

Mineral Bone Disease after Kidney Transplantation



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Plan of the presentation

1. Biochemical abnormalities after kidney transplantation (KT)
2. Bone disease after KT
3. Vascular involvement after KT
4. Treatment

1. Biochemical abnormalities after KT

- Depend on the kidney function after KT
- Depend on dialysis duration
- Rapid change over the first 6-12 months post-transplant

After successful KT

Parameter	Pre-Tx	Post-Tx – 3 mo	Post-Tx – 12 mo
FGF 23	↑↑	↘↘, rapid N	N
sKlotho	↓↓	↗	↓/N
PTH	↑↑	↘	Mostly N
Ca	↓	↗	Mostly N
Phosphate	↑↑	↘↘ hypophosphatemia risk	N
25-OH Vitamin D	↓↓	↓	↓

After successful KT

Parameter	Post-Tx	Clinical importance
FGF 23	↘↘, rapid N	Reduced mortality + CVD
sKlotho	↗	Unclear data, better GFR ? No importance ?
PTH, AP	↘	Improved bone health
Ca	↗	Improved bone and vascular health
Phosphate	↘↘ hypophosphatemia risk	Improved bone and vascular health
25-OH Vitamin D	↓	Ca/P and pleiotropy

Evenepoel P, et al. Recovery of hyperphosphatemia and renal phosphorus wasting one year after successful renal transplantation. *Clin J Am Soc Nephrol.* (2008) 3:1829–36

Quick decrease in levels

May be ↑ ND than healthy controls

Tan SJ, et al. Changes in markers of mineral metabolism after living kidney donation. *Transplant Direct.* (2017) 3:e150.

persistently increased after ND to controls

Young A, et al. Bone and mineral metabolism and fibroblast growth factor 23 levels after kidney donation. *Am J Kidney Dis.* (2012) 59:761–9.

FGF 23 after KT

Predicts all cause mortality and graft loss

Wolf M, et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. *J Am Soc Nephrol.* (2011) 22:956–66.

Lower: Improved vasodilatation

Yilmaz MI, et al. Longitudinal analysis of vascular function and biomarkers of metabolic bone disorders before and after renal transplantation. *Am J Nephrol.* (2013) 37:126–34.

↑: 3m after donation
N: long term after donation

Westerberg PA, et al. Fibroblast growth factor-23 and mineral metabolism after unilateral nephrectomy. *Nephrol Dial Transplant.* (2010) 25:4068–71.

sKlotho after KT

↑ after KT

Tan SJ, et al. Mineral adaptations following kidney transplantation. *Transpl Int.* (2017) 30:463–73.

After ND:
↓ than healthy subjects

Tan SJ et al. Changes in markers of mineral metabolism after living kidney donation. *Transplant Direct.* (2017) 3:e150.

Lower than healthy subjects

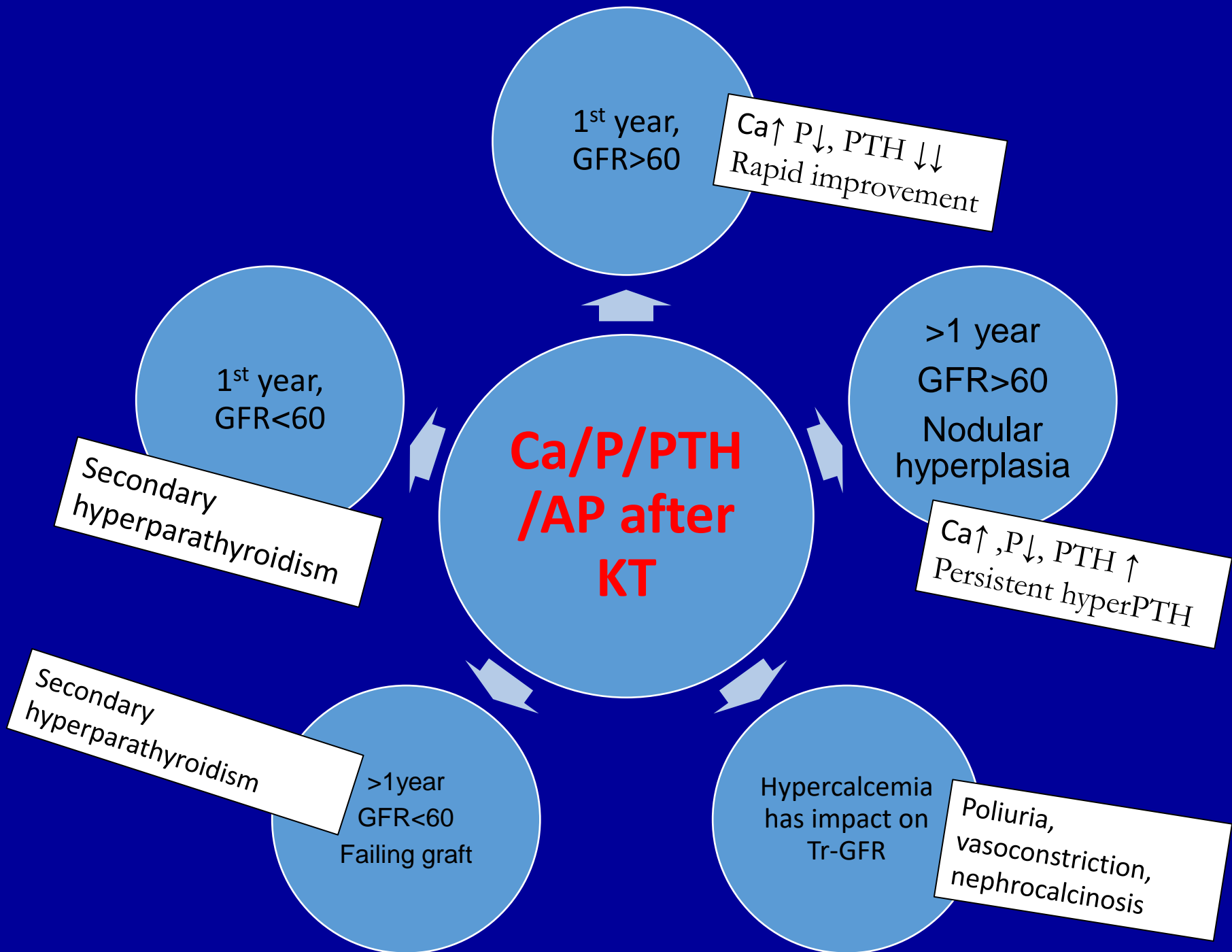
Thongprayoon C, et al. Serum klotho in living kidney donors and kidney transplant recipients: a meta-analysis. *J Clin Med.* (2020) 9:61834. doi: 10.3390/jcm9061834

↓ after ND

Ponte B, et al. Acute and long term mineral metabolism adaptation in living kidney donors: a prospective study. *Bone.* (2014) 62:36–42.

