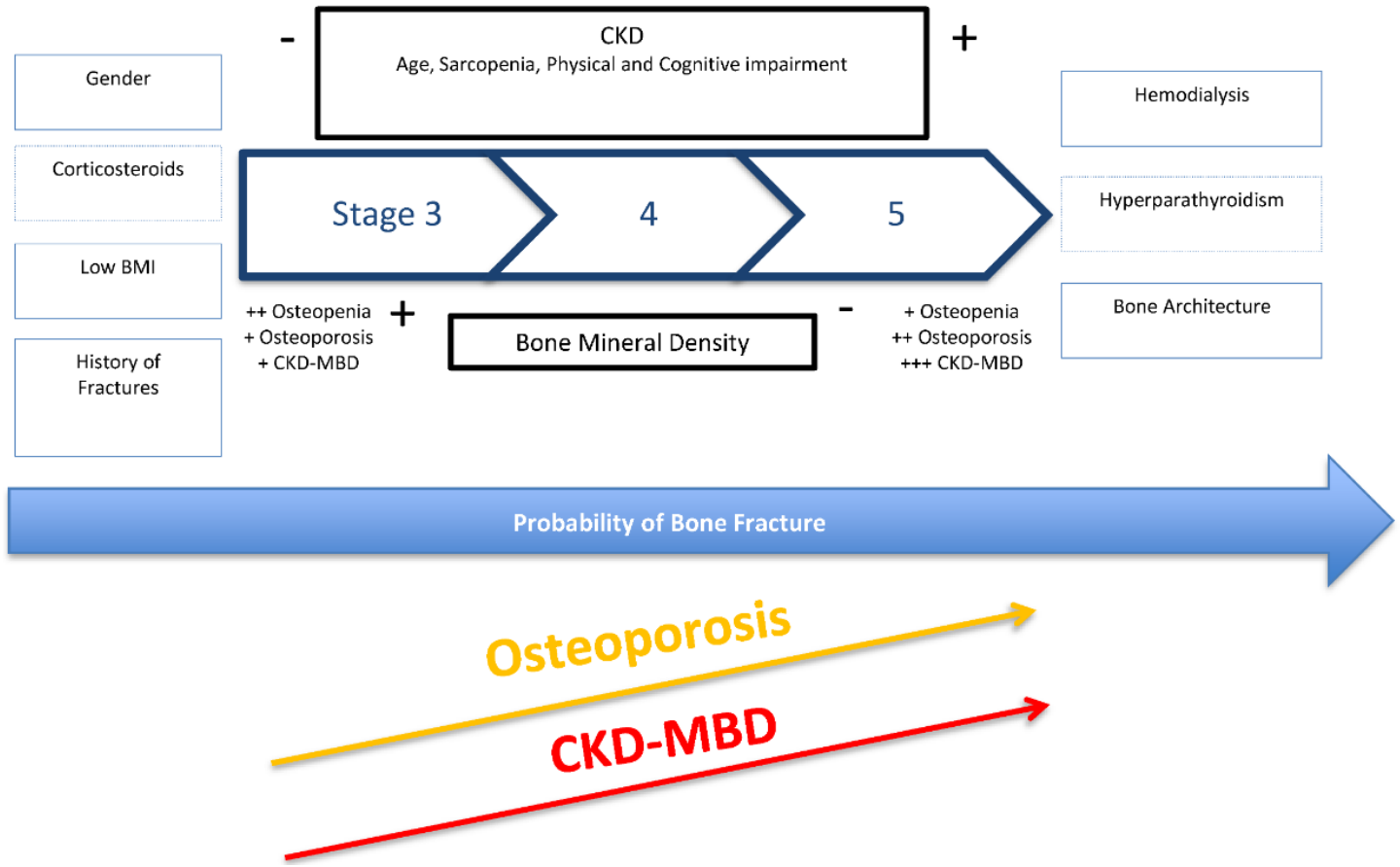
Objectives

- Co-exist of CKD and osteoporosis
- The effects of CKD-MBD on bone strength
- Bone quality versus bone quantity
- The burden and consequences of osteoporotic fractures
- The challenges of diagnostic and therapeutic options in CKDs

chronic kidney disease (CKD)-associated osteoporosis

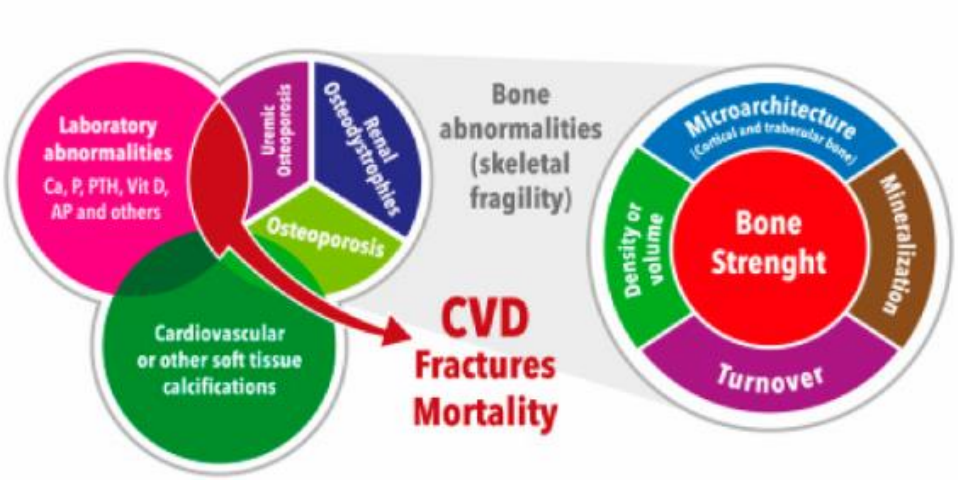
- Worldwide, the prevalence of CKD is >10% and it increases with age (28% among those aged > 70 to 80 years)

- Osteoporosis is also frequent in those over 50 years old, so these two conditions are coexist



CKD M-MBD and vascular calcification

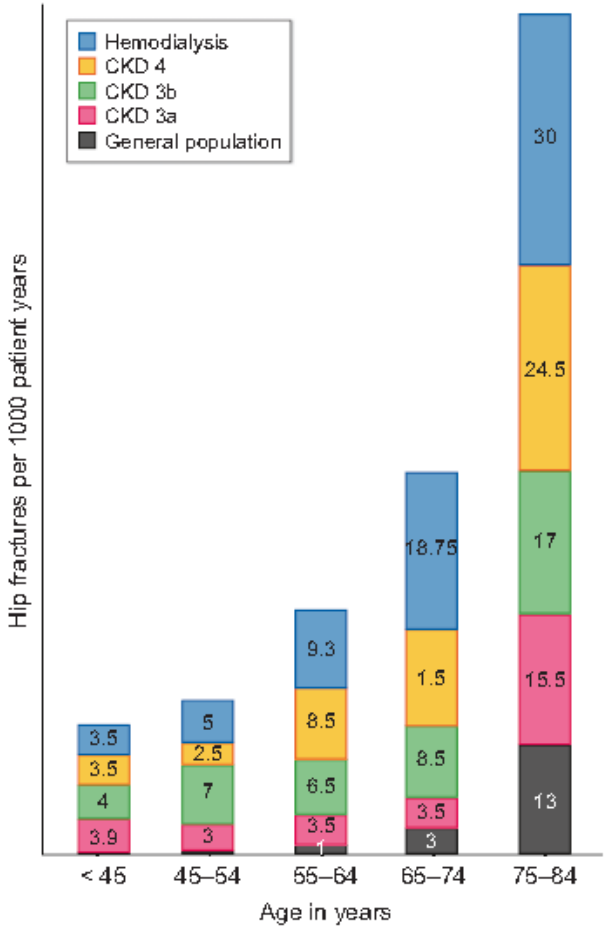
- Bone loss has been associated with the progression of aortic Calcification in the general population
- an association between the presence of vertebral fractures and VC in HD patients was also observed



Imbalance between inhibitory and promoters factors:

- inhibitory factors: pyrophosphates, fetuin-A, osteoprotegerin ,Matrix-Gla protein
- Promoters: Ca, P, bone morphogenic protein-2 (BMP-2), BMP-4, RANK-L

Fracture risk in CKD as a condition of accelerated aging



- The incidence of hip fracture across the spectrum of CKD is 2–4 times higher than people without CKD matched for age and sex
- Fracture incidence increases steadily as kidney function declines from 15 to 20, 24, 31, and 46 per 1000 person-years for CKD G1-2, 3A, 3B, and 4, respectively
- older than 65 years, women (10%)and men (5%)

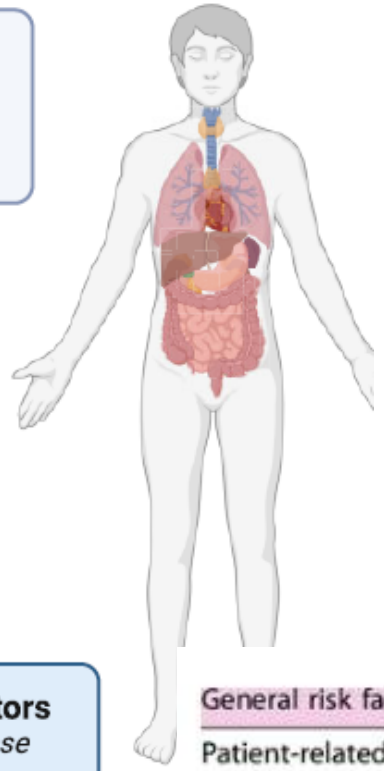
The risk of longer hospitalizations and mortality following a hip fracture remains substantially higher in people with CKD

Traditional risk factors
Age-related osteoporosis
LIfe-style (diet, exercise)
Hypogonadism

Systemic illness
Cause of CKD
Comorbidities

Polypharmacy
Immunosuppressants
Drugs affecting mineral metabolism
Falls risk

CKD-associated risk factors
Debut and duration of disease
Chronic inflammation
Metabolic acidosis
Mineral metabolism disturbances



