KDIGO Controversies Conference on Chronic Kidney Disease-Mineral and Bone Disorder: Progress and Knowledge Gaps Towards Personalizing CKD-MBD Care

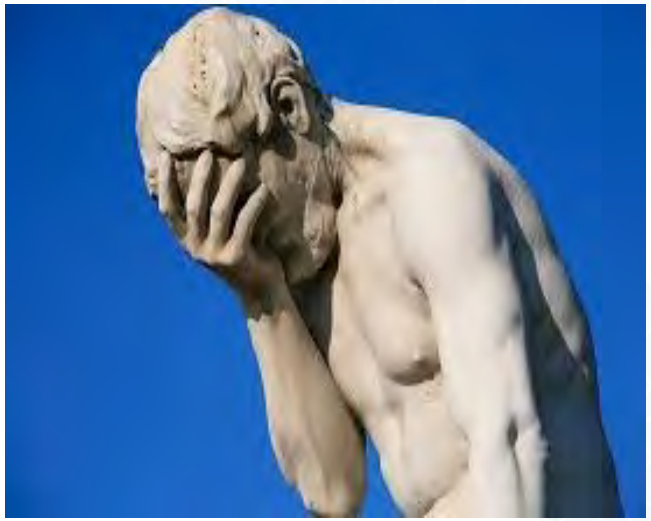
ROD and Osteoporosis in CKD

Marie-Hélène Lafage Proust

DISCLOSURES

- Research Grant: Kiowa Kirin
- Education Grant: Jansen, Merck

ROD and Osteoporosis in CKD



- Osteoporosis in CKD: is it different from the general population? which drugs should we use , for whom and when?
- Bone Effects of SHPT therapy: differences between calcimimetics and vitamin D analogs
- Is bone biopsy always necessary? What is normal in bone histomorphometry: different reference ranges among study groups impacting mostly the definition of normal turnover and mineralization
- ROD physiopathology: recent advances
- …..

Osteoporosis in CKD

- Current Knowledge:
  - CKD increases the risk for fracture
  - Fractures are osteoporotic (hip, humerus, ..)

- Combination of Risk factors for fractures
  - For primary osteoporosis: Age, low BMI, female gender, falls, prevalent fracture
  - From secondary OP : Hypogonadism, diabetes, PP inhibitors, loop diuretics, Glucocorticoids…
  - From CKD: KT history, PTX history, dialysis vintage, acidosis, *Phosphate*…

- Recent data after 2000
  - 7566 dialysis patients, 1504 KT patients, Danish background population (4 091 776)

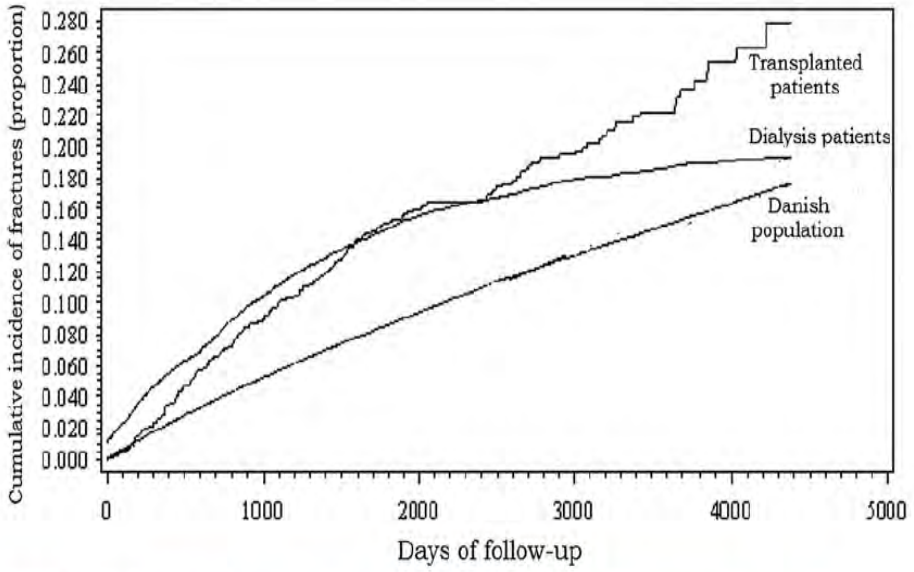


FIGURE 2: Cumulative incidence curves for fractures with death as competing end point.