Higher on mTORi

Mizusaki K, et al. Inhibition of the mammalian target of rapamycin may augment the increase in soluble Klotho levels in renal transplantation recipients. *Blood Purif.* (2019) 47(Suppl.2):12–8.



↑VD after
KT

Frequent VD
insufficiency
(up to 80%)

Filipov JJ, et al. Relationship between vitamin D status and immunosuppressive therapy in kidney transplant recipients. *Biotechnol Biotechnol Equip.* 2015;29(2):331-335.

**VD
after KT**

Ca/P/Bone
metabolism

Infection,
CVD,
mortality

Filipov et al. Cholecalciferol Supplementation and Its Effect on Proteinuria in Bulgarian Kidney Transplant Recipients. *C. R. Acad. Bulg. Sci.*, 74 (6), 2021: 920-7.

Renal
protection

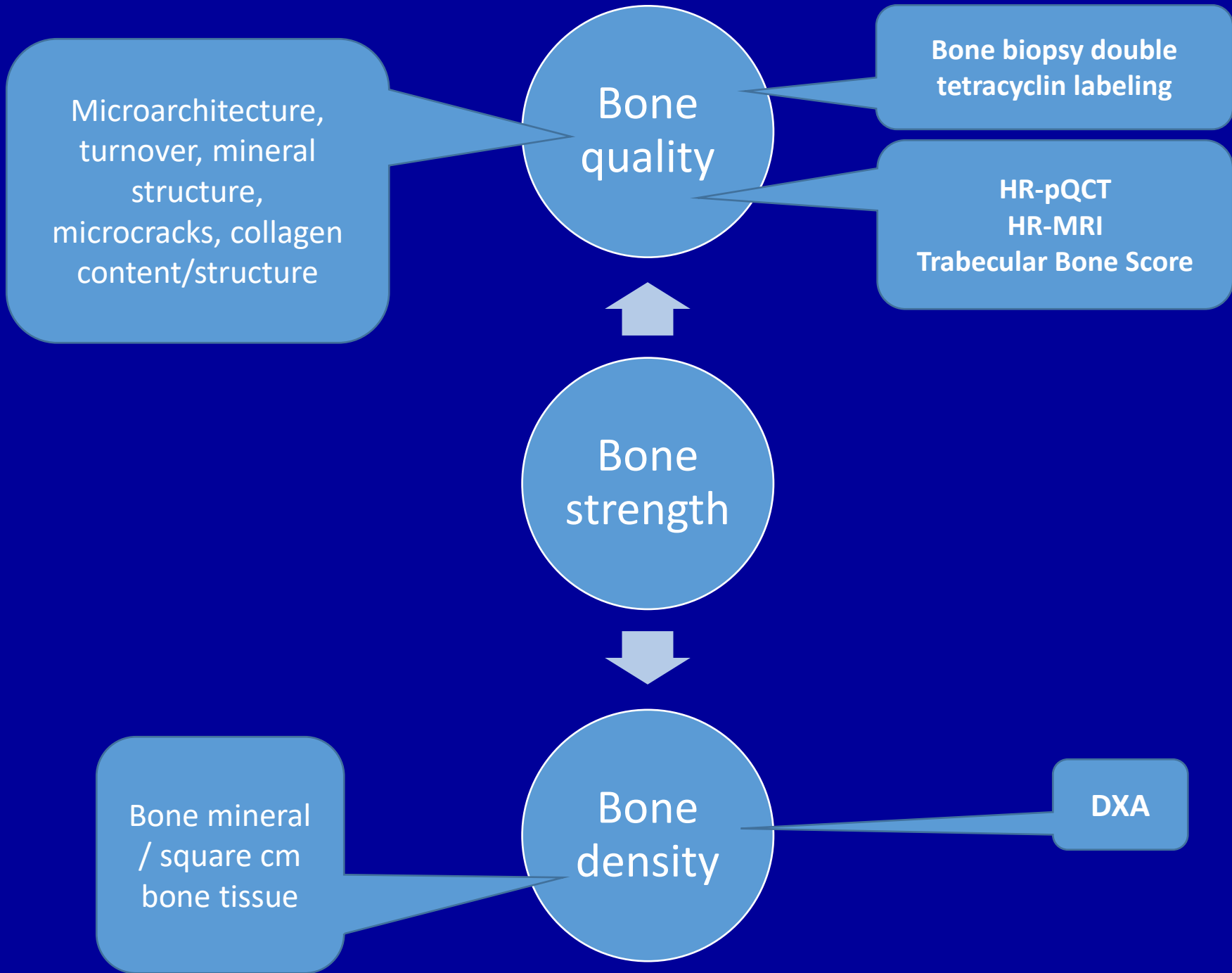
Neoplasia

Rejection

2. Post-transplant bone disease

Post-transplant bone disease

- Osteoporosis
- Renal osteodystrophy
- Osteonecrosis
- Bone fracture



Factors, influencing bone health after KT

Traditional	CKD related	Transplantation-related
Malnutrition	↑ PTH	Steroid use
Age	↓VD	Cumulative steroid dose
Hypogonadism	Systemic inflammation	Persistent ↑PTH
Smoking	Metabolic acidosis	Other IS agents
Lower BMI	Dialysis vintage	Deceased donor
Low physical activity	History of glomerulonephritis	Low GFR
Females		Diabetes
Family history of osteoporosis		Hypomagnesemia
History of fractures		
Diabetes		

Post-KT bone disease: epidemiology & significance

- Major BMD loss – 1 st year post-transplant
- Higher risk for fracture – first 6 months
- Major fracture sites:
 - distal (ankle/foot/radius) > **hip > spine**
- Fractures → increased mortality (hip + spine)
- Decreasing fracture rates over the last years

Iseri K, et al. Fractures after kidney transplantation: Incidence, predictors, and association with mortality. Bone. 2020;140:115554.

Bouquegneau A, et al. Bone Disease after Kidney Transplantation. Clin J Am Soc Nephrol. 2016 ;11(7):1282-1296.