Risk factors contribute to bone fragility in CKD

General risk factors	CKD-specific
Patient-related (non-modifiable) • Age • Sex • Ethnicity • Past history of fracture	• Hyperparathyrodism • Low nutritional and activated vitamin D • Disordered mineral metabolism • Chronic inflammation • Metabolic acidosis • Premature hypogonadism • Medications o Steroids o Phosphate binders (eg, aluminium) o CNI • Dietary restriction • Dialysis-related amyloidosis
General (modifiable) • Low physical activity • Smoking • Alcohol • Medications (eg, streoids) • Diabetes • Sarcopenia • Chronic inflammatory disorders	• Higher prevalence of general risk factors for osteoporosis

Risk factors contribute to bone fragility in CKD

underlying etiology of CKD :

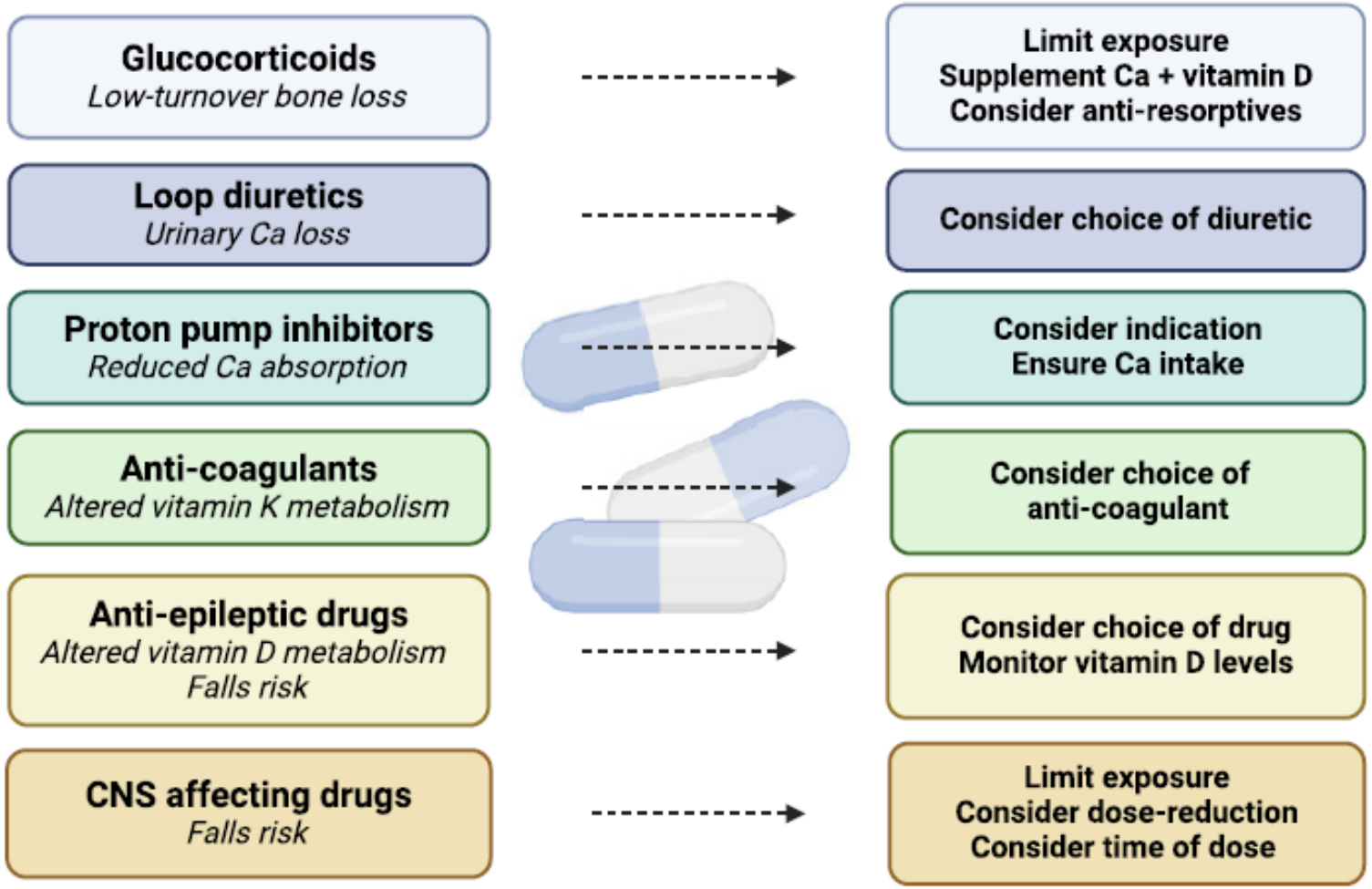
- Patients with autosomal dominant polycystic kidney disease exhibit a particular bone phenotype characterized by low bone turnover with preserved bone mass and elevated sclerostin levels
- Diabetes mellitus adversely affects bone quality, with increased fracture risk : Elevated sclerostin levels, accumulation of advanced glycation end-products (AGEs), inflammation, and oxidative stress are possible causes of bone quality impairment in diabetic CKD patients
- SLE patients show a high rate of vertebral fractures with normal BMD, suggesting an impairment of bone quality

Risk factors contribute to bone fragility in CKD

- Chronic metabolic acidosis:, stimulates osteoclastic activity and inhibits osteoblastic activity
- Hypogonadism: CKD who had been diagnosed with osteoporosis, the prevalence of early menopause was 9.4%
- Estrogen deficiency leads to increased osteoblast apoptosis as well as increased osteoclastic half-life and activity, leading to a negative bone balance
- corticosteroid: bone resorption is initially increased by enhanced osteoclast differentiation and maturation, and subsequently, osteoblastogenesis is inhibited and osteoblast and osteocyte apoptosis are promoted, resulting in decreased bone formation with long-term use

Clinical Kidney Journal

Limit exposure to drugs affecting bone health



CKD are more prone to falls

- General frailty, muscle weakness, impaired mobility, cognitive decline, neuropathy, and poly pharmacy
- The fear of falling can lead to decreased physical activity, further increasing the risk.
- The most common sites of fracture are the femur (neck or intertrochanteric region) , forearm, and humerus
- Vertebral fractures are also very common in patients with CKD, but frequently underdiagnosed as many are asymptomatic

Assess musculoskeletal function and frailty

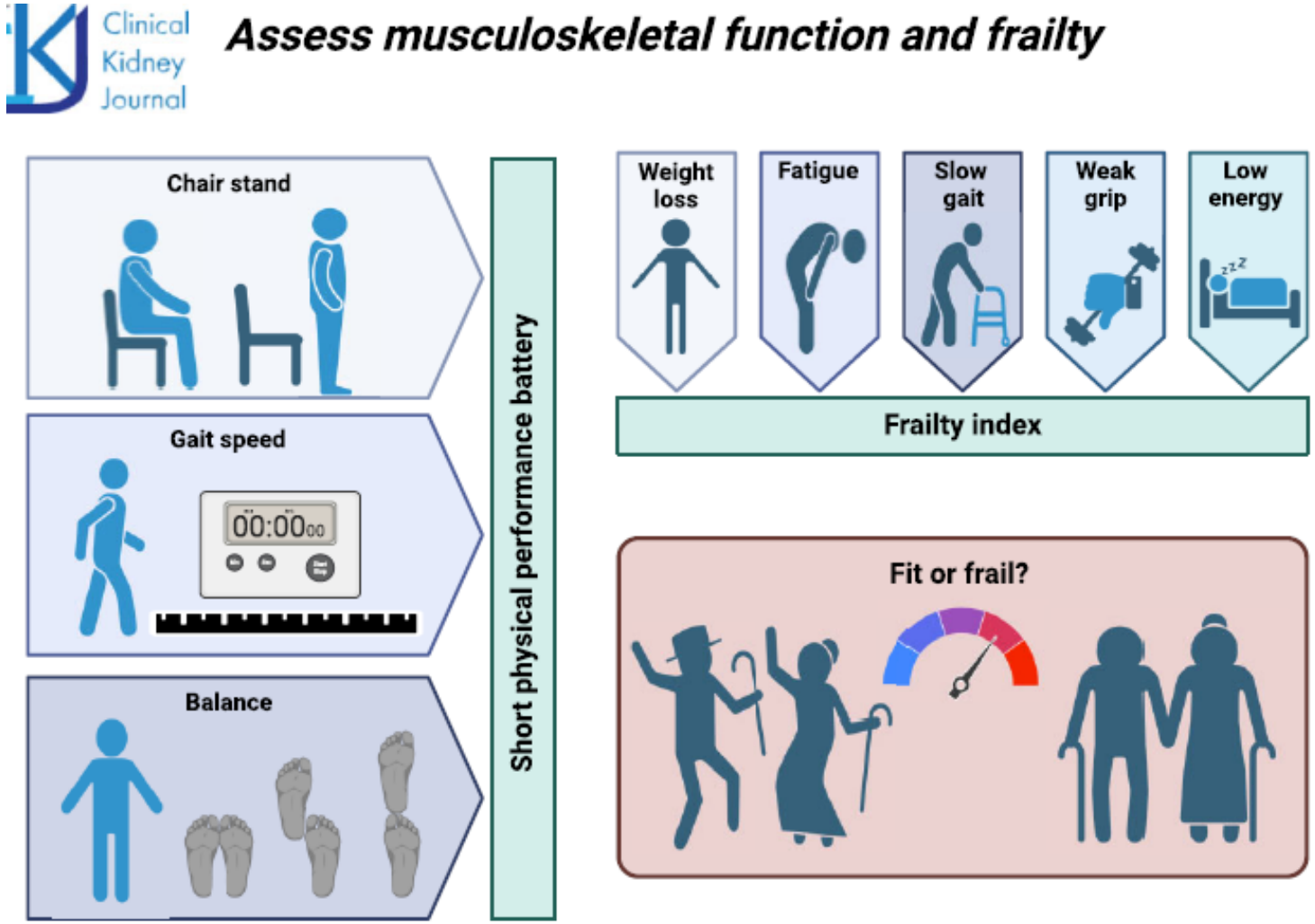
- Mechanical loading: A key for the development and maintenance of bone strength
- Sarcopenia : loss of muscle mass and function,contributes to falls and fractures