- (HR) for any fracture:
- Dialysis: 3.14 (95% CI):2.97–3.31] 1.85 after adjustment
- KT: 1.94 (95% CI: 1.72–2.18) 1.82 after adjustment

- Trend for decreased incidence of fractures in KT patients?

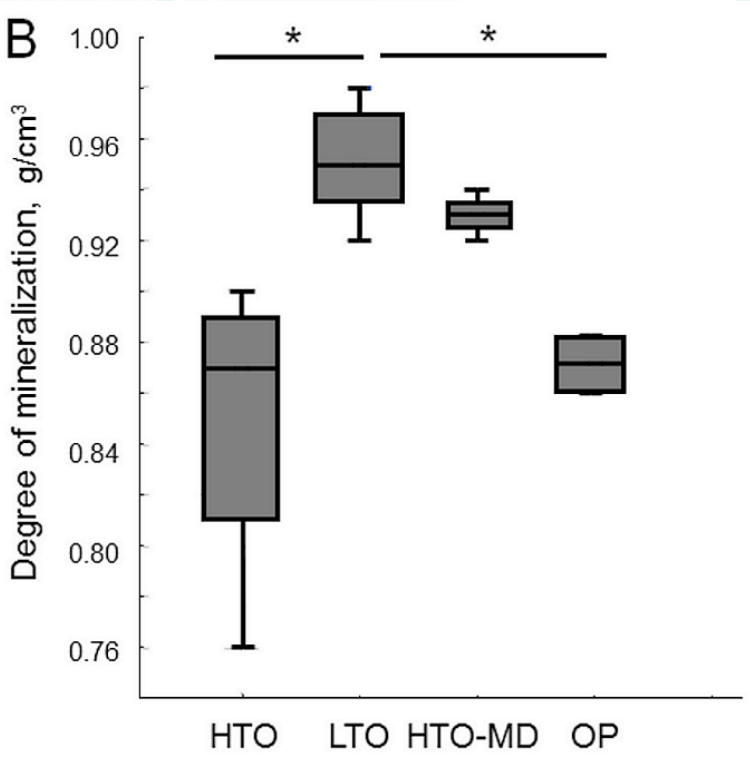
Ball AM, et al. JAMA 2002; 288: 3014–3018
Coco M, Am J Kidney Dis 2000; 36: 1115–1121
Alem AM, Kidney Int 2000; 58: 396–399
Covino et al Am J Med Sci 2021

Castro-Alonso et al J. Clin. Med. 2020, 9, 1604;

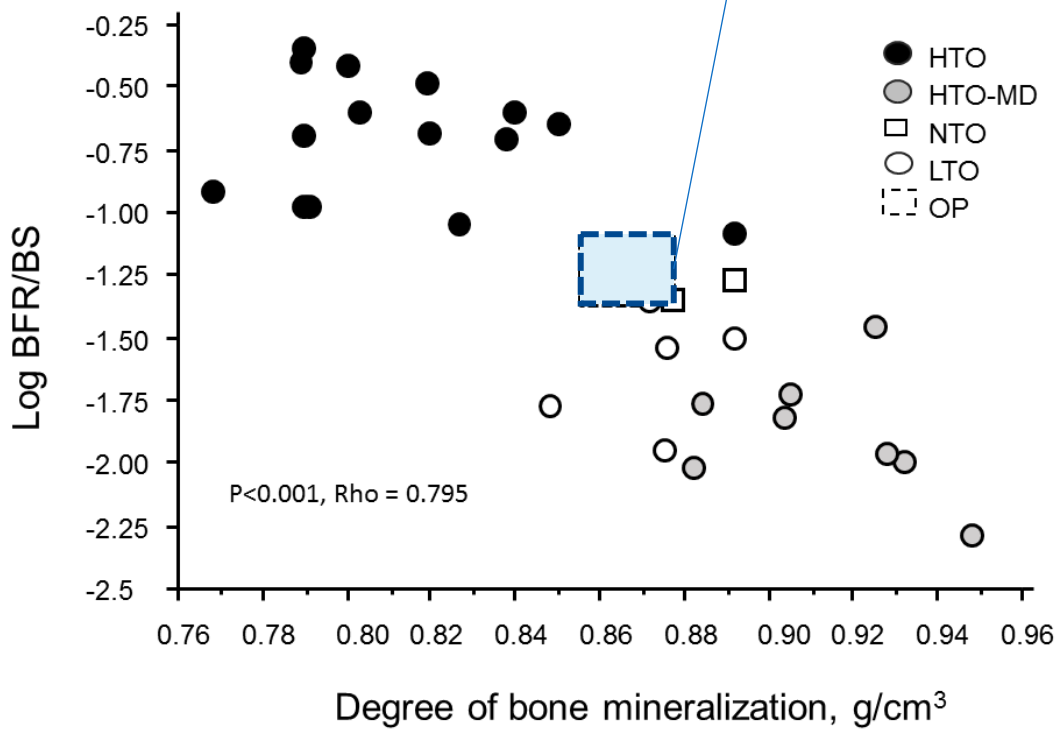
Hansen D et al Nephrol Dial Transplant (2016) 31: 1654–1662
Nair S, et al. Am J Transplant, 2014; 14:943–951:
Perrin et al Transplantation 2016