Bone disease: KT vs dialysis

	Dialysis	Post-transplant
Location	Hip	Distal skeleton
Pathogenesis	CKD, general factors+ Post-transplant (IS, rejection, donor)
Total fracture risk	Inconsistent results	Inconsistent results
Hip fracture risk	Higher	Lower
Mortality	Higher	Lower
Bone turnover	↑/↓ (PD/HD)	Further ↓ (CS)
Trabecular volume	N	Steroid-dependent decrease

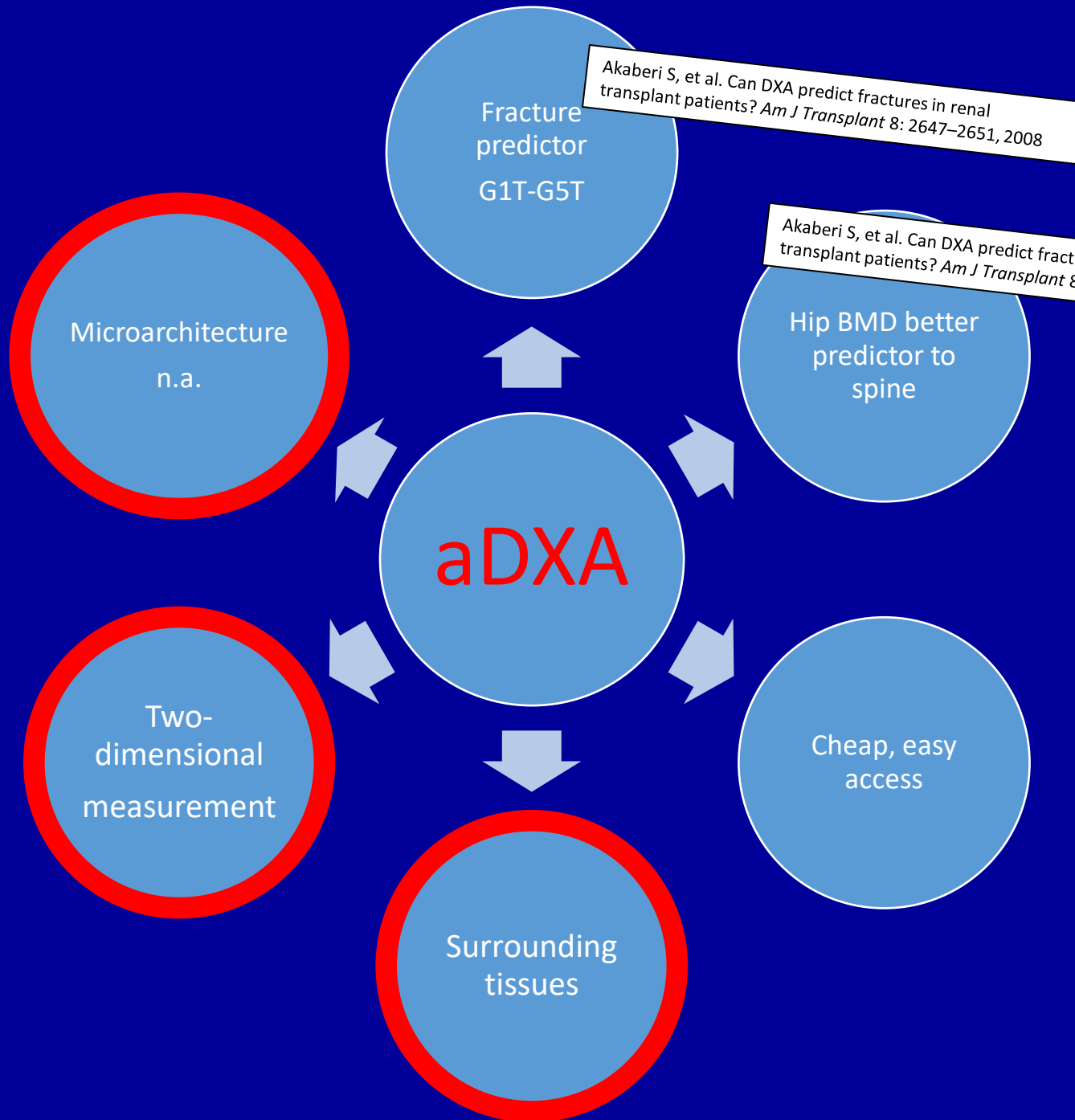
S. Keronen, et al. Changes in bone histomorphometry after kidney transplantation Clin. J. Am. Soc. Nephrol., 14 (6) (2019), pp. 894-903

P. Evenepoel, et al. Bone histomorphometry in de novo renal transplant recipients indicates a further decline in bone resorption 1 year posttransplantation. Kidney Int., 91 (2) (2017), pp. 469-476

Post-transplant bone disease: diagnosis

- Imaging techniques : DXA, TBS, HR-pQCT
- Serum markers: bone formation/resorption
- Bone histology

A. Imaging



Trabecular bone score (TBS)

- Based on previous lumbar spine – DXA
- Software re-analyzed information
- Evaluates pixel gray-level variations
- Indicates bone microarchitecture
- Evaluates bone strength

Lower TBS
in KTR

Naylor KL, et al. Trabecular bone score in kidney transplant recipients. *Osteoporos Int.* 2016 Mar;27(3):1115-1121.

↑ Fracture
risk after
KT

**TBS
after KT**

Dialysis
vintage no
effect

Perez-Saez MJ, et al. Bone density, microarchitecture, and tissue quality long-term after kidney transplant. *Transplantation* (2017) 101:1290-4.