- Assess the function of the musculoskeletal system through a set of short exercises(gait speed, balance tests, standing up from a chair)

- Evaluation of bone and muscle mass : body composition can be measured by dual-energy X-ray absorptiometry(DXA) or computed tomography(CT) enabling simultaneous

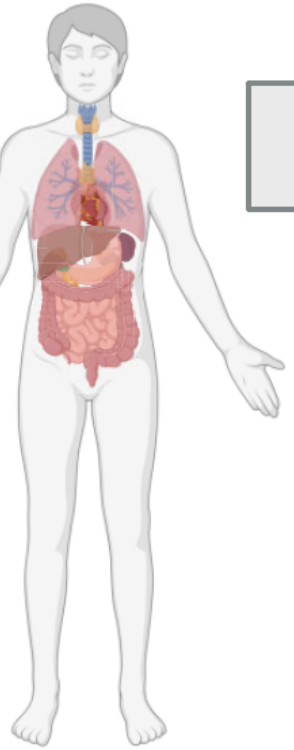
Fried Frailty Phenotype:

- weight loss
- fatigue
- decreased grip strength
- slow gait speed
- low physical activity

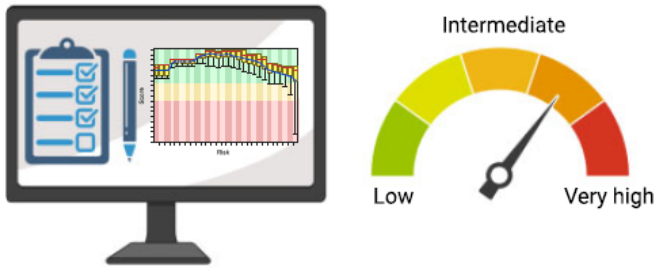


Fracture risk prediction tools

- FRAX®, QFracture®, and Garvan has been shown to perform acceptably for patients with CKD
- 10-year probabilities of a major osteoporotic fracture or a hip fracture.
- FRAX®plus : number of falls in the previous year
- previous fracture, particularly if caused by low- energy trauma implies bone fragility and is a strong predictor of future fractures



Use a fracture risk assessment tool
FRAX, QFracture, Garvan



Take action
Communicate risk
Consider intervention threshold

Fracture risk factors

Major (RR > 2)	Minor
• BMD T-score ≤ −2.5 SD • Age ≥ 65 years • Women • Previous fragility fracture (spine, hip, wrist) • BMI ≤ 20 kg/m^2 • First-degree relative with hip fracture • Glucocorticoids (≥5 mg/day of prednisone or equivalent for ≥3 months) • ≥2 Falls in the past year	• Hyperparathyroidism • Eating disorders • Chronic malnutrition or malabsorption • Hypogonadism or early menopause (40–45 years) • Treatment with aromatase inhibitors, gonadotropin-releasing hormone agonists • Active smoking • Alcohol (>3 U/day) • Diabetes mellitus type 1 • Rheumatoid arthritis • Hyperthyroidism • Immobilization

BMD: bone mineral density; BMI: body mass index.

FRAXR (Fracture Risk Assessment Tool) score

Please answer the questions below to calculate the ten-year probability of fracture with or without BMD.

Continent Select a continent

Country Select a country

Local Reference Reference (optional)

1. Age (between 40 and 90 years) Age

2. Sex Female Male

3. Weight

kg 0 kg / cm

4. Height cm 0

5. Previous Fracture X

6. Parent Fractured Hip X

7. Current smoking X

8. Glucocorticoids X

9. Rheumatoid arthritis X

10. Secondary osteoporosis X

11. Alcohol 3 or more units/day X

12. Femoral neck BMD Select BMD

Calculate Clear

FRAXR (Fracture Risk Assessment Tool) score

- Intermediate: FRAXR ≥ 5% for major osteoporotic fracture
- high risk: FRAXR > 3% for hip fracture or ≥7.5% with BMD or ≥10% without BMD for major osteoporotic fracture

additional factors:

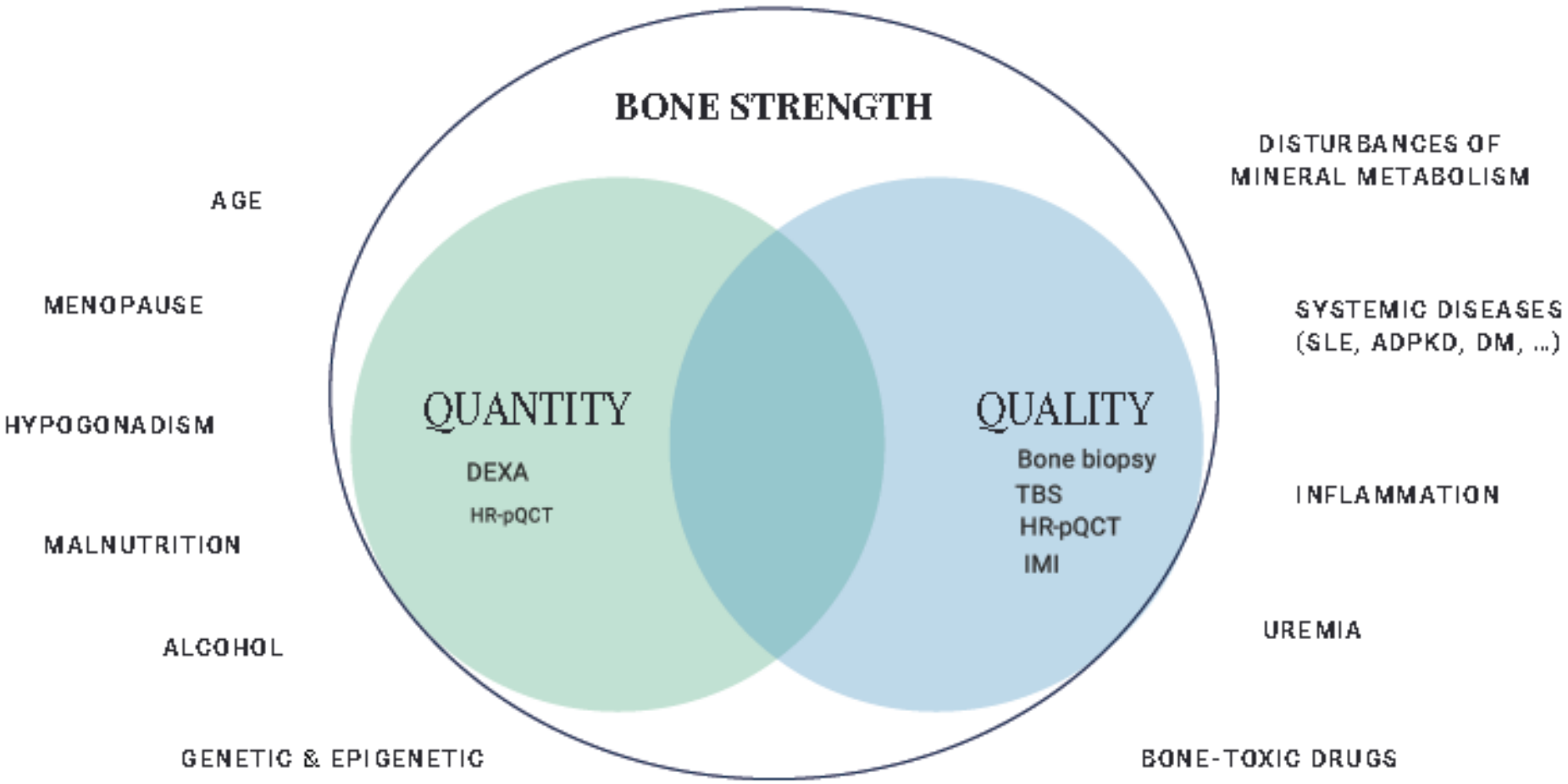
- number of falls and recency of an osteoporotic fracture
- Vertebral fracture assessment and/or lateral spine imaging is recommended if there is a history of ≥4 cm height loss, kyphosis
- recent or ongoing long-term oral glucocorticoid therapy (equivalent to ≥5 mg prednisone or equivalent per day for ≥3 months
- T-score ≤ −2.5 SD

