Osteoporosis in CKD
from bone density to bone quality

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Definition

- Osteoporosis is currently defined as a decrease in the overall mechanical bone strength, causing an increased risk of low-impact fractures (e.g. falls from the patient's own height)
- Bone strength is determined not only by the quantity of bone (mostly determined by bone mineral density BMD), (measured by DXA) but also by the bone quality, determined by the microarchitecture and mechanical properties of bone.
- till date the trabecular bone score (TBS) is the only practical tool of microarchitecture assessment (available since 2013)

Why CKD-OP should be addressed separately

- Patients with (CKD) have a higher risk of fractures than the general population, and the incidence of fractures increases as CKD progresses
- The incidence of hip fracture across the spectrum of CKD is 2–4 times higher than that observed among people without CKD matched for age and sex.
- hip fractures occur at younger ages, resulting in longer hospitalizations and a higher mortality risk in Pts with CKD compared to the healthy individuals
- in patients with CKD after having fractures, for instance, the 1-year post-hip fracture mortality is up to 64% in those on dialysis Osteoporos Int 33, 2259–2274 (2022)
- It has been estimated that a patient on hemodialysis (HD) who suffers a hip fracture will do so **on average 10 years earlier** than the general population
- 27% of Pts with osteoporosis had grade 3 CKD and 3% had estimated glomerular filtration rate (eGFR) lower than 35 mL/min

Is that only age or something else?

- As 35% of patients with CKD are older than 65 years, loss of bone mass related to aging is expected in this population. However, patients with CKD also present premature aging, and bone loss appears early
- In a study that compared 113 patients with CKD (mean GFR of 37 mL/min) and 89 age-matched healthy controls, BMD was observed to be markedly reduced in young patients with CKD.
- 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.
- it has been observed that The rate of bone loss among patients receiving dialysis was 1.2% of BMD at the total hip per year

Malluche, H.H.; Monier-Faugere, M.C.; Blomquist, G.; Davenport, D.L. Two-Year Cortical and Trabecular Bone Loss in CKD-5D: Biochemical and Clinical Predictors. Osteoporos. Int. **2018**, 29, 125–134.

why CKD osteoporosis is so much different?

- The coexistence of traditional (age, lifestyle, nutrition, physical function, genetic, epigenetic, and hormone dependent factors) and non-traditional factors specific to CKD (uremia, acidosis, inflammation, primary kidney disease) shapes the current concept of “CKD-associated osteoporosis” where it may be especially important to assess not only bone quantity but also bone quality
- 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

Prognosis of CKD by GFR and Albuminuria Categories

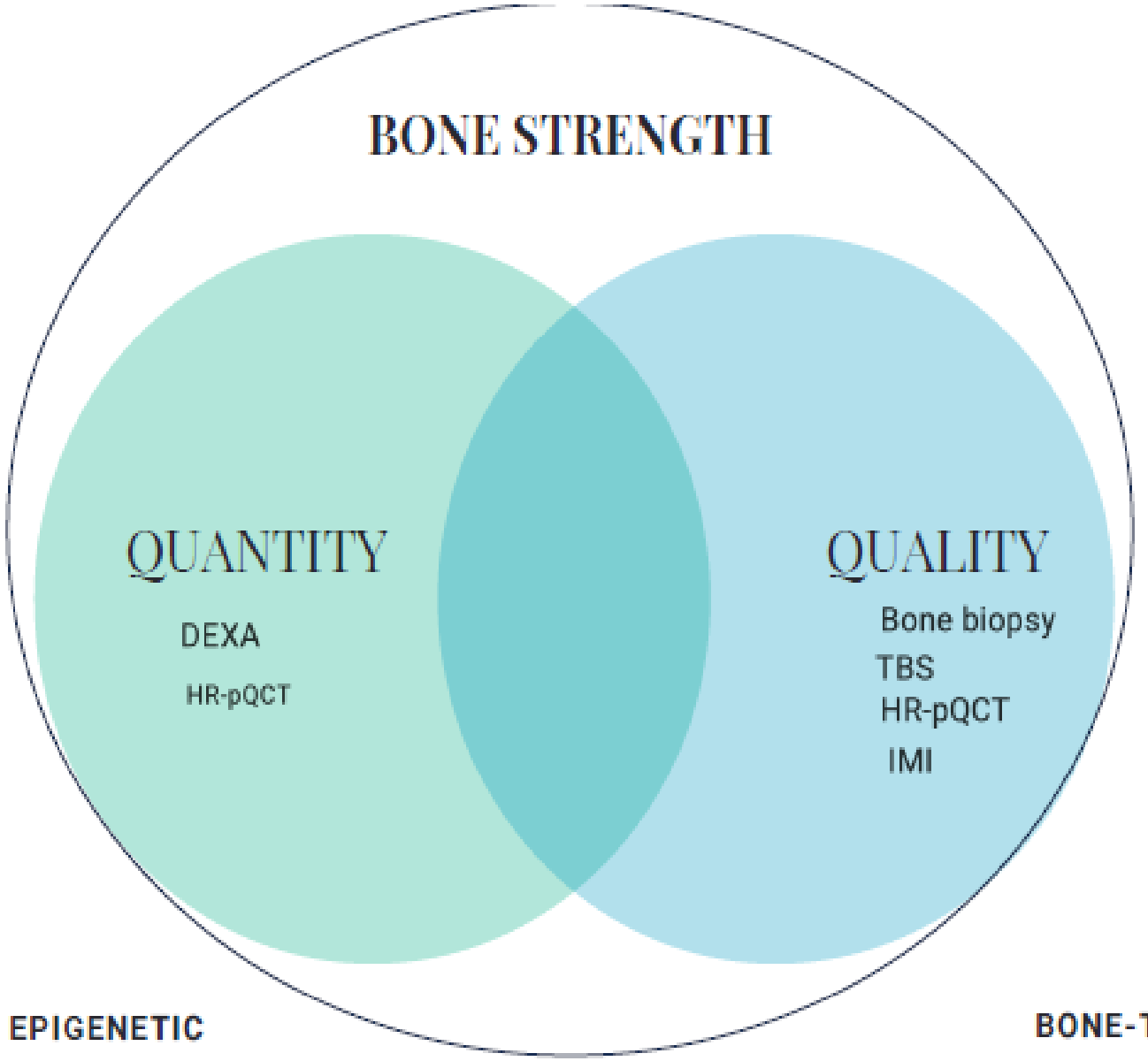
GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