Predicts
non-
vertebral
fracture

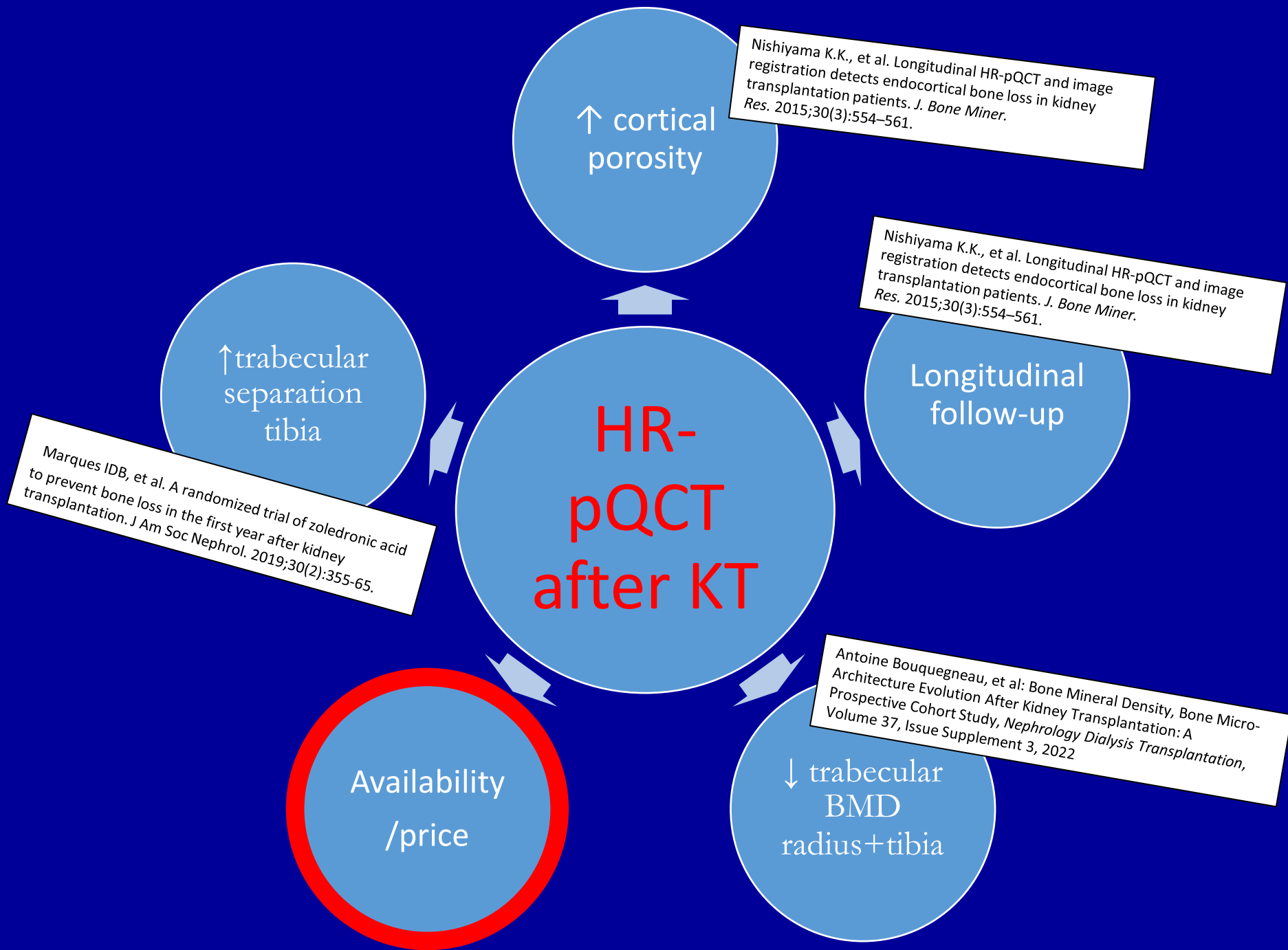
Aleksova J, et al. The trabecular bone score is associated with bone mineral density, markers of bone turnover and prevalent fracture in patients with end stage kidney disease. *Osteoporos Int.* (2018) 29:1447-55.

Normal
BMD , but
low TBS

Luckman M, et al. Spine trabecular bone score as an indicator of bone microarchitecture at the peripheral skeleton in kidney transplant recipients. *Clin J Am Soc Nephrol.* (2017) 12:644-52.

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

- CT extremity scanner, imaging up to 3 min
- Obtains 3D bone geometry
- Bone density – overall, compartment – specific
- Microarchitecture evaluation
- Tested regions: distal radius/tibia
- Radiation 3 μSv , DXA – 9 μSv



High resolution MRI (HR-MRI)

- MRI technique
- Distal extremities
- Proximal femur evaluation also possible
- Similar to HR-pQCT information obtained
- Higher strength of MRI – better clinical correlation

MRI+TBS
outperform
DXA+pQCT

Sharma, AK, et al. Changes in bone microarchitecture following kidney transplantation—Beyond bone mineral density. *Clin Transplant*. 2018; 32:e13347.

HR-
MRI

Rajapakse CS, et al. Micro-MR imaging-based computational biomechanics demonstrates reduction in cortical and trabecular bone strength after renal transplantation. *Radiology*. 2012 Mar;262(3):912-20.

Decreased
cortical
bone

Rajapakse CS, et al. Micro-MR imaging-based computational biomechanics demonstrates reduction in cortical and trabecular bone strength after renal transplantation. *Radiology*. 2012 Mar;262(3):912-20.

Decreased
trabecular
bone

B. Serum markers

Bone formation	Bone resorption	Turnover regulators
tALP	Deoxypyridinoline	Receptor activator of NF- κ B ligand (RANKL) \uparrow resorption
bALP	Hydroxylysine	Osteoprotegerin \downarrow osteoclastogenesis
Osteocalcin	Pyridinoline	Dickkopf-1 \downarrow formation
Procollagen type 1 N-terminal Propeptide	Bone Sialoprotein	Sclerostin \downarrow formation
Procollagen type 1 C-terminal Propeptide	Osteopontin (OP)	
	Cathepsin K	
	Carboxy-terminal Crosslinked Telopeptide of type 1 collagen (CTX-1) (β Crosslaps)	
	Tartrate-resistant acid Phosphatase 5b (TRAP 5b)	
	Amino-terminal Crosslinked Telopeptide of type 1 collagen	
	PTH	

In the general population

Bone formation	Bone resorption	Turnover regulators
tALP	Deoxypyridinoline	Receptor activator of NF- κ B ligand (RANKL) \uparrow resorption
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	PTH	

In the general population + CKD 1-2 ?