initiation of anti-osteoporotic treatment

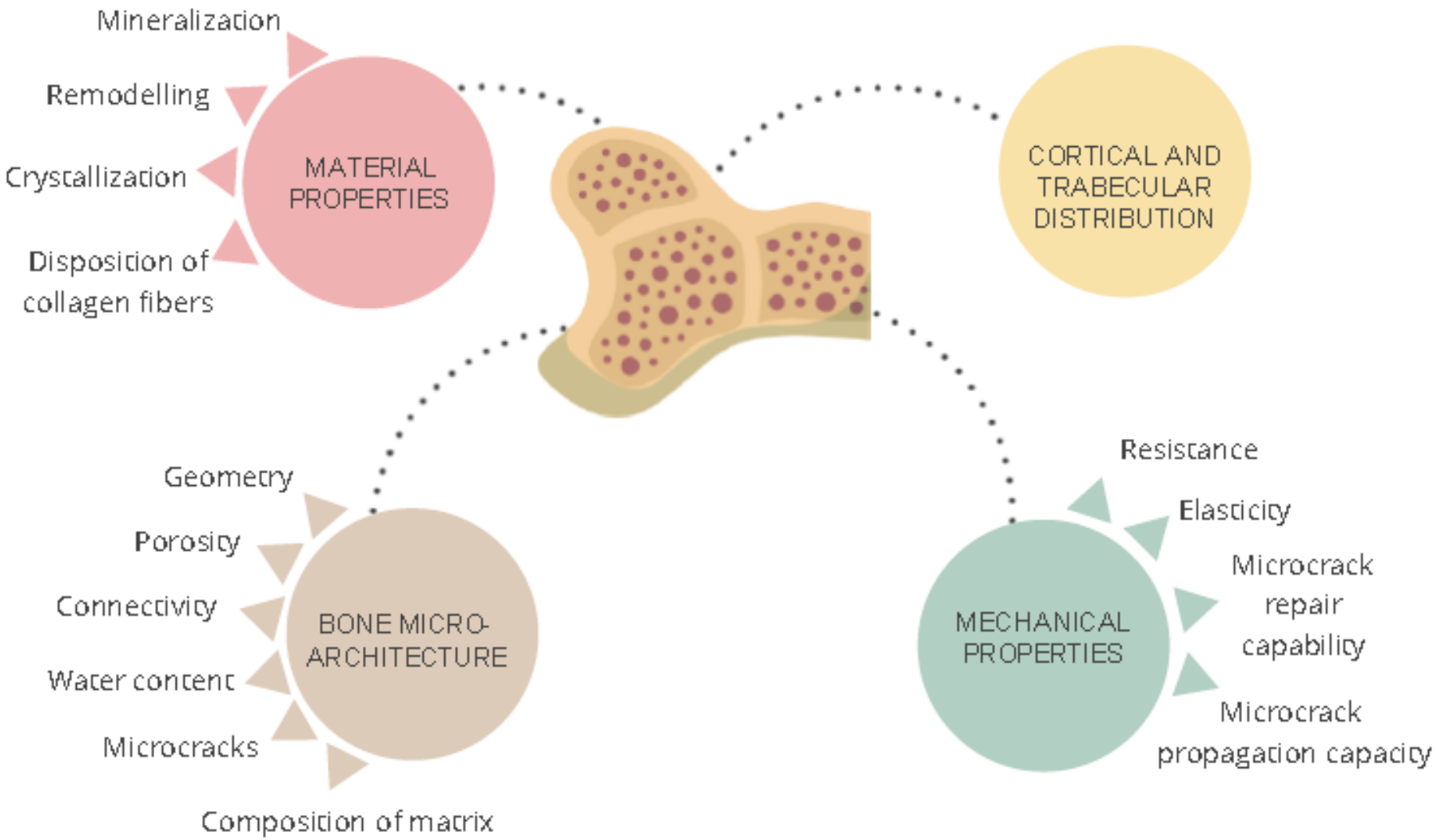
- when FRAXR is ≥3% for hip fracture or ≥10–20% for major osteoporotic fracture
- patients who have experienced a previous fragility fracture
- postmenopausal women and men aged > 50 years who are on long-term corticosteroid treatment or at high doses

BMD is not only useful for osteoporosis assessment but also to decide the most appropriate anti-osteoporotic treatment (i.e., BMD <−3 SD or <−3.5 SD indicates a high risk of fracture), to assess the treatment response, and to check adherence (i.e., with denosumab)

Determinants of bone strength in chronic kidney disease



Determinants of bone quality



Bone mineral density evaluation in CKD

- KDIGO guidelines in 2009 did not recommend routine BMD testing in CKD G3-5D:

  "BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of ROD (evidence 2B)

- guidelines were updated in 2017 recommending that "in patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (evidence 2B)

Although quantification of BMD through DXA is the gold standard for evaluating bone fragility, this may underestimate the risk of fracture in a patient with CKD since a main limitation of this technique is that it essentially measures bone quantity

Decreased Bone Mass in CKD

- The human skeleton is composed of cortical and trabecular bone, with the former representing up to 80% of the skeletal mass.
- The main role of cortical bone is to provide mechanical support, whereas trabecular bone also serves an endocrine function
- The proportions of the two bone compartments depend on the skeletal site, with a predominance of cortical bone in the hip and mid-radius and trabecular bone in the spine.
- Secondary hyperparathyroidism causes mainly cortical bone loss (disproportionally high fracture burden in the peripheral skeleton)
- patients with low turnover had more vertebral fractures than patients with osteitis fibrosa, in whom fractures were predominantly appendicular

Decreased Bone Mass in CKD

- As 35% of patients with CKD are older than 65 years, loss of bone mass related to aging is expected in this population.
- Patients with CKD had significantly reduced BMD at the spine (−6.3%), femur (−12.1%), forearm (−5.7%), and whole body (−4.2%) compared with healthy controls.
- patients receiving dialysis experience a loss of 1.2% of BMD at the total hip per year

DXA for Bone Quantity Measurement

- DXA is a non-invasive radiographic technique that measures BMD (g/cm2) at the total hip, femoral neck, lumbar spine (L1/L2–L4), and distal forearm (distal third of radius).
- has long been the gold standard for the assessment of bone strength in the general population
- BMD is a good predictor of peripheral and hip fractures across the spectrum of CKDG 3-5D

Definitions

T-score, which expresses the number of standard deviations of BMD with respect to a young woman aged between 20 and 29 years (maximum peak bone mass)

- Osteopenia: T-score between −1 and −2.5 SD
- Osteoporosis: T-score ≤ −2.5 SD
- Severe osteoporosis: T-score between −3.5 and −4.5 SD
- Established osteoporosis fragility fracture with a T-score ≤ 2.5 SD.
- the presence of a hip fracture is currently considered a diagnosis of “osteoporosis,” as well as a non-hip fracture with “only” densitometric osteopenia

The Z-score represents the deviation of bone mass from the expected value for the patient’s age and sex and is used for the diagnosis of osteoporosis in premenopausal women or men aged < 50 years

Indications for DXA

- Postmenopausal women
- cases of fragility fractures
- presence of two or more clinical risk factors
- treatment with aromatase inhibitors, anti-androgenic drugs, or glucocorticoids, and comorbidities associated with secondary osteoporosis

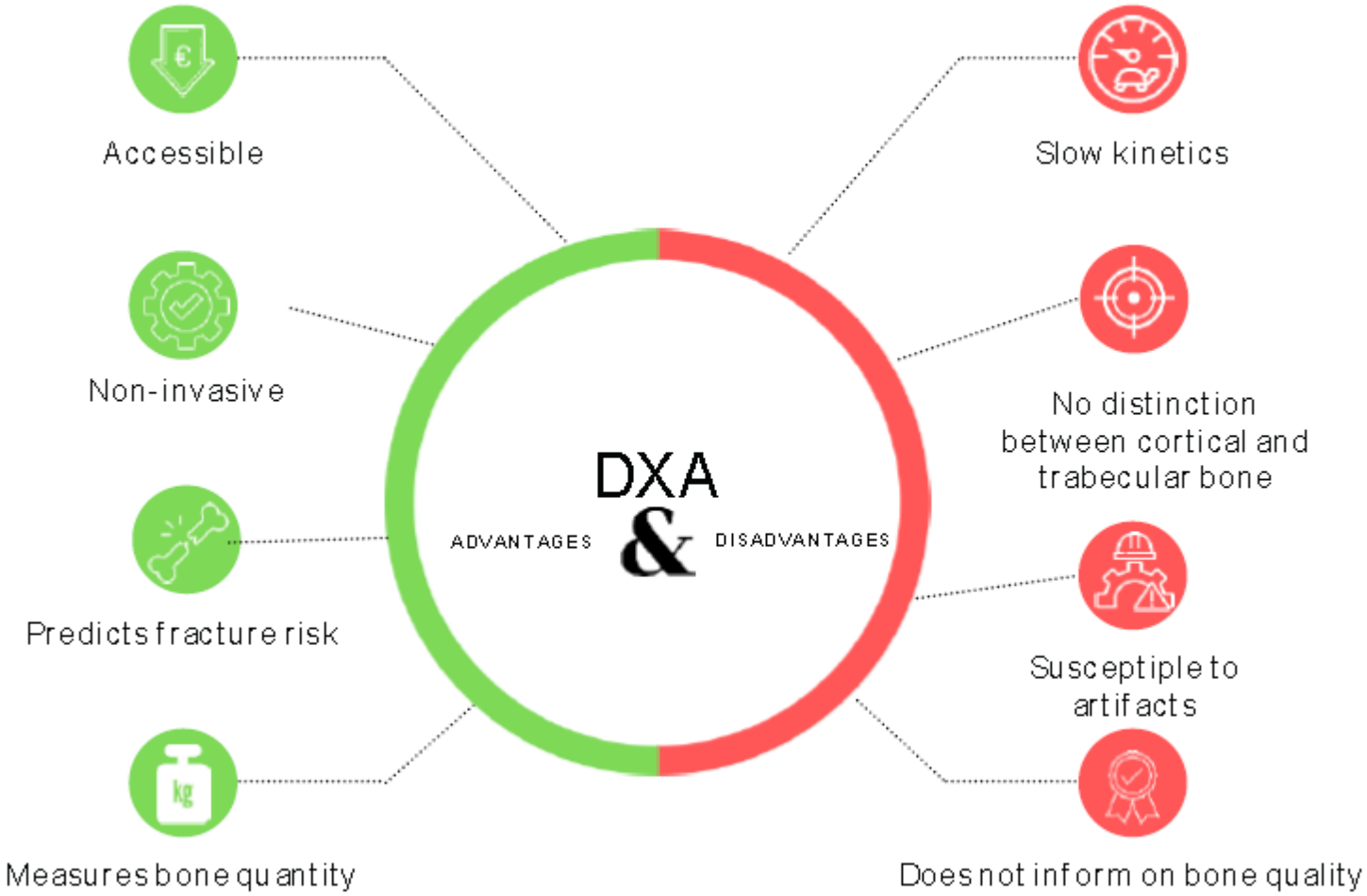
- In patients with mild CKD (up to G3a), the management of osteoporosis should follow the recommendations for the general population
- For the management of osteoporosis in more advanced stages (G4-5/5D), densitometry should be considered in postmenopausal women and patients > 50 years old
- some authors suggest first calculating fracture risk scores such as FRAXR (Fracture Risk Assessment Tool) score