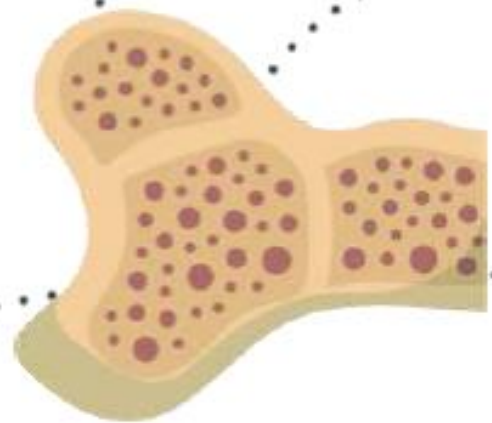
Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppls*. 2013;3:1-150.

A fault that withdrawn very late

- Unfortunately, as bone fragility in a patient with CKD has been attributed to renal osteodystrophy the KDIGO guidelines in 2009 did not recommend routine BMD testing in CKD G3-5D with the rationale that “BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of Renal osteodystrophy
- however, several prospective studies demonstrated that low BMD does correlate with increased fracture risk across the entire spectrum of CKD
- As new evidence has been introduced, guidelines were updated in 2017 recommending that “in patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, BMD testing was suggested if results will impact treatment decisions


BONE STRENGTH
QUANTITY
DEXA
HR-pQCT
QUALITY
Bone biopsy
TBS
HR-pQCT
IMI
AGE
MENOPAUSE
HYPOGONADISM
MALNUTRITION
ALCOHOL
GENETIC & EPIGENETIC
DISTURBANCES OF MINERAL METABOLISM
SYSTEMIC DISEASES (SLE, ADPKD, DM, ...)
INFLAMMATION
UREMIA
BONE-TOXIC DRUGS

BONE QUALITY



MATERIAL PROPERTIES

- Mineralization
- Remodelling
- Crystallization
- Disposition of collagen fibers

CORTICAL AND TRABECULAR DISTRIBUTION

BONE MICRO-ARCHITECTURE

- Geometry
- Porosity
- Connectivity
- Water content
- Microcracks
- Composition of matrix

MECHANICAL PROPERTIES

- Resistance
- Elasticity
- Microcrack repair capability
- Microcrack propagation capacity

Key players of bone loss in CKD

- **Secondary hyperparathyroidism** causes mainly cortical bone loss This explains the disproportionally high fracture burden in the peripheral skeleton
- a small study of 31 patients receiving dialysis who underwent bone biopsy showed that patients with low turnover had more vertebral fractures than patients with osteitis fibrosa, in whom fractures were predominantly appendicular

  Piraino, B.; Chen, T.; Cooperstein, L.; Segre, G.; Puschett, J. Fractures and Vertebral Bone Mineral Density in Patients with Renal Osteodystrophy. Clin. Nephrol. **1988**, 30, 57–62.
- it is important to consider not only the total bone mass but also to what extent the different bone compartments (cortical/trabecular) are affected
- The uremic environment entails alterations in the hypothalamic regulation of gonadotropin secretion, gonadal toxicity, and increased prolactin releas

Key players of bone loss in CKD cont'd

- **Estrogen deficiency** leads to increased osteoblast apoptosis as well as increased osteoclastic half-life and activity
- The HELP (Hemodialysis and estrogen levels in postmenopausals) multicenter study revealed that postmenopausal women on dialysis have decreased estradiol levels

  Kramer, H.M.; Curhan, G.; Singh, A. Hemodialysis and Estrogen Levels in Postmenopausal (HELP) Patients: The MulticenterHELP Study. Am. J. Kidney Dis. 2003, 41, 1240–1246
- Testosterone also plays an important role in bone as it is involved in estradiol aromatization, Testosterone deficiency is observed in 44% of the male Pts on dialysis

  populationCarrero, J.J.; Qureshi, A.R.; Nakashima, A.; Arver, S.; Parini, P.; Lindholm, B.; Bárány, P.; Heimbürger, O.; Stenvinkel, P. Prevalence and Clinical Implications of Testosterone Deficiency in Men with End-Stage Renal Disease. Nephrol. Dial. Transplant. 2011, 26, 184–190.
- **Chronic metabolic acidosis**, a frequent condition in CKD, stimulates osteoclastic activity and inhibits osteoblastic activity, decreasing BMD