Is it different from the general population?

- Degree of bone secondary mineralisation of bone in patients with various type of ROD lesions (HD or KT) (synchroton radiation microtomography)



n=14 Non uremic age matched osteoporotic patients



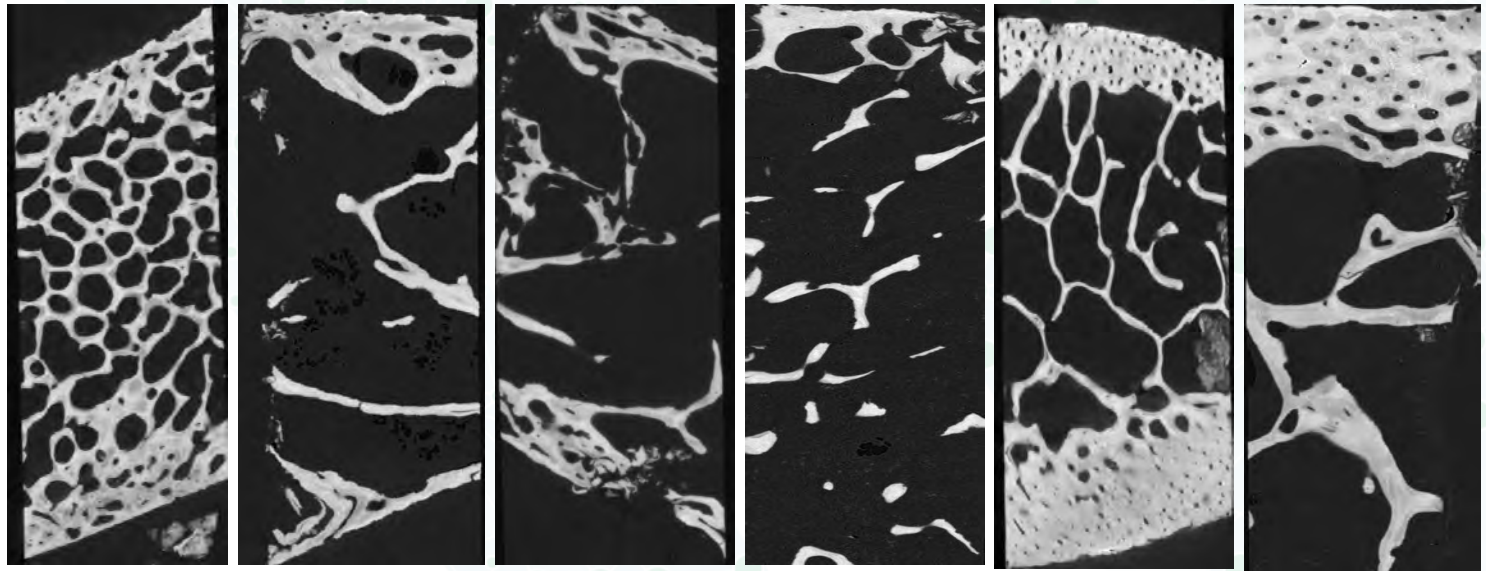
(Personal data)

44 bone samples: 19 ♂ and 11♀, mean age: 55 ± 18 yrs.
30 CKD, 8 Low bone TO (LTO), 15 High Bone TO (HTO),
5 HTO-Mineralization Defect (HTO-MD, mixed disease)
2 Normal Bone TO (NTO).

Nuzzo S, et al, J Bone Miner Res. 2002;17(8):1372-82
Boivin G. . In: GR Dickson (ed), Methods of Calcified Tissue Preparation, 11. 1984: 391-412.