Limitations of DXA

- cannot differentiate between cortical and trabecular bone
- high inter operative variability in assessing forearm BMD
- local decrease in BMD due to relative immobilization of the AVF arm and/or increased sympathetic tone
- aortic calcifications may result in the overestimation of BMD in the lumbar area

bone fragility depends not only on the amount of bone but also on structural or material properties that are not captured by densitometry, such as trabecular microarchitecture, elasticity, and the quality of the collagen matrix

Advantages and disadvantages of DXA

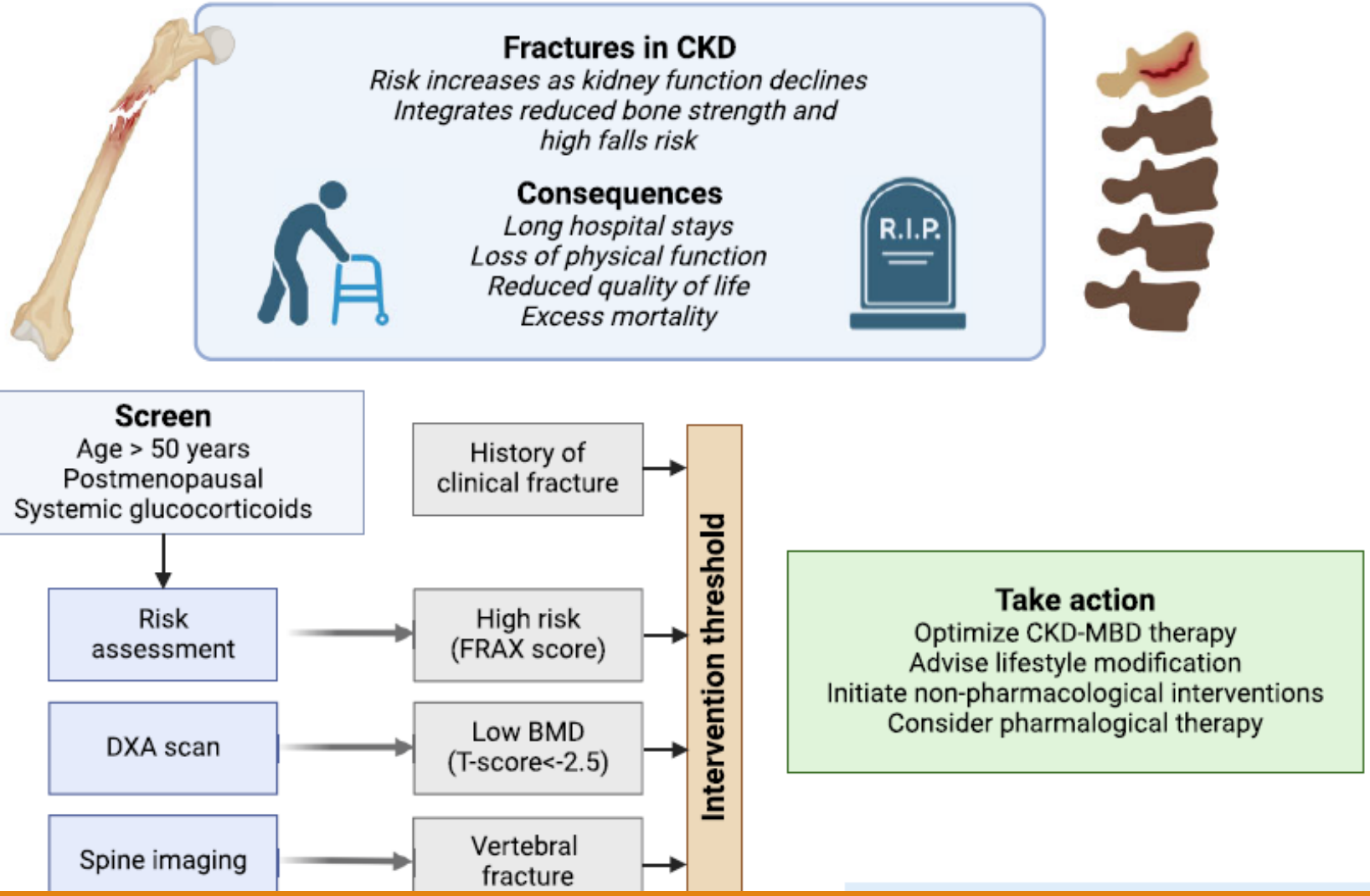


Risk screening

- patients older than 50 years
- postmenopausal women
- specific high- risk situations:

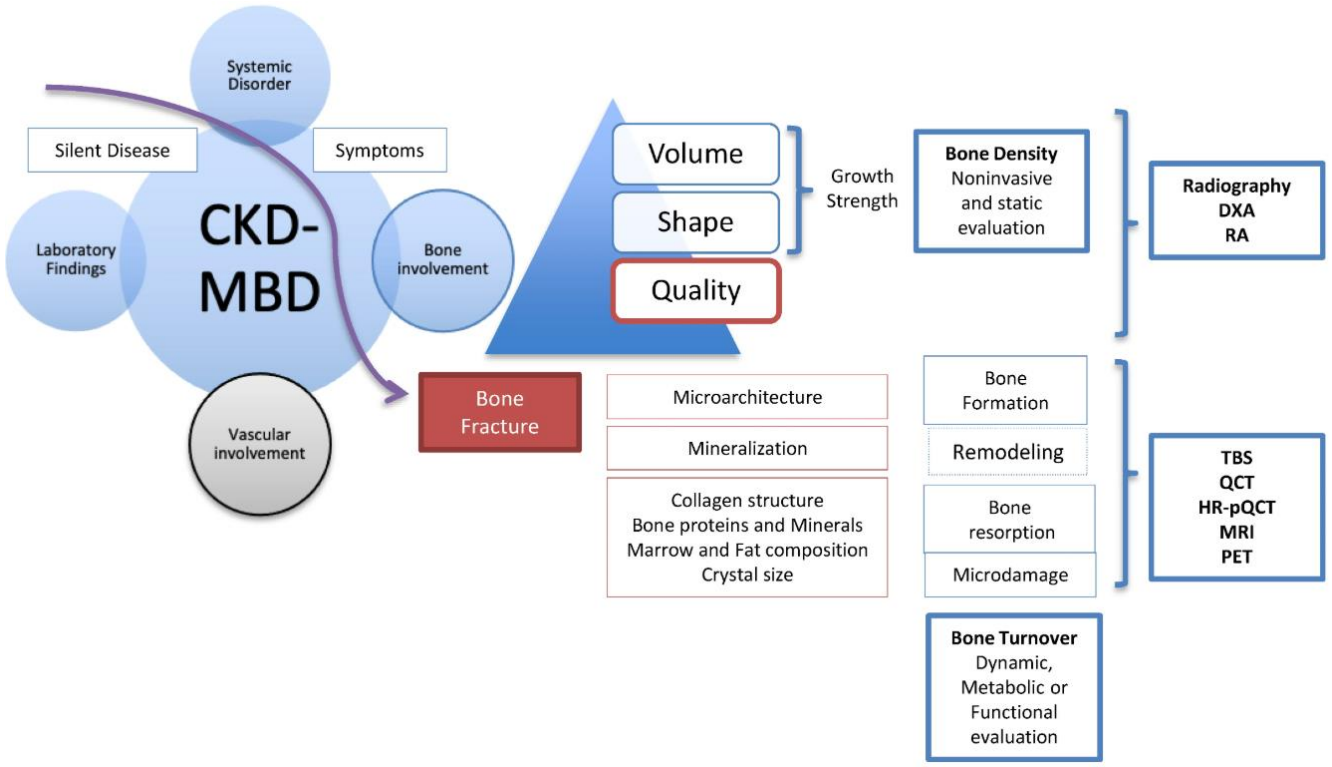
  systemic glucocorticoid therapy,

  musculoskeletal symptoms



Bone Quality

material, structural, and mechanical properties, capacity to generate and repair bone micro damage



Bone quality is affected by Uremia

- Change of orientation of the collagen fibers, establishment of pathological junctions (pathological crosslinks) that lead to the union of immature mineralized crystals

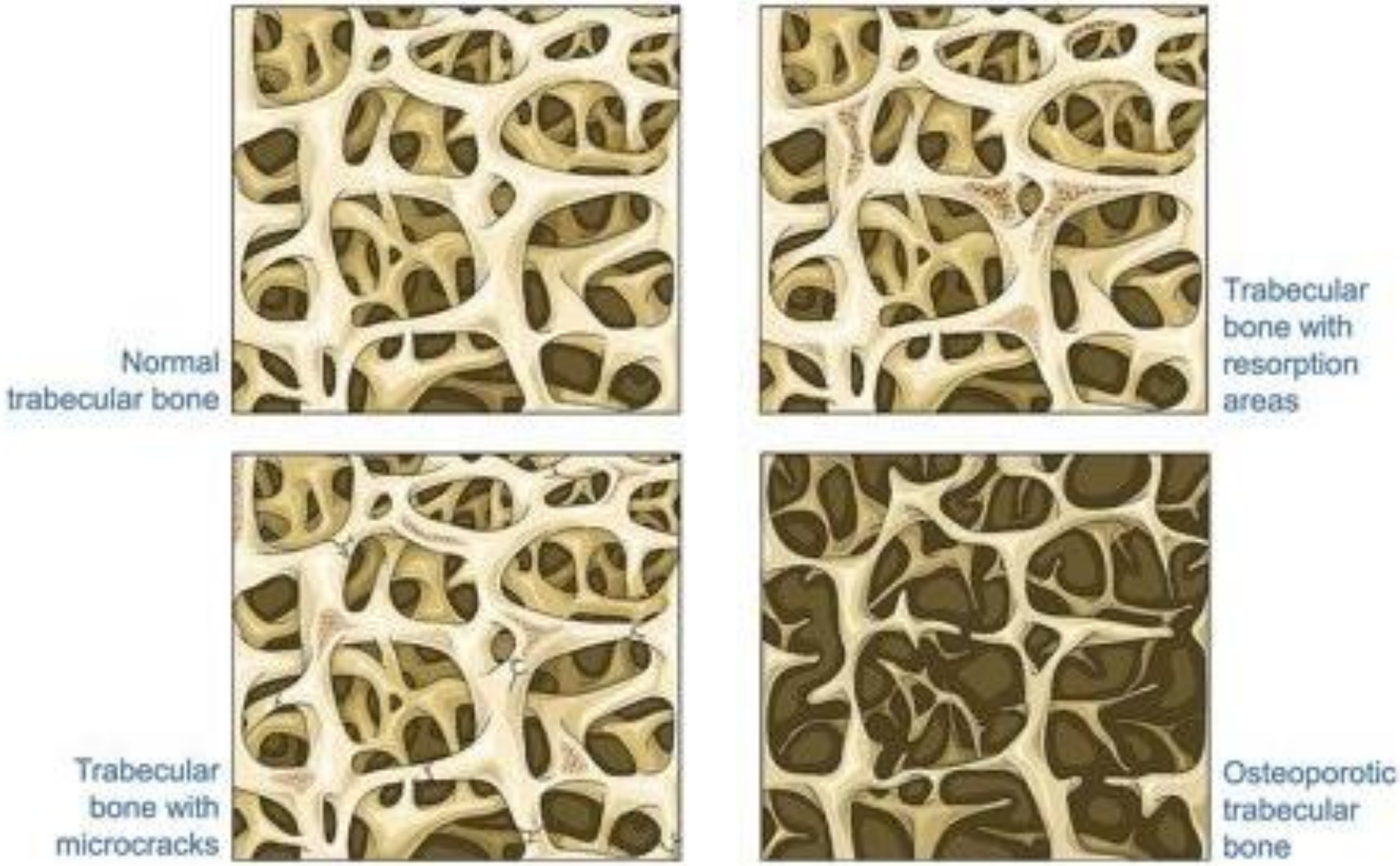
- In patients with high bone turnover due to secondary hyperparathyroidism, a lower rate of mineralization of the bone matrix and lower number of crosslinks of mature collagen fibers