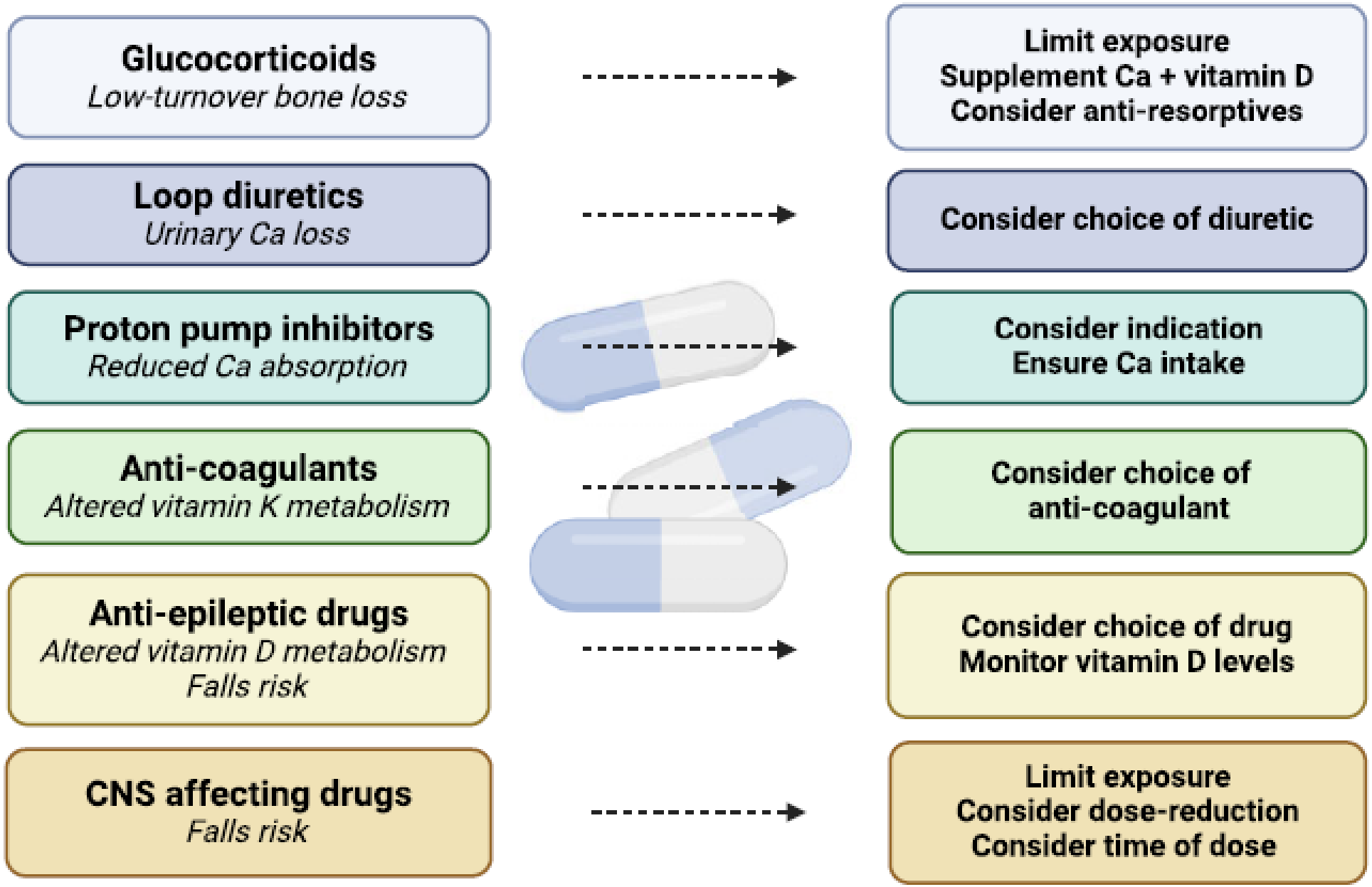
“calcification paradox”

- CKD patients suffer from an imbalance between inhibitory factors (e.g., pyrophosphates, fetuin-A, osteoprotegrin, Matrix-Glaprotein)and promoters[e.g. Ca, P, (BMP-2), BMP-4, RANK-L] of vascular calcification (VC)
- These factors are related not only to the CardioVascular process but also to bone loss
- Bone loss has been associated with the progression of aortic calcifications even in the general population

In this context, parallel to BMD assessment by DXA, a lateral view of the thoracic and lumbar spine (vertebral fracture assessment) should be performed for the diagnosis of vertebral fractures

Medications affecting mineral metabolism, bone health or fracture risk

Class of drugs	Mechanism
Systemic glucocorticoids	Low turnover bone loss [163, 164]; inhibits bone formation and stimulates bone resorption Fracture risk increased with both higher doses and longer exposure [165, 166]
Medications affecting the central nervous system (anti-depressants, benzodiazepines, narcotics)	Risk of falling; increased fracture risk in the background population [48]
Anti-epileptic drugs	Vitamin D metabolism; reduced levels of vitamin D [167, 168]
Diuretics	Calcium metabolism; increased urinary calcium loss with loop-diuretics; calcium retention with thiazides Fracture risk increased with loop-diuretics [2, 48] and decreased with thiazides [169, 170] in the general population
Proton pump inhibitors	Reduced absorption of cations such as calcium and magnesium; possibly direct bone toxicity. Increased fracture risk both in the general population [48] and in CKD [171, 172]
Anti-coagulants (Vitamin K antagonists)	Vitamin K metabolism; reduced action of vitamin K dependent proteins [173, 174] Effect on bone health unclear [175, 176].