Bone formation	Bone resorption	Turnover regulators
tALP	Deoxypyridinoline	Receptor activator of NF- κ B ligand (RANKL) \uparrow resorption
bALP	Hydroxylysine	Osteoprotegerin \downarrow osteoclastogenesis
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	Tartrate-resistant acid Phosphatase 5b (TRAP 5b)	
	Amino-terminal Crosslinked Telo peptide of type 1 collagen	
	PTH	

CKD 3 – 5D

Bone formation	Bone resorption	Turnover regulators
tALP	Deoxypyridinoline	Receptor activator of NF-κB ligand (RANKL) ↑ resorption
bALP	Hydroxylysine	Osteoprotegerin ↓ osteoclastogenesis
Osteocalcin	Pyridinoline	Dickkopf-1 ↓ formation
Procollagen type 1 N-terminal Propeptide	Bone Sialoprotein	Sclerostin ↓ formation
Procollagen type 1 C-terminal Propeptide	Osteopontin (OP)	
	Cathepsin K	
	Carboxy-terminal Crosslinked Teloepptide of type 1 collagen (CTX-1) (β Crosslaps)	
	Tartrate-resistant acid Phosphatase 5b (TRAP 5b)	
	Amino-terminal Crosslinked Teloepptide of type 1 collagen	
	PTH	

CKD
biochemistry

After KT

Bone formation	Bone resorption	Turnover regulators
tALP	Deoxypyridinoline	Receptor activator of NF- κ B ligand (RANKL) \uparrow resorption
bALP	Hydroxylysine	Osteoprotegerin \downarrow osteoclastogenesis
Osteocalcin	Pyridinoline	Dickkopf-1 \downarrow formation
Procollagen type 1 N-terminal Propeptide	Bone Sialoprotein	Sclerostin \downarrow formation
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	Tartrate-resistant acid Phosphatase 5b (TRAP 5b)	
	Amino-terminal Crosslinked Telo peptide of type 1 collagen	
	PTH	

CKD
biochemistry

Heimgartner N, et al. Predictive Power of Bone Turnover Biomarkers to Estimate Bone Mineral Density after Kidney Transplantation with or without Denosumab: A post hoc Analysis of the POSTOP Study. *Kidney Blood Press Res.* 2020;45(5):758-767.

Evenepoel P, et al. Bone mineral density, bone turnover markers, and incident fractures in de novo kidney transplant recipients. *Kidney Int.* 2019 Jun;95(6):1461-1470.

CKD 3T – 5T

Bone formation	Bone resorption	Turnover regulators
tALP	Deoxypyridinoline	Receptor activator of NF-κB ligand (RANKL) ↑ resorption
bALP	Hydroxylysine	Osteoprotegerin ↓ osteoclastogenesis
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	Amino-terminal Crosslinked Teloptide of type 1 collagen	
	PTH	

CKD
biochemistry

C. Bone histology

Bone biopsy – importance, indications

- Golden standard, renal osteodystrophy types, guide for treatment
- 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 (Not Graded)
- In **CKD G3a–G5D + biochemical abnormalities of CKD-MBD and low BMD ± fragility fractures**, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, **with consideration of a bone biopsy (2D)**
- **KT < 12 months, GFR > 30 ml/min/1.73m², low BMD**: It is reasonable to consider a bone biopsy to **guide treatment** (Not graded)
- Inconsistent PTH trend, unexplained calcemia/fractures

Bone histology

- **Turnover:** skeletal remodelling, bone formation/resorption

1. double-tetracycline labeling.

2. low – normal - high

- **Mineralization:** bone collagen calcification

1. Static evaluation – osteoid volume/thickness

2. Dynamic – double tetracycline labelling

3. normal - abnormal

- **Volume:** amount of bone / unit volume tissue

1. Measured in cancellous bone

2. low – normal - high

TMV classification

Type of ROD	T	M	V
Osteitis fibrosa	High	Normal	High
Adynamic bone disease	Low	Normal	Low/normal
Mild SHT-bone disease	Medium	Normal	Medium
Osteomalacia	Low	Abnormal	Low/medium
MUO osteopathy	High	Abnormal	normal
Normal histology	Normal	Normal	Normal

+ Signs of osteoporosis

thinned trabeculae
decreased osteon size

enlarged Haversian and marrow spaces

Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G; Kidney Disease: Improving Global Outcomes (KDIGO). Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2006 Jun;69(11):1945-53.

Bone biopsy: disadvantages

- Expensive
- Invasive
- Pain
- Need for experienced pathologists and laboratory
- Need for experienced operators
- Adequate sampling

- **Still not routinely used, low number of procedures**

Evenepoel P, et al. Bone histomorphometry in de novo renal transplant recipients indicates a further decline in bone resorption 1 year posttransplantation. *Kidney Int.* 2017;91(2):469-476.

↘ Turnover
Osteoclast activity linked to TRAP 5b

Osteoblasts ↓
Bone loss (T>C)
Risk for AD

Carvalho, C., et al. (2016) Evolution of bone disease after kidney transplantation: A prospective histomorphometric analysis of trabecular and cortical bone. *Nephrology*, 21: 55–61.

Lehmann G, et al. Renal osteodystrophy after successful renal transplantation: A histomorphometric analysis in 57 patients. *Transplant Proc* 39: 3153–3158, 2007

Variable predominant ROD type

Malluche HH, et al. Bone disease after renal transplantation. *Nat Rev Nephrol* 6: 32–40, 2010

Bone biopsy after KT

More biopsies needed ?

No correlation to biomarkers, imaging

Evenepoel P, et al. ERA-EDTA Working Group on CKD-MBD : Bone biopsy practice patterns across Europe: The European renal osteodystrophy initiative—a position paper. *Nephrol Dial Transplant* 32: 1608–1613, 2017

↘ resorption/formation
Magnitude of pre-Tx ROD

Drüeke, T.B.; Evenepoel, P. The Bone after Kidney Transplantation. *CJASN* 14(6):p 795-797, 2019.

Predictors for bone fracture after KT

Paramether	Fracture risk
Time after KT: first 6 months	↑
Gender: Female	↑
Older recipient, deceased donor	↑
Pre-transplant dialysis	↑
Previous fracture	↑
Treatment acute rejection	↑
Diabetic nephropathy	↑
Preemptive TR	↓
BMD: osteopenia and osteoporosis	↑
FRAX score	Needs further evaluation
Bone markers	Need further evaluation
Bone biopsy	Inconsistent results after KT, need for further evaluation: biopsy result – fracture risk

3. Vascular calcification after KT

Importance

- Associated with higher CV mortality after KT
- Location arterial + valvular calcification
- Relatively common – up to 25%
- Influenced by preceding CKD
- Progression may be slowed down after KT