- decrease bone elasticity(resisting a fracture after an impact)

Bone quality is affected by Uremic

compared to healthy women, women on dialysis show cortical bone involvement :

- decreased cortical thickness
- increased cortical porosity
- Trabecular microarchitecture impairment, with less trabecular bone and greater separation between trabeculae


Normal trabecular bone
Trabecular bone with resorption areas
Trabecular bone with microcracks
Osteoporotic trabecular bone

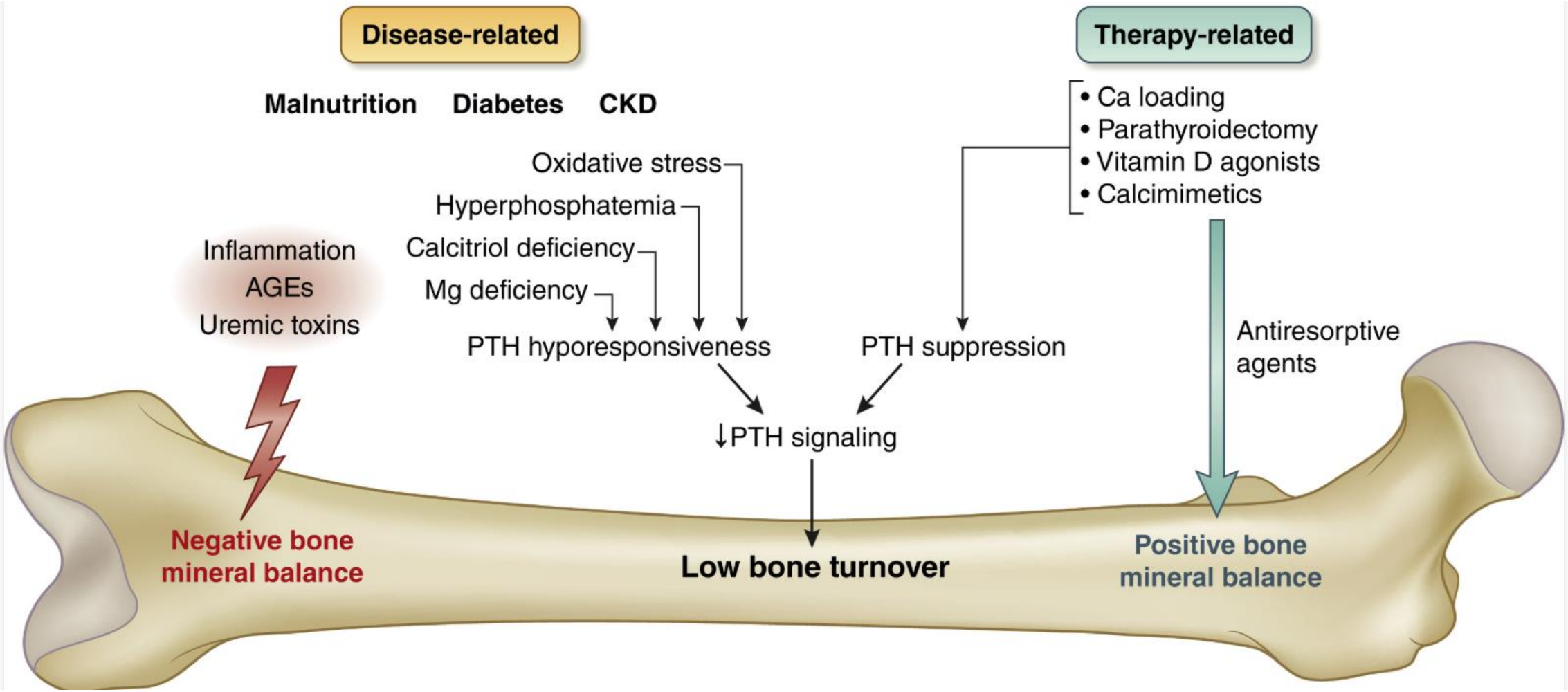
Bone remodeling

- old bone is replaced by new bone(maintenance of mineral homeostasis and bone strength)
- recruitment of osteoclasts leads to bone resorption so that, after apoptosis of these osteoclasts, osteoblasts are recruited, leading to the formation and subsequent mineralization of new bone.
- bone resorption and bone formation are coupled in space and time
- Renewal of the entire skeleton can take approximately 10 years.
- progressive loss of bone (inadequate formation following resorption) estimated at 0.5–1% per year from middle age onward and accelerating in women after menopause

Bone Turnover

- The ability to repair the microcracks that occur spontaneously in the bone will also determine its mechanical integrity.
- In patients with low bone turnover, the repair of microcracks may be impaired, lower trabecular volume and decreased trabecular thickness
- patients with high bone turnover present an increase in porosity and thinning of cortices, decrease in the mineralization ratio of the bone matrix due to the shorter time between remodeling cycles

extra-axial (hip) fractures are more frequent in patients with hyperparathyroidism, while axial (vertebral) fractures may be more frequent in patients with low bone turnover


Disease-related
Malnutrition
Diabetes
CKD
Therapy-related
• Ca loading
• Parathyroidectomy
• Vitamin D agonists
• Calcimimetics
Oxidative stress
Hyperphosphatemia
Calcitriol deficiency
Mg deficiency
Inflammation
AGEs
Uremic toxins
PTH hyporesponsiveness
PTH suppression
Antiresorptive agents
↓PTH signaling
Negative bone mineral balance
Low bone turnover
Positive bone mineral balance

The relationship between PTH and the risk of fracture

- The relationship is linear in the early stages of CKD
- at more advanced stages, it becomes an inverted J curve

conditions associated with decreased PTH (malnutrition, inflammation, elderly patients, DM, etc.) could per se be the cause of the increased risk of fracture


A
B
C
D
E
F

Radiological findings

(**A**) severe secondary hyperparathyroidism: sub periosteal resorption of the distal phalanx of the middle finger, and at the intermediate phalanx of the index finger

(**B**) "brown tumor" at the distal radius metaphyseal: well-limited lytic lesion with endosteal scalloping

(**C**) Periarticular calcifications of the glenohumeral ligaments, appearing as cloud-like densities that diffuse into the adjacent tenosynovial tissues.

(**D**) "Salt and pepper" aspect of the calvaria seen as well-defined lucencies suggesting bone resorption.

(**E**) vertebral fracture in lateral spine X-ray

(**F**) Multiple oblique spiral fractures in the proximal, middle and distal third of the humerus in a hemodialysis patient with osteomalacia.

biomarkers to predict turnover

- Alkaline phosphatase and bone-specific alkaline phosphatase (BSAP) are 2 biomarkers of bone formation that are not affected by GFR.
- Procollagen type 1 N-terminal propeptide (P1NP) and tartrate-resistant acid phosphatase (TRAP5b) are markers of bone formation and resorption that are not renally cleared and hold considerable promise.
- the positive predictive values often ranged from 50%-90% for high and low bone turnover states determined by histomorphometry
- BTMs are not as reliable at assessing bone turnover by bone biopsy for most patients with CKD

Table 1. Markers of Bone Turnover

Biomarker Class	Renal Clearance	Hemodialysis Clearance	Association With Turnover Type[a]
Bone metabolism			
PTH	Yes	Yes (Fragments)	High
FGF-23	Yes	No	High
α-Klotho	Yes	No	Low
Sclerostin	Yes	Yes	Low
Bone formation			
BSAP	No	Yes	High
Osteocalcin	Yes	Yes	High
P1NP/P1CP	No	Yes	High
Bone resorption			
NTX/CTX	Yes	Unknown	High
TRAP5b	No	No	High

Abbreviations: BSAP, bone-specific alkaline phosphatase; CTX, β-C-terminal telopeptide; FGF-23, fibroblast growth factor 23; NTX, cross-linked N-telopeptides of type I collagen; P1NP, procollagen type 1 C-terminal propeptide; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; TRAP5b, tartrate-resistant acid phosphatase.

[a]Higher concentrations of bone turnover markers are associated with high or low bone turnover.