Glucocorticoids
Low-turnover bone loss
Limit exposure
Supplement Ca + vitamin D
Consider anti-resorptives
Loop diuretics
Urinary Ca loss
Consider choice of diuretic
Proton pump inhibitors
Reduced Ca absorption
Consider indication
Ensure Ca intake
Anti-coagulants
Altered vitamin K metabolism
Consider choice of anti-coagulant
Anti-epileptic drugs
Altered vitamin D metabolism
Falls risk
Consider choice of drug
Monitor vitamin D levels
CNS affecting drugs
Falls risk
Limit exposure
Consider dose-reduction
Consider time of dose

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
- on the other side, phosphate is essential for bone mineralization
- Kidney transplant recipients who experience transient hypophosphatemia after transplantation have delayed bone mineralization
- Intensive dialysis regimens, such as nocturnal HD, have been associated with a decrease in phosphate levels that requires discontinuation of phosphate binders and even leads to osteomalacia

Vitamin deficiencies

- **Vitamin D** deficiency can also cause mineralization deficits Levels of 25 (OH) vitamin D < 10 ng/mL have been associated with an increased prevalence and incidenceof fractures in CKD
- The recent update of the Spanish guidelines on the approach to mineral metabolism suggests maintaining calcidiol levels at >20–30 ng/mL, although optimal levels, especially in the case of osteopenia and osteoporosis, would be >30 ng/mL including an appropriate calcium intake
- Also, **Vitamin K (specially K2)** promotes mineralization, osteoblast-to-osteocyte transition, and an anticatabolic phenotype by γ-carboxylation-dependent and independent mechanisms being essential for bone quality
- Studies have linked an elevated risk of bone fractures to factors such as insufficient vitamin K intake or low circulating levels of vitamin K
- there are no guidelines or recommendations advising on the monitoring or supplementation of vitamin K in patients with CKD

Cannot ignore Diseases themselves

➢**Some etiologies of CKD per se affect bone quality**

- DM is the most common cause of Elevated sclerostin levels, accumulation of advanced glycation end-products(AGEs), inflammation, and oxidative stress are possible causes of bone quality impairment
- Autosomal dominant polycystic kidney disease appears to have a bone-specific phenotype characterized by low bone turnover, a better-preserved bone cortex, and elevated sclerostin levels
- SLE with lupus nephritis and long term steroid use

Impact of CKD on Bone Quality

- Bone quality is determined by the **material**, **structural**, and **mechanical** properties of bone, as well as by its capacity to generate and repair bone microdamage
- In CKD high bone turnover due to secondary hyperparathyroidism, lowers the rate of mineralization of the bone matrix as well as lowering number of crosslinks of mature type 1 collagen fibers These changes decrease bone elasticity, which is essential in resisting a fracture after an impact
- Elasticity is key to preventing long bone fractures, including femur ,It has been shown that there is inverse correlation between creatinine clearance and bone elasticity

Bone Turnover

- Disorders in bone turnover affect bone quality, but via different mechanisms In patients with low bone turnover, the repair of microcracks may be impaired so that damage accumulates (as during the aging process), resulting in decreased bone strength over time
- Compared to Pts with high or normal bone turn over, Pts with low turnover present microstructural alterations such as lower trabecular volume and decreased trabecular thickness
- On the contrary, Pts 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, prevents complete mineralization

Bone Turnover

- These differences could explain why **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
- The relationship between PTH (not directly a reflection of bone turnover) and the risk of fracture is linear in the early stages of CKD
- At more advanced stages, it becomes an inverted J curve, suggesting that the conditions associated with decreased PTH (malnutrition, inflammation, elderly patients, DM, etc.) could per se be the cause of the increased risk of fracture
- No significant differences found in fracture frequency between high and low turnover states however, mineralization defects were associated with a higher fracture rate.

Almeida Araújo, S.M.H.; Ambrosoni, P.; Santos Lobão, R.R.; Caorsi, H.; Moysés, R.M.A.; Carvalho Barreto, F.; Olaizola, I.; Cruz,E.A.S.; Petraglia, A.; Dos Reis, L.M.; et al. The Renal Osteodystrophy Pattern in Brazil and Uruguay: An Overview. Kidney Int.**2003**, 63, S54–S56

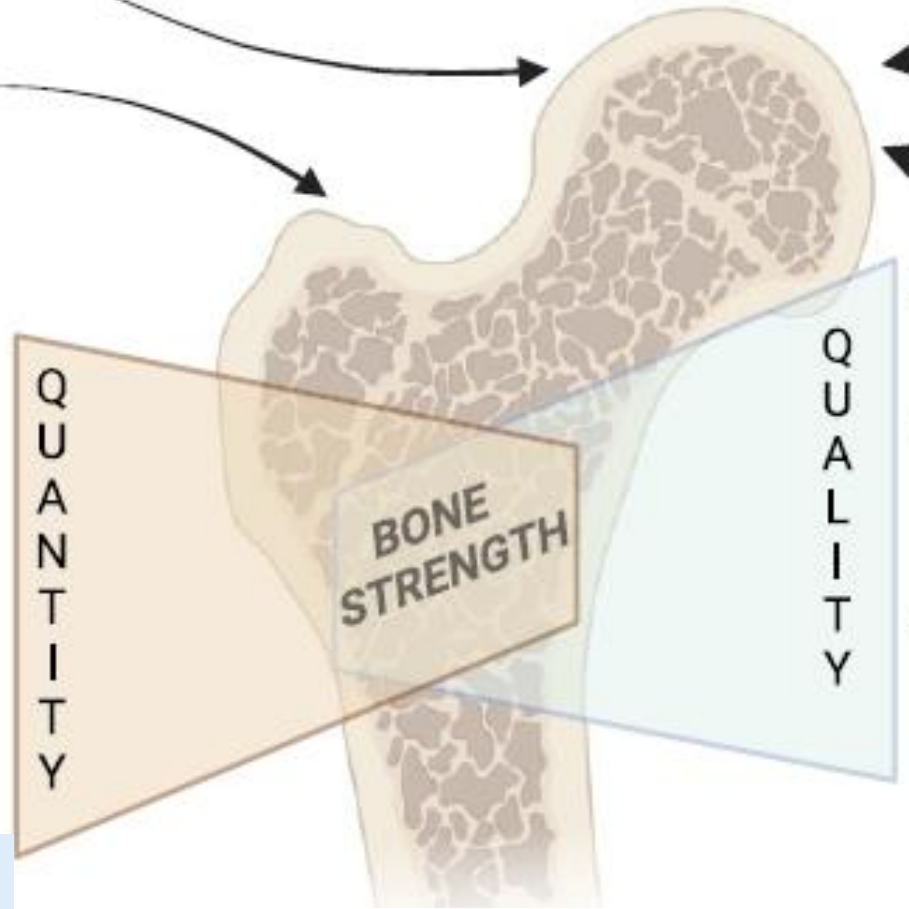
HIP STRENGTH ANALYSIS
Hip axis length
Buckling ratio