Risk factors

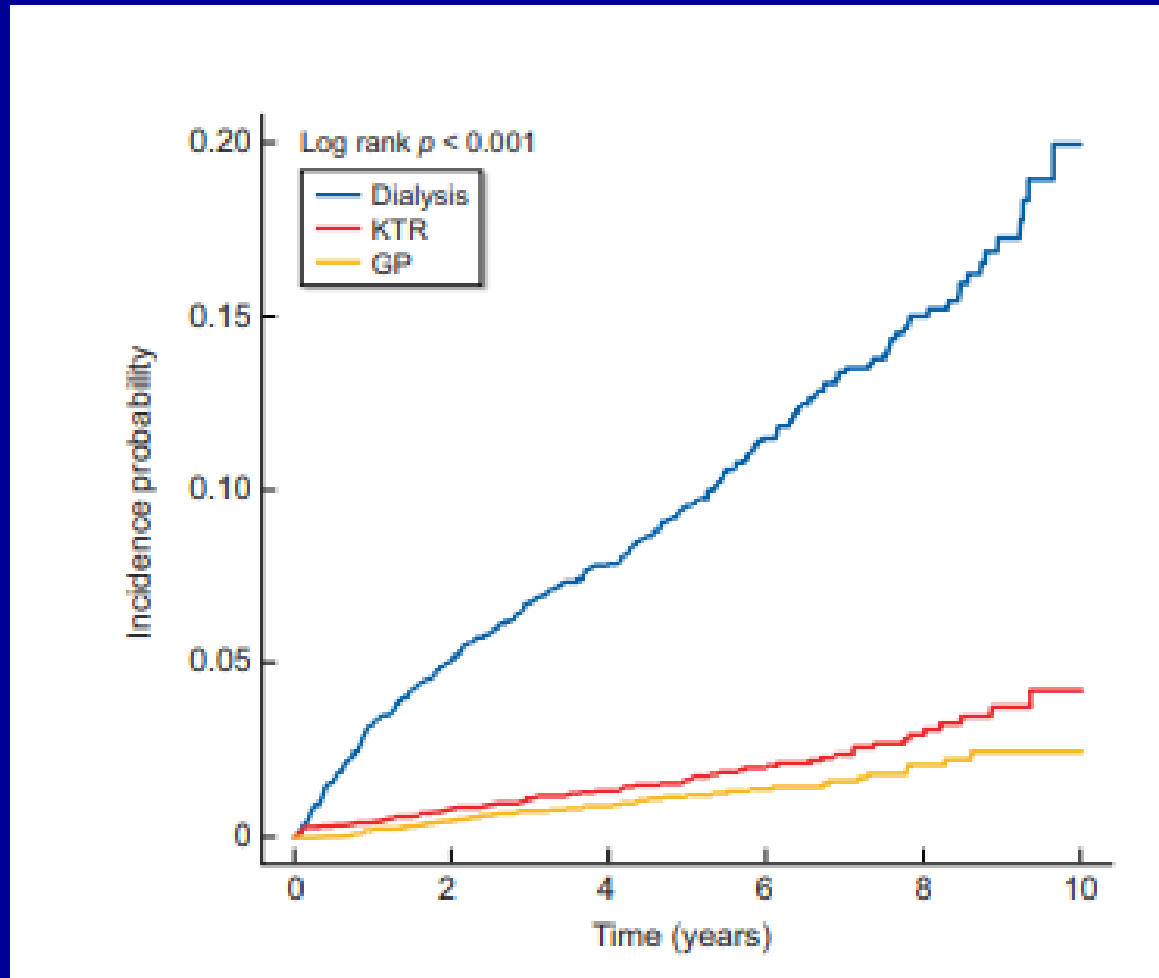
General	Transplant	CKD	Calcification inhibition
Diabetes	Steroids	sHPTH	↓Matrix Gla protein (Vit. K antagonists)
Dyslipidemia	mTOR inhibitors	Systemic inflammation	Hypomagnesemia
Hypertension	CNIs	Oxidative stress	Low Fetulin A
Older age			

Podestà MA, et al. Cardiovascular calcifications in kidney transplant recipients. *Nephrol Dial Transplant.* 2022;37(11):2063-2071.