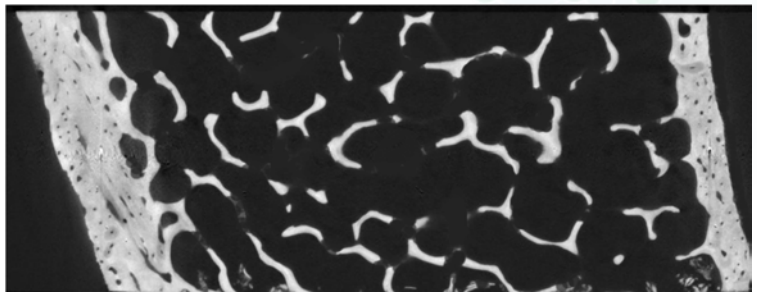
Is it different from the general population?

← CKD →



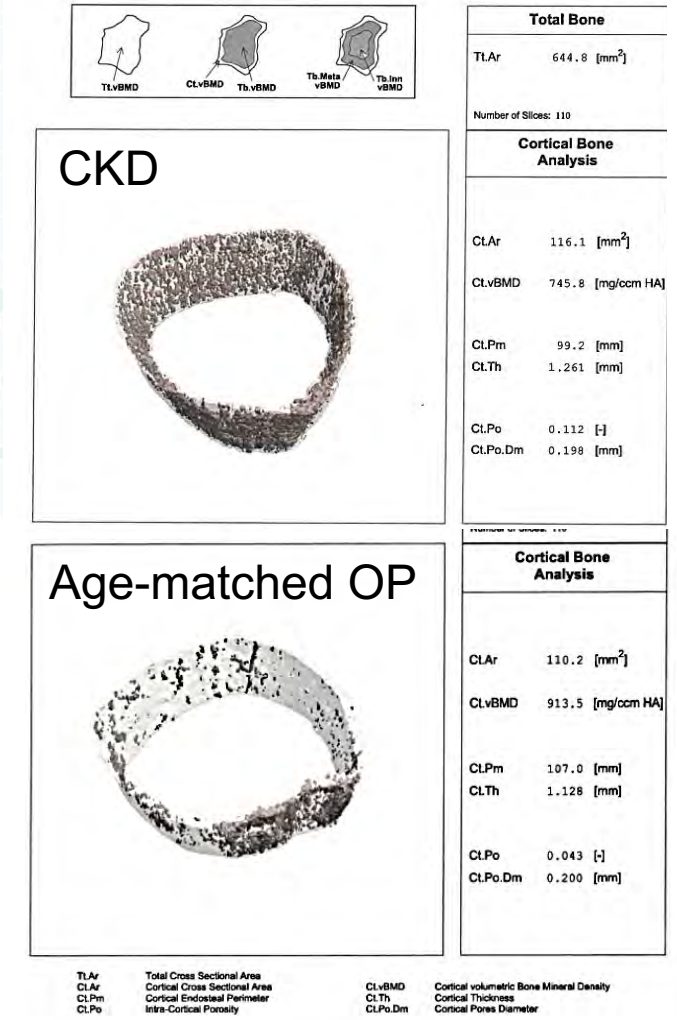
LTO HTO LTO HTO HTO HTO

← Non uremic OP →



Trabecular achitecture deterioration
Increase in cortical porosity

Diagnosis Treatment



Sharma et al Am J of Nephrol 201847(6):376-384, personal data

Nickolas TL, J Bone Miner Res, 2013;28:1811–20.
Allen et al Curr Osteoporos Rep. 2020 June ; 18(3): 242–246

Which drugs should we use, for whom and when?

- Current Knowledge:
  - DXA BMD predicts Fx risk in CKD regardless of CKD stage
  - T score <-2.5 discriminant
  - Target Population: Pts at high risk Female, age >50…etc
  - Sensitivity/ specificity issues

- Better identification of patients at Risk
  - TBS, 3D Shaper
  - MRI
  - FRAX score (or other scores for evaluating the risk for fracture in CKD ?
  - Add BTM
  - KDIGO (2020, Eval KT candidates)

SECTION 18: BONE AND MINERAL METABOLISM

Disorder (CKD-MBD) guideline *(2D)*.

18.3: Bone mineral density (BMD) should not be measured as part of the transplant evaluation *(Not Graded)*.

Yenchek RH, et al. Clin J Am Soc Nephrol 2012;7:1130–6
West SL, et al. J Bone Miner Res 2015;30:913–9.
VE.Gómez-Islasab et al Bone Rep 2020, 13, 100298
Iimori S, et al Nephrol Dial Transplant. 2012;27:345–351.
Prasad B, et al. Can J Kidney Health Dis 2019;2054358119870539

Eun Song et al Transplantation Proceedings, 51, 2704e2709 (2019)
Evenepoel et al Kidney International (2019) 95, 1461–1470

Which drugs should we use, for whom and when?