3D-DXA
Cortical/ trabecular vBMD
Cortical thickness

FINITE ELEMENT ANALYSIS
Bone stiffness
Failure load

TRABECULAR BONE SCORE
Trabecular microarchitecture

REMS
Fragility Score



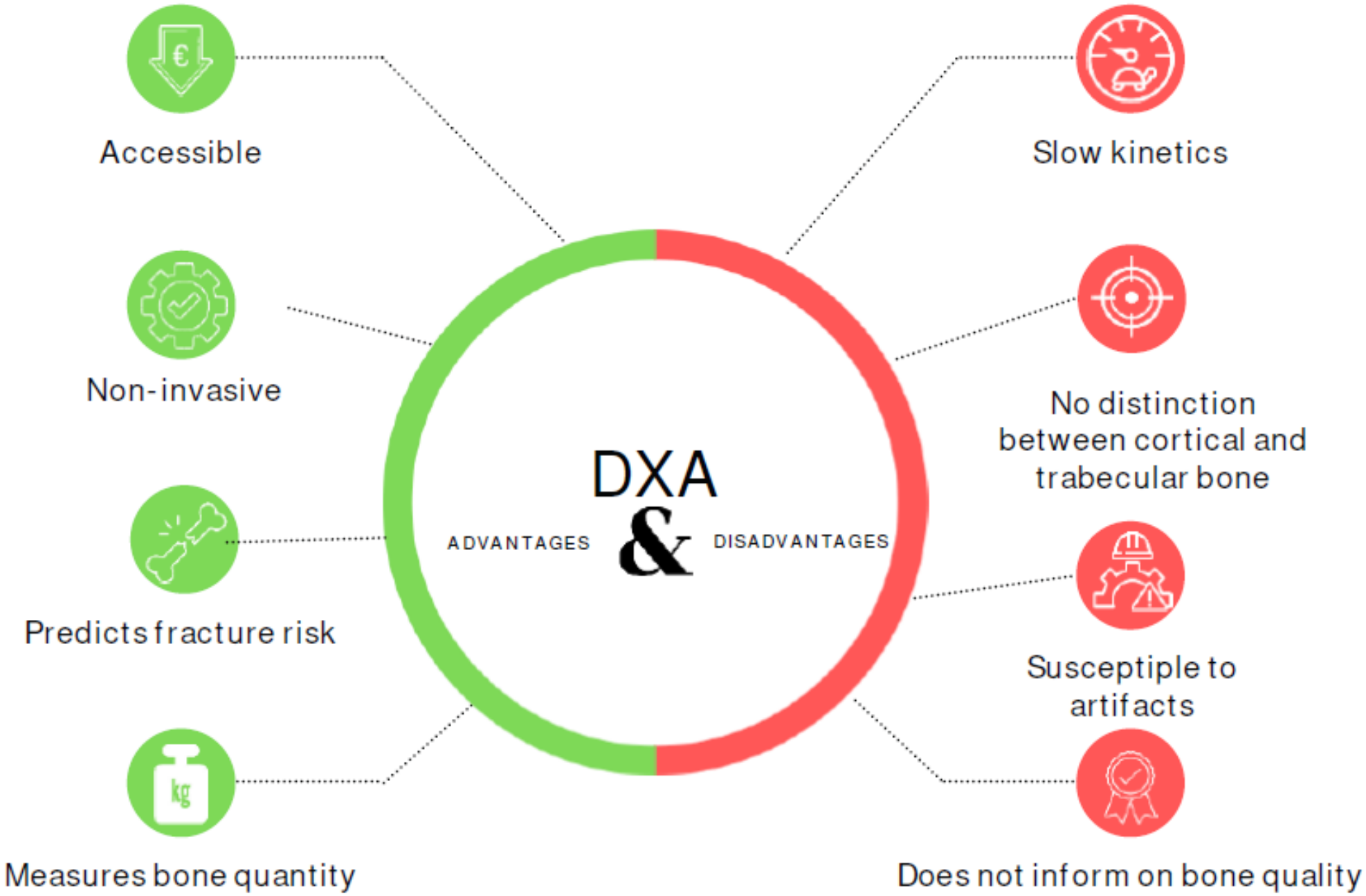
- Bone mineral density

Geometry
- *Size*
- *Shape*

Micro-architecture
- *Trabecular thickness, connectivity*
- *Cortical thickness, porosity*