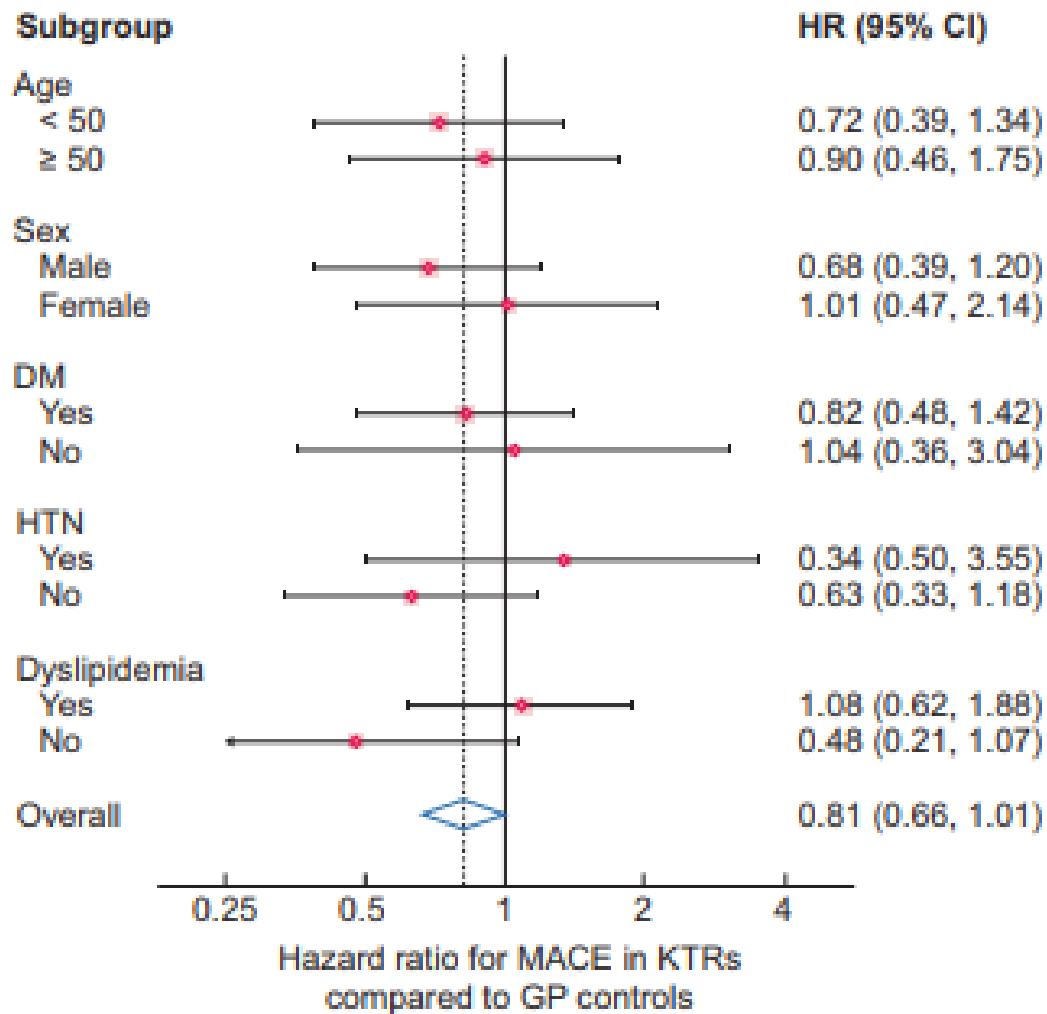
Diagnosis

- CT scan
- Lateral X ray: abdominal, pelvic
- Echocardiography
- DXA scan

CV incidence and mortality after KT

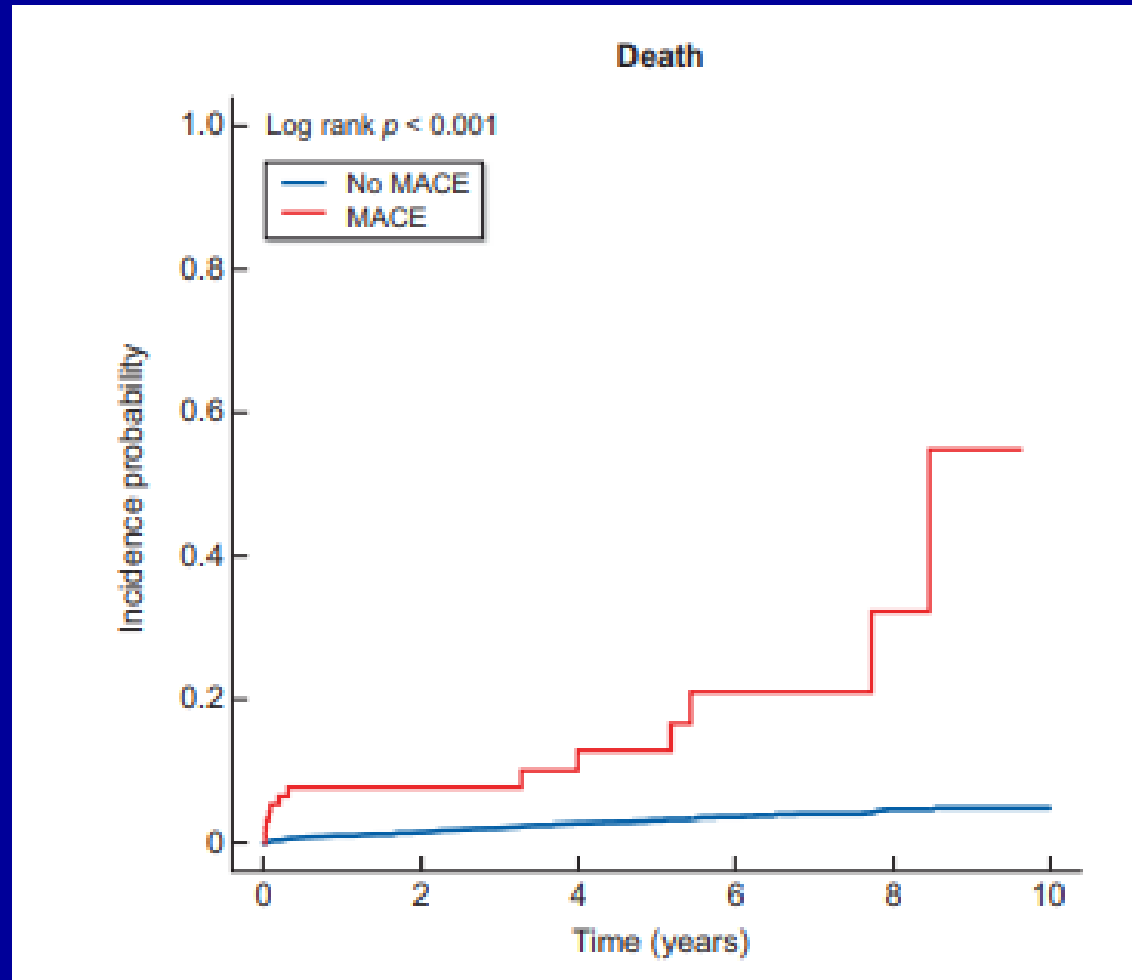


Kim JE, et al. De novo major cardiovascular events in kidney transplant recipients: a comparative matched cohort study. *Nephrol Dial Transplant.* 2023;38(2):499-506.