- Current Practice:
  - Patients with prevalent fracture
- Current questions:
  - Regardless of CKD stage?
  - Primary prevention?
    - In HD patients identified at high risk?
    - In HD patients identified at high risk on KT waiting list?
    - KT patients at risk (1st year?)




Which drugs should we use?

Treatment of ROD

- Phosphate binders (Ca/non Ca)
- Iron based Phosphate binders
- Vitamin D & derivatives

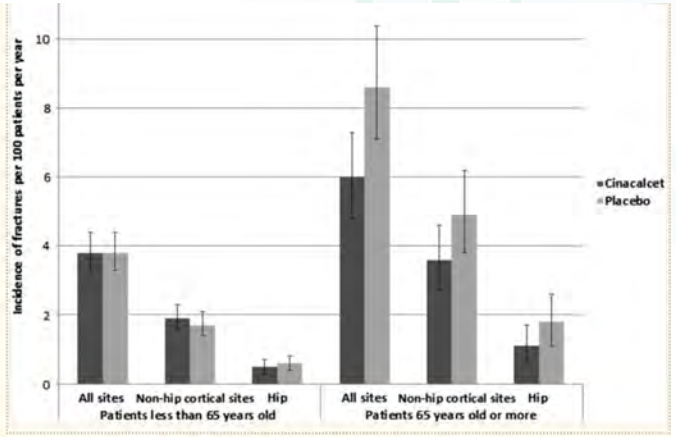
↑ Stage 5d ↓

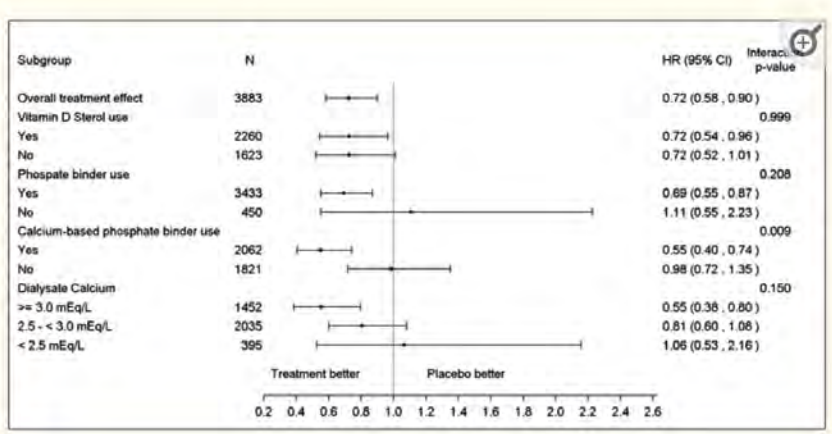
- Dialysate calcium concentration ,
- Cinacalcet, Etelcalcetide
- PTX

- Current questions:

Effects of SHPT therapy: Differences between calcimimetics and vitamin D analogs on

- BMD
- BTM
- Fractures





Chertow GM et al. N Engl J Med 2012;367:2482-2494,Moe SM et al, J Am Soc Nephrol. 2015 Jun;26(6):1466-75.