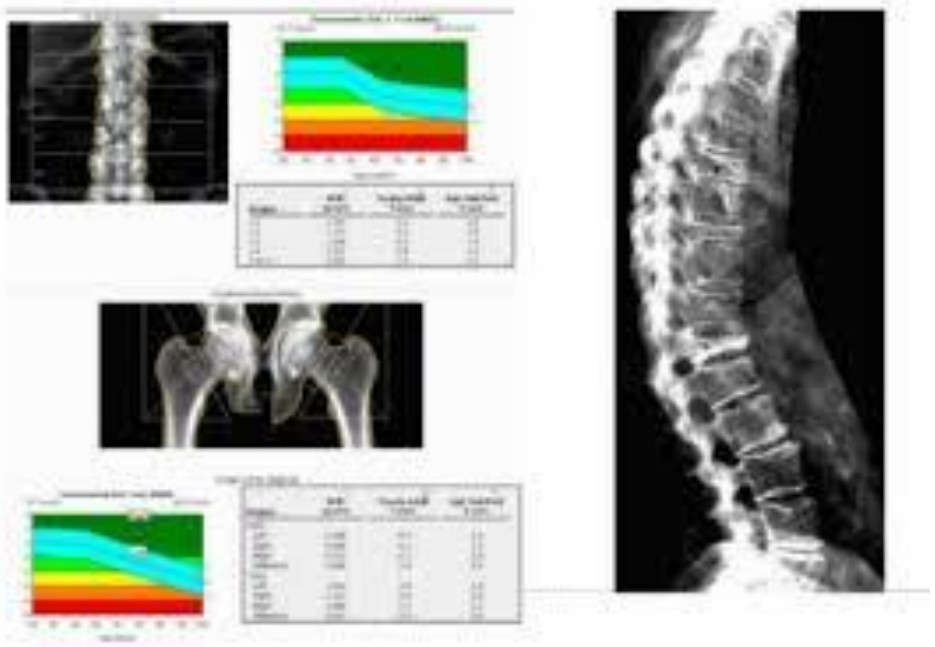
Composition
- *Matrix composition*
- *Collagen fiber arrangement*
- *Mineralization*

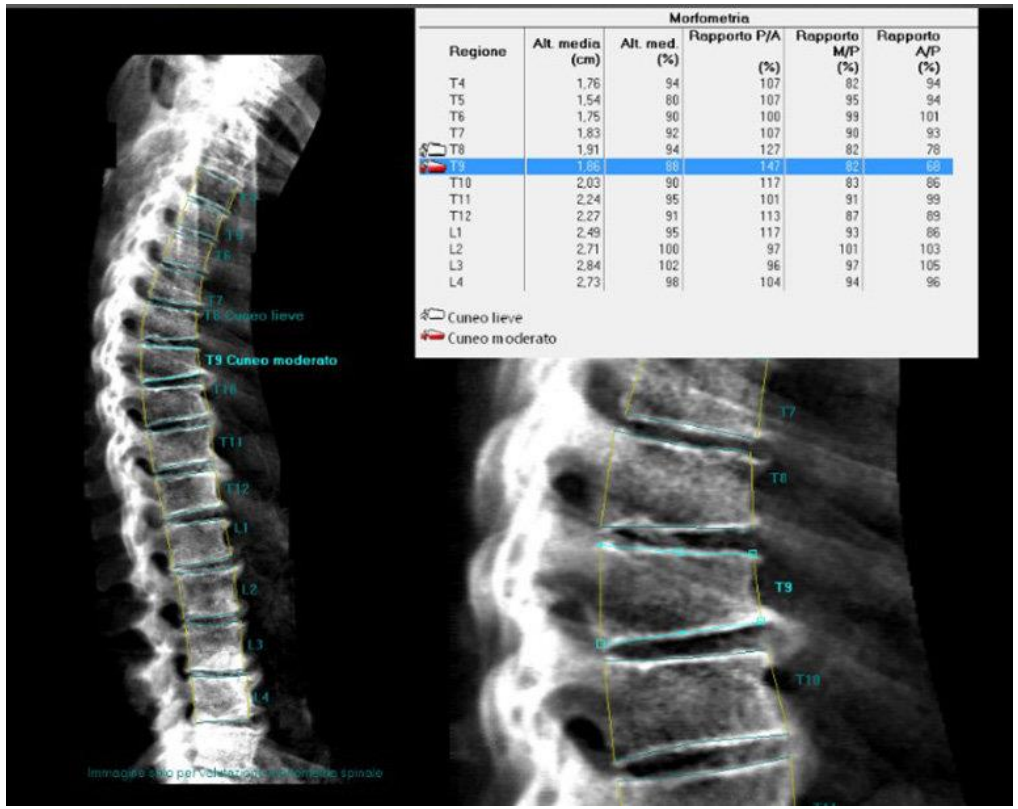
Jørgensen HS, Lloret MJ, Lalayiannis A, Shroff R, Evenepoel P
@CKJsocial


DXA
&
ADVANTAGES
DISADVANTAGES
Accessible
Non-invasive
Predicts fracture risk
Measures bone quantity
Slow kinetics
No distinction between cortical and trabecular bone
Susceptiple to artifacts
Does not inform on bone quality

Simple forgotten methods

Lateral abdominal radiography (thoracolumbar) is a simple and economical method that allows (i) screening for a vertebral fracture that is often asymptomatic, it signals a high risk of new fracture or Morphometric analysis of DXA spine image with accompanying chart