Phosphate Balance

- Hyperphosphatemia has been considered a risk factor for osteoporosis, primarily due to the associated increase in PTH
- Hyperphosphatemia and high phosphate intake stimulate sclerostin (a potent inhibitor of the Wnt/B-catenin pathway), which inhibits bone formation and mineralization
- transient hypophosphatemia after transplantation have delayed bone mineralization

calcium and vitamin D in CKD

- Overt calcium deficiency potentially contributes to inadequate control of hyperparathyroidism
- Excess calcium can lead to vascular calcification and abnormal cardiac structure and function
- The fractional intestinal absorption of calcium is approximately 15% in the CKD population
- Calcium-containing phosphate binders are an important source of calcium in patients with CKD G4-5D and can contribute up to 70% of the overall calcium intake
- nutritional vitamin D to maintain serum 25-hydroxyvitamin D levels > 75 nmol/L(> 30 ng/ml) and use of active vitamin D analogs to prevent hypocalcemia and hyperparathyroidism

Vitamin K

- Vitamin K plays a key role in the carboxylation of various vitamin K-dependent proteins involved not only in blood coagulation but also in bone health, being essential for bone quality.
- no guidelines or recommendations advising on the monitoring or supplementation of vitamin K in patients with CKD

Techniques for Assessing Bone Quality

- bone biopsy
- serum bone turnover markers
- high-resolution peripheral quantitative computed tomography
- TBS
- micro magnetic resonance imaging
- Fourier transform infrared spectroscopy
- 3D-DXA

Bone Biopsy

- The bone histomorphometric study remains the "gold standard" for the diagnosis and classification of ROD.
- both bone quantity (volume) and bone quality (turnover and mineralization)
- Characteristics of the cortical bone (porosity and thickness) and trabecular architecture

limitations of the bone biopsy

- invasive procedure, painful
- single time point and at a unique site (anterior iliac crest)
- trained expert personnel, especially for the analysis

Bone Biopsy

same guidelines from 2009 supported bone biopsy in at least five situations:

- unexplained fractures
- Persistent bone pain
- hypercalcemia or unexplained hypophosphatemia
- aluminum toxicity
- Prior to initiation of bisphosphonate therapy in patients with CKD-MBD

2017 KDIGO guidelines do not consider a biopsy mandatory before initiating treatment with an antiresorptive agent. it is regarded as reasonable to perform one if knowledge of the type of ROD will impact treatment decisions in patients with CKD G3a-5D (not graded)

Trabecular Bone Score

- predictor of fracture independent of BMD
- correlates with the trabecular microarchitecture of the bone
- A TBS >1350 indicates that the trabecular microarchitecture is dense and the trabecular structure is well connected

Lower TBS has also been associated with a higher number of cardiovascular events and higher mortality in HD patients, suggesting that it could be an indicator of frailty in this population

Trabecular Bone Score

- Naylor et al. conducted a retrospective study in a cohort of 679,114 adult patients 40 years over, stratified by different estimated GFR, in which they demonstrated that low TBS scores independently associated with a 60% higher risk of suffering a major osteoporotic fracture

- Another recent study with a higher representation of CKD (1624 patients with an estimated GFR between 30–60 mL/min/1.73 m2 and 441 with an estimated GFR < 30 mL/min/1.73 m2) found that while lower TBS scores were associated with worse kidney function, the addition of TBS to the FRAXR score with BMD did not significantly improve fracture risk prediction

High-resolution peripheral quantitative computed tomography (HR-pQCT)

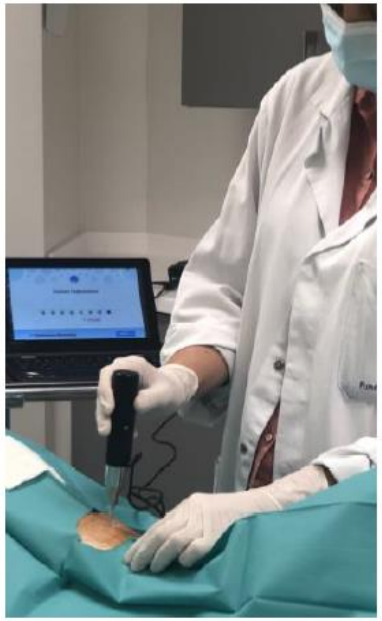
- detailed examination of the trabecular compartment and cortical poroity, as well as the volumetric parameters of bone mass.
- distal radius or distal tibia
- superior to DXA in discriminating fractures in patients with CKD

Limitations:

- High cost of these imaging techniques has prevented extensive use in clinics, limiting their use to research purposes

Impact Micro indentation(IMI)

- mechanical characteristics of cortical bone in vivo
- It is based on the principle that the depth of penetration of a micron-sized probe into the bone surface, with local reproduction of microcracks by separation of microfibers of mineralized collagen, reflects the resistance of the bone to fracture after mechanical impact



IMI (bone strength)

IMI could be especially useful in patients with secondary osteoporosis and metabolic bone disorders in which BMD is not the sole determinant of bone strength:

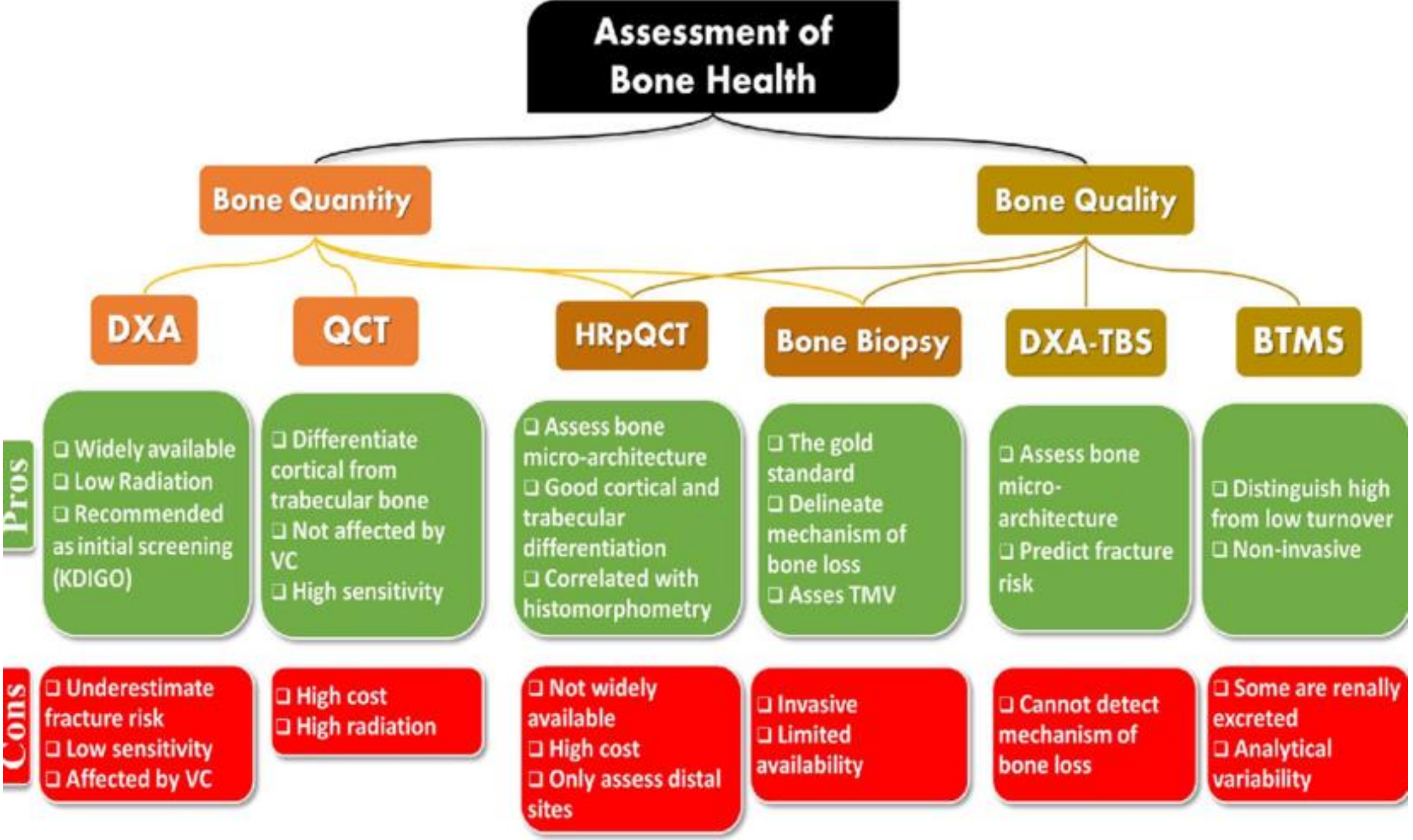
DM , hyper- and hypothyroidism, acromegaly, HIV, monoclonal gammopathy of undetermined significance (MGUS) and CKD