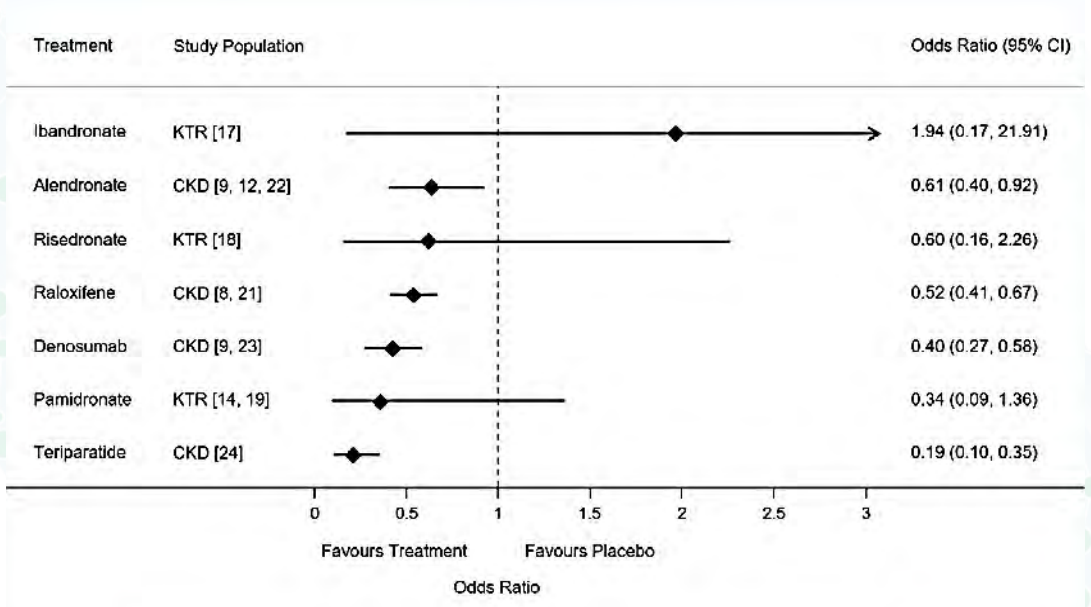
Which drugs should we use?

Treatment of osteoporosis

- GFR > 30ml/mn
  - Bisphosphonates,
  - Teriparatide, *abaloparatide*
    Denosumab
  - Raloxifene
  - Romososumab

- GFR < 30ml/mn
  - Denosumab

17 studies/ 10,214 patients With stage 2–5 CKD, or KT



Forest plots of relative risk of vertebral or clinical fractures

Chen HH et al Frontiers in Pharmacology 2022, 822178

Jamal SA, et al. J Bone Miner Res 2007;22:503–8; 2. Miller PD, et al. J Bone Miner Res 2005;20:2105–15;3. Ishani A, et al. J Am Soc Nephrol, 2008;19:1430, 4;Miller PD, et al. Osteoporosis Int 2007;18:59–68; 5-Jamal SA, et al. J Bone Miner Res 2011;26:1829–35, Miller et al JBMR, 37, 8:2022, 1437–1445.

Are BPs safe for renal fonction and effective in CKD 3-5?

- GFR<45ml/min (CKD3-5) , >40 year of age, follow-up 3-4 yrs
- CPRD cohort : 53,986 unexposed patients / 2613 under BPs
- SIDIAP: 40,800 unexposed /1408 BPs patients under BPs

PS Matched

CKD progression

	CPRD	
	BP	Non-BP
Unmatched no. events	614	15,411
Unmatched incidence rates	90.8 (83.9, 98.3)	73.3 (72.1, 74.4)
Unadjusted HR	**1.25 (1.15, 1.36)**	
Fully adjusted HR	**1.18 (1.08, 1.29)**	
PS-matched no. events	576	1996
PS-matched incidence rates	89.1 (82.1, 96.7)	85.6 (82.0, 89.5)
PS-matched sub-HR	**1.14 (1.04, 1.26)**	

	CPRD	
	BP	Non-BP
Unmatched no. events	614	15,411
Unmatched incidence rates	90.8 (83.9, 98.3)	73.3 (72.1, 74.4)
Unadjusted HR	**1.25 (1.15, 1.36)**	
Fully adjusted HR	**1.18 (1.08, 1.29)**	
PS-matched no. events	576	1996
PS-matched incidence rates	89.1 (82.1, 96.7)	85.6 (82.0, 89.5)
PS-matched sub-HR	**1.14 (1.04, 1.26)**	

- Annualized change in total hip BMD as a function of BP treatment and baseline CKD stage

	Non-users (N = 3908)	BP users, all (N = 1789)	BP users, MPR ≥ 80% (N = 1121)
Adjusted for age, sex, prior MOF, recent GC use			
BMD change, adjusted[a]			
CKD 1	−0.4 (−0.5; −0.2) [N = 1558]	0.9 (0.8; 1.1) [N = 729]*	1.2 (1.1; 1.4) [N = 458]*
CKD 2	−0.4 (−0.5; −0.3) [N = 1935]	1.0 (0.7; 1.1) [N = 883]*	1.3 (1.2; 1.5) [N = 555]*
CKD 3A	−0.6 (−0.8; −0.3) [N = 304]	0.6 (−0.2; 0.9) [N = 136]*	1.0 (0.6; 1.4) [N = 86]*
CKD 3B	−0.6 (−1.7; 0.4) [N = 90]	0.2 (−1.3; 0.9) [N = 33]	0.4 (−0.5; 1.2) [N = 18]
CKD 4	−2.0 (−3.7; −0.3) [N = 19]	1.5 (−1.0; 4.0) [N = 7]	[N < 5]
CKD 5	[N < 5]	[N < 5]	[N < 5]