Trabecular Bone Score

- Trabecular bone score (TBS) is a textural index determined by analysis of the lumbar DXA image that correlates with the trabecular microarchitecture of the bone
- TBS was evaluated by determining the variogram of the trabecular bone projected image, calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle. TBS was then calculated as the slope of the log-log transform of this variogram
- In the general population, this is a predictor of fracture independent of BMD and it has been incorporated into risk prediction scales such as FRAX
- It was found that those with low TBS were associated with 1.5 times higher risk of fracture compared with those with normal TBS

BMD= 0.972

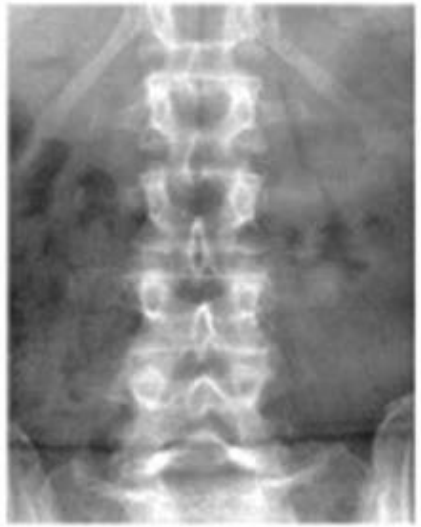
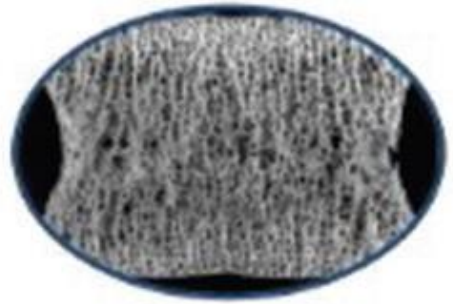
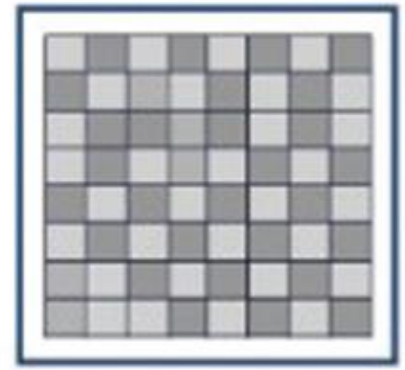
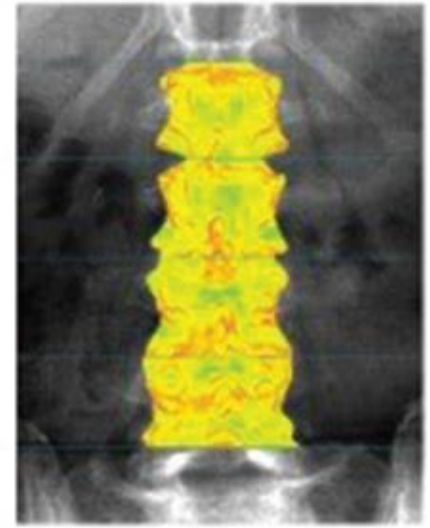


Illustration of Well-structured trabecular bone





TBS= 1.459



Experimental variogram

BMD= 0.969

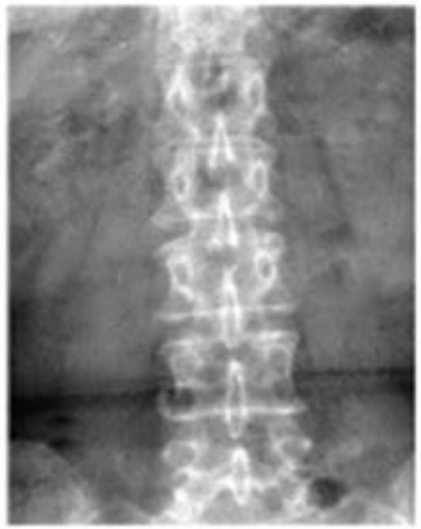
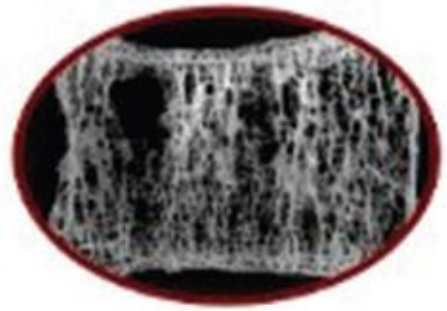
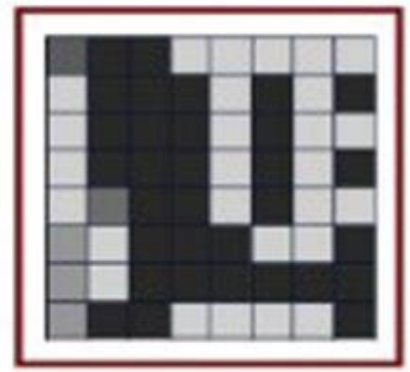
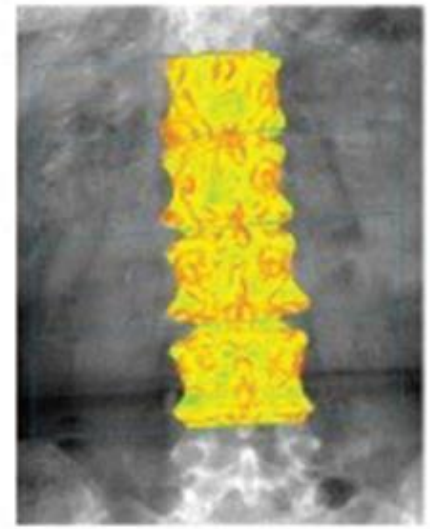