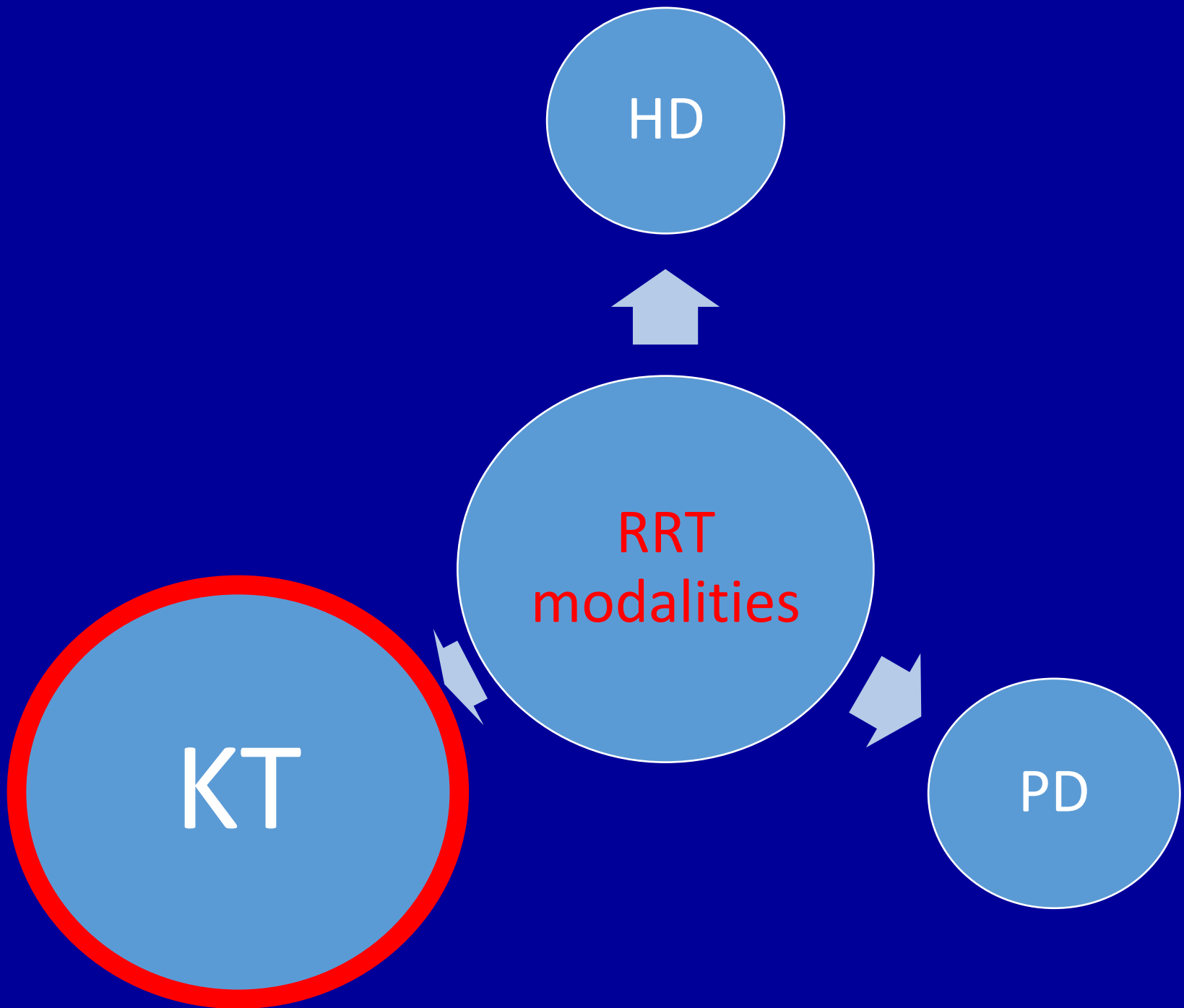
Kim JE, et al. De novo major cardiovascular events in kidney transplant recipients: a comparative matched cohort study. *Nephrol Dial Transplant.* 2023;38(2):499-506.

MACE and mortality after KT



Kim JE, et al. De novo major cardiovascular events in kidney transplant recipients: a comparative matched cohort study. *Nephrol Dial Transplant.* 2023;38(2):499-506.

Post-KT mineral bone disease: treatment



Post-KT mineral bone disease: treatment and prevention

Biochemistry	Bone	CV involvement
Treatment sHPTH	Steroid minimization	BP control
Ca/P correction	Vitamin D/vitamin D analogue	Dyslipidemia
VD supplementation	Cinecalcet	Treatment sHPTH
Parathyroidectomy	Antiresorptive therapy	Diabetes control
	Recombinant PTH (teriparatide)	Immunosuppression optimization
	Lifestyle modifications	Lifestyle modification

Antiresorptive therapy after KT

- Bisphosphonates + Denosumab
- Lower bone turnover
- Can theoretically worsen pre-existing ABD
- Results – inconsistent
- Bone biopsy can be considered, but not obligatory
- Can be used in patients with high fracture risk

Bisphosphonates and risk of ABD

Author	Bisphosphonate	BMD	Biopsy
Coco et al	<i>Pamidronate vs Calcitriol+Ca</i>	Slower decline of vertebral BMD in pamidronate	Increased risk of ABD
Haas et al	<i>Zoledronate + Ca vs Ca</i>	Improvement of lumbar BMD vs controls	No risk of ABD
Coco et al	<i>Risedronate+Calitriol vs Calcitriol</i>	No change in lumbar BMD	↑osteoid formation, No risk of ABD
Marques et al	<i>Zoledronate vs controls</i>	Improvement in BMD in both groups	Reduced trabecular bone loss in zoledronate No risk of ABD

Coco M, et al. Prevention of bone loss in renal transplant recipients: A prospective, randomized trial of intravenous pamidronate. J Am Soc Nephrol 14: 2669–2676, 2003

Haas M, et al. Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. Kidney Int 63: 1130–1136, 2003

Coco M, et al. Effect of risedronate on bone in renal transplant recipients. J Am Soc Nephrol 23: 1426–1437, 2012

Marques IDB, et al. A randomized trial of zoledronic acid to prevent bone loss in the first year after kidney transplantation. J Am Soc Nephrol 30: 355–365, 2019

Denosumab after kidney transplantation

- Humanized monoclonal antibody
- Inhibits the receptor activator of the Nf-kB ligand
- Risk for hypocalcemia, urinary tract infections
- No immunological risk
- Limited trials after KT

Denosumab after kidney transplantation

Author	Design	BMD	Bone biopsy
Alfieri et al.	Denosumab , no control arm	Increased BMD femur and spine	n.a.
Bonani et al.	Denosumab vs controls	Increased femoral and lumber BMD	n.a.
McKee et al.	Denosumab vs bisphosphonates retrospective	Better BMD increase on Denosumab	n.a.
Afifi et al	Denosumab vs Ibandronate	Better BMD on Denosumab	n.a.
Sayed et al.	Denosumab vs Alendronate vs controls	Improvement in BMD on therapy, Denosumab \approx Alendronate	n.a.

Alfieri C, et al. Bone Effect and Safety of One-Year Denosumab Therapy in a Cohort of Renal Transplanted Patients: An Observational Monocentric Study. *J Clin Med.* 2021;10(9):1989.

Bonani M, et al. Effect of twice-yearly denosumab on prevention of bone mineral density loss in de novo kidney transplant recipients: a randomized controlled trial. *Am J Transplant.* (2016) 16:1882–91.

McKee H, et al. Correction to: Comparison of the clinical effectiveness and safety between the use of denosumab vs bisphosphonates in renal transplant patients. *Osteoporos Int.* 2020;31(5):981.

Afifi, M.K., et al. Optimization of osteoporosis and osteopenia management among renal transplant recipients. *Futur J Pharm Sci* 7, 230 (2021).

Sayed, SA, et al. Evaluation of the efficacy and tolerability of alendronate versus denosumab in kidney transplant patients with reduced bone mineral density. *Pharmacotherapy.* 2023; 43: 904-912.

Mineral Bone Disease after Kidney Transplantation: conclusions

- High prevalence
- Numerous risk factors
- Higher mortality
- Poorer quality of life
- Serum biomarkers not very informative
- More bone biopsies needed?
- Modifiable factors present
- More data on treatment expected

**Thank you for your
attention !**