[a] Adjusted for baseline differences in age, sex prior MOF, rece

* p < 0.05 compared with non-user group

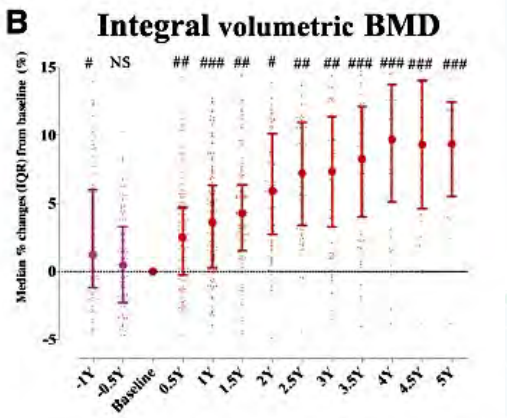
Robinson et al JBMR 36, 5: 2021: 820–832.

Abrahamsen B et al Bone 137 (2020) 115371

Is denosumab effective and safe in CKD?

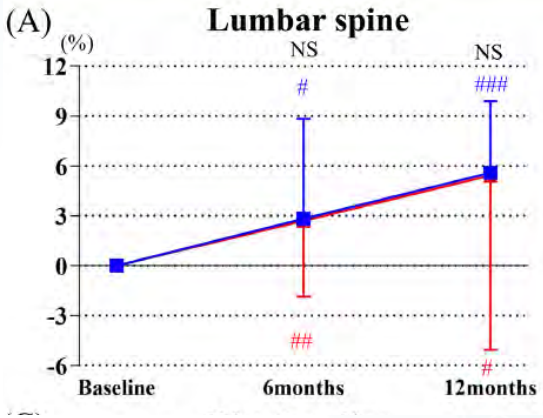
Calcium balance?

124 HD pts, 37% with diabetes, 71.



Iseri et al CJASN 18: 1195–1203, 2023.
Mc Kee et al Osteoporosis Int, 2020, 31:973–980

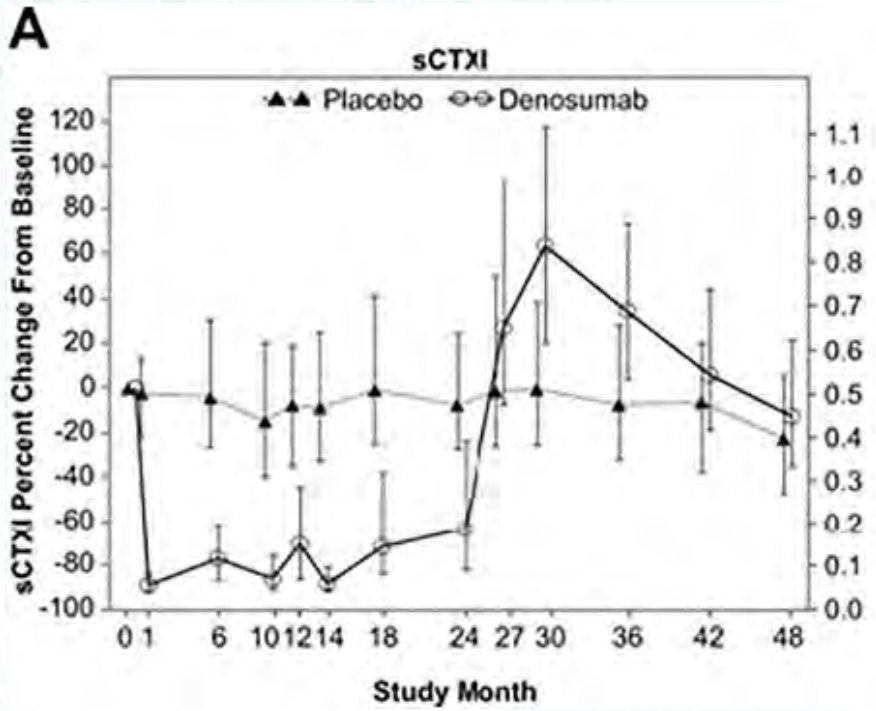
78 HD pts Dmab + Ca vit D for 2 weeks
Vs alendrnate



- No change in vessel status (ABI, PWv, CACs…) .after 1 year
- Risk of mild to severe hypocalcemia ncrease with CKD severity

Cowan et al JBMR. 38. 5, 2023, 650–658.
Iseri et al JBMR, 34, 6; 2019, 1014–1024

Discontinuation or never stop?