Illustration of Altered trabecular bone





TBS= 1.243



A TBS >1350 indicates that the trabecular microarchitecture is dense and the trabecular structure is well connected

Table 2: TBS cut-offs proposed for postmenospausal women

TBS score (no units)	Bone status
>1.350	Normal
1.200 and 1.350	partially degraded bone
≤1.200	degraded bone

Trabecular Bone Score

- (TBS), that derived from **spine** dual-energy x-ray absorptiometry (DXA) images, is a FRAX®-independent risk factor for fracture. The TBS adjustment to FRAX assumes the presence of **femoral neck** BMD in the calculation
- A recent study on CKD Pts (1624 Pts with an estimated GFR between 30–60 mL/min/1.73 m2 and 441 with a 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 FRAX® score with BMD did not significantly improve fracture risk prediction
- Other studies have found TBS to be useful in predicting fracture risk in renal transplant, HD patients and even predialysis CKD doi: 10.3389/fmed.2025.1556782

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 ($\geq$5 mg/day of prednisone or equivalent for $\geq$3 months) • $\geq$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.

“Do & Do not” tips when assessing bone health in CKD

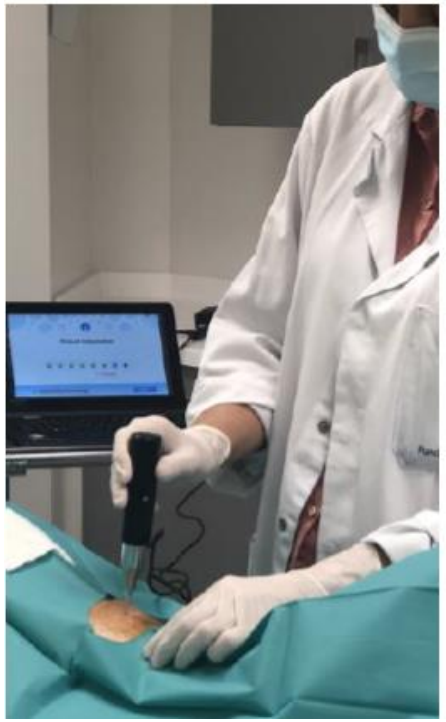
Musculoskeletal function	Assess physical performance and overall frailty Encourage increased exercise	Do not neglect the importance of recent falls
Dietary Calcium and Vitamin D intake	Assess dietary Ca intake Monitor 25OHD	Do not monitor $1,25(OH)_2D$
Biomarkers of MBD	Monitor PTH, ALP, Ca, and P routinely Include 25OHD and serum bicarbonate Consider biomarkers of bone formation (BALP, intact PINP) and resorption (TRAP5b) to guide therapy and monitor treatment response	Do not measure sex steroids Do not neglect that traditional bone turnover markers are cleared by the kidneys (CTX, total PINP)
Imaging	Consider routine DXA for patients >50 years or postmenopausal Include vertebral fracture assessment Consider lateral X-ray for prevalent vertebral fractures and abdominal aortic calcification	Do not perform DXA without a plan of action for the results
Novel imaging (QCT, pQCT, HR-pQCT)	Consider adding information from bone strength analyses available from traditional bone imaging Consider pQCT if available for information on cortical bone	Do not use routinely

Impact Micro Indentation

- (IMI) is a novel technique designed to assess bone strength from a global perspective and in a minimally invasive way, providing information on both bone quality and bone quantity
- Osteoprobe is a portable, hand-held device for performing IMI The device expresses the bone strength result as BMSi (Bone Material Strength index), which represents the ratio between the distance the needle probe penetrates the bone (anterior tibial face) and the distance it penetrates a reference standard (a methyl methacrylate phantom).
- Tolerance and acceptance by patients are excellent, and the complication rate is minimal, allowing interactive exploration

Rokidi, S.; Paschalis, E.P.; Klaushofer, K.; Vennin, S.; Desyatova, A.; Turner, J.A.;Watson, P.; Lappe, J.; Akhter, M.P.; Recker, R.R.Organic Matrix Quality Discriminates between Age- and BMD-Matched Fracturing versus Non-Fracturing Post-MenopausalWomen: A Pilot Study. Bone 2019, 127, 207–214

- In a study comparing the behavior of BMSi in patients with and without fractures (normal kidney function), BMSi values were lower in patients compared to those without fragility fractures, despite similar BMD
- IMI could be especially useful in patients with secondary osteoporosis and metabolic bone disorders (e.g., those with CKD) in which BMD is not the sole determinant of bone strength



High-Resolution Peripheral Quantitative CT

- (HR-pQCT) is a technique that analyzes bone microstructure in a non-invasive manner
- HR-pQCT captures images of the distal radius or distal tibia, whereas a bone biopsy obtains material from the iliac crest
- These bones are in different mechanical and metabolic characteristics, and as a result, comparisons of the techniques can yield only modest correlations
- HR-pQCT has a resolution of approximately 80 µm and allows 3D imaging and detailed examination of the trabecular and cortical porosity, as well as the volumetric parameters of bone mass
- HR-pQCT and magnetic resonance imaging (MRI) have been postulated to be superior to DXA in discriminating fractures in patients with CKD

Thanks a lot for your attention