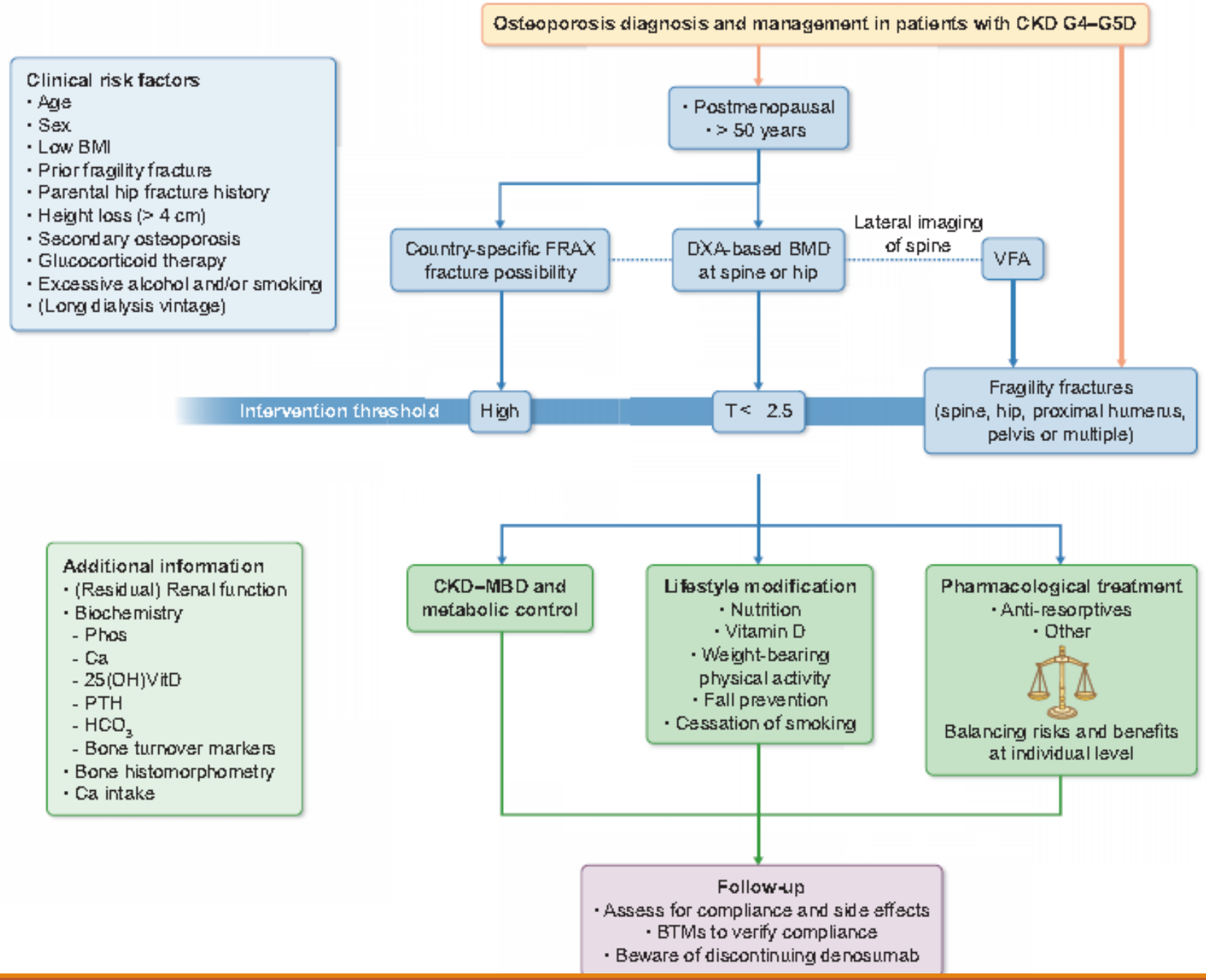
- Patients with kidney failure had lower bone mass, a worse bone trabecular index, and a lower resistance index measured by IMI
- the impact of corticosteroids on bone resistance, measured by IMI, has been evaluated in kidney transplant recipients

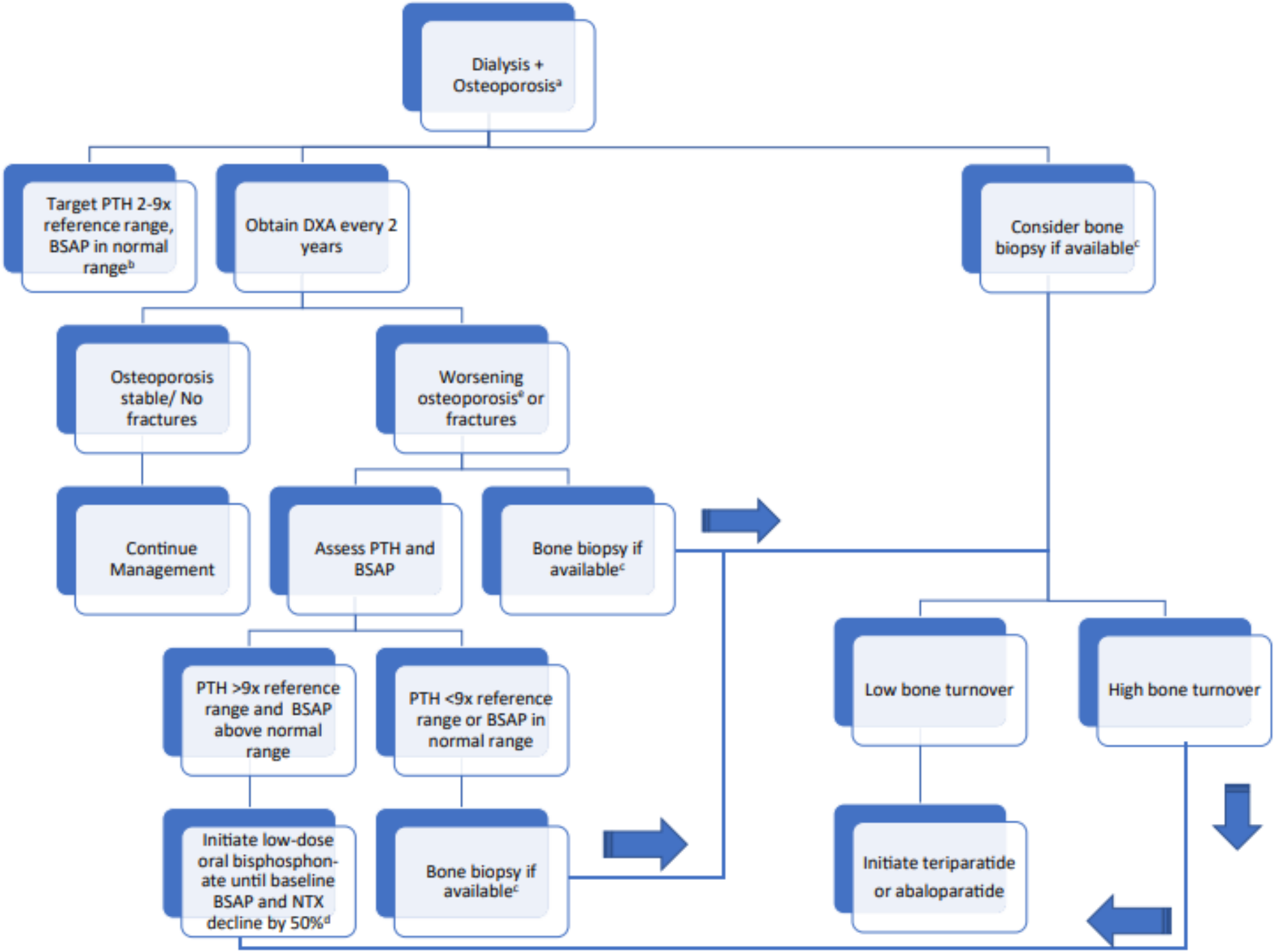
conclusion

Techniques may prove complementary to the assessment of BMD by DXA for the assessment of fracture risk in patients with CKD at the individual level:

- bone biopsy (bone volume, mineralization, and turnover)
- TBS
- HR-pQCT (trabecula microarchitecture, cortical porosity, and volumetric parameters of bone mass)
- IMI (bone strength)


Assessment of Bone Health
Bone Quantity
Bone Quality
DXA
QCT
HRpQCT
Bone Biopsy
DXA-TBS
BTMS
Pros
❑ Widely available
❑ Low Radiation
❑ Recommended as initial screening (KDIGO)
❑ Differentiate cortical from trabecular bone
❑ Not affected by VC
❑ High sensitivity
❑ Assess bone micro-architecture
❑ Good cortical and trabecular differentiation
❑ Correlated with histomorphometry
❑ The gold standard
❑ Delineate mechanism of bone loss
❑ Asses TMV
❑ Assess bone micro-architecture
❑ Predict fracture risk
❑ Distinguish high from low turnover
❑ Non-invasive
Cons
❑ Underestimate fracture risk
❑ Low sensitivity
❑ Affected by VC
❑ High cost
❑ High radiation
❑ Not widely available
❑ High cost
❑ Only assess distal sites
❑ Invasive
❑ Limited availability
❑ Cannot detect mechanism of bone loss
❑ Some are renally excreted
❑ Analytical variability


Osteoporosis diagnosis and management in patients with CKD G4–G5D
Clinical risk factors
• Age
• Sex
• Low BMI
• Prior fragility fracture
• Parental hip fracture history
• Height loss (> 4 cm)
• Secondary osteoporosis
• Glucocorticoid therapy
• Excessive alcohol and/or smoking
• (Long dialysis vintage)
• Postmenopausal
• > 50 years
Country-specific FRAX fracture possibility
DXA-based BMD at spine or hip
Lateral imaging of spine
VFA
Intervention threshold
High
T< 2.5
Fragility fractures (spine, hip, proximal humerus, pelvis or multiple)
Additional information
• (Residual) Renal function
• Biochemistry
- Phos
- Ca
- 25(OH)VitD
- PTH
- HCO_3
- Bone turnover markers
• Bone histomorphometry
• Ca intake
CKD–MBD and metabolic control
Lifestyle modification
• Nutrition
• Vitamin D
• Weight-bearing physical activity
• Fall prevention
• Cessation of smoking
Pharmacological treatment
• Anti-resorptives
• Other
Balancing risks and benefits at individual level
Follow-up
• Assess for compliance and side effects
• BTMs to verify compliance
• Beware of discontinuing denosumab


Dialysis + Osteoporosis[a]
Target PTH 2-9x reference range, BSAP in normal range[b]
Obtain DXA every 2 years
Consider bone biopsy if available[c]
Osteoporosis stable/ No fractures
Worsening osteoporosis[e] or fractures
Continue Management
Assess PTH and BSAP
Bone biopsy if available[c]
PTH >9x reference range and BSAP above normal range
PTH <9x reference range or BSAP in normal range
Initiate low-dose oral bisphosphonate until baseline BSAP and NTX decline by 50%[d]
Bone biopsy if available[c]
Low bone turnover
High bone turnover
Initiate teriparatide or abaloparatide

THANK YOU