Aubry-Rozier B, et al. Osteoporos Int 2016;27:1923–5;
Ansastasilakis AD, et al. JBMR 2017;32:1291–96;
Tsourdi E, et al. Bone 2017;105:11–17;
Pimentel A, et al. Kidney Int 2017;92:1343–55;
Cummings SR, et al. JBMR 2018;33:190–8;
Thongprayoon C, et al. Osteoporos Int 2018;29:1737–45;

Should treatment be based on bone turnover assessment?

- Current practice :
- When ROD is severe it should be improved before anti OP treatments are prescribed
- Anti resorptive drugs in HTO, anabolic drugs in low turnover

But:

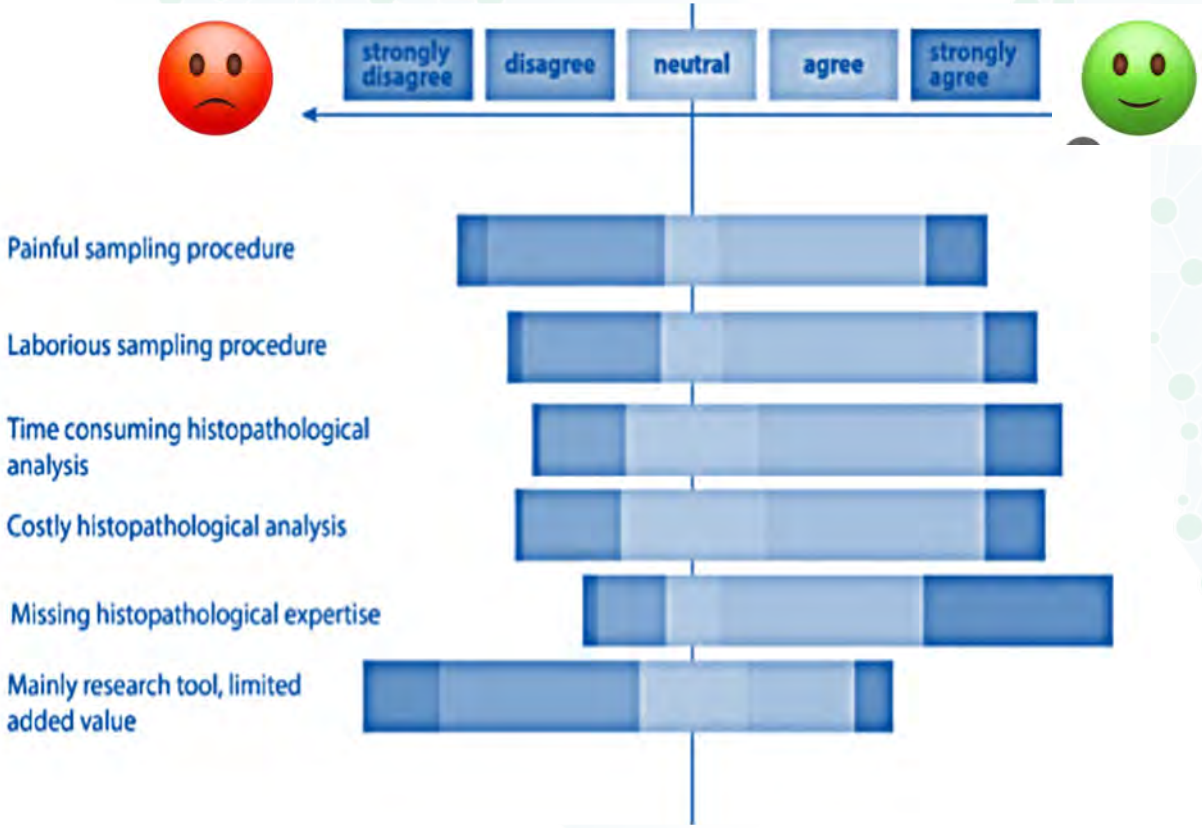
- 6 months Dmab (+calcitriol and calcium) in HD patients with serum PTH >1000pg/ml and Alk Phos 500UI/l: BMD increased by 23%. No evaluation of Vascular safety or long term evolution (*Chen-Liang et al J Clin Endocrinol Metab, 2014, 99(7):2426–2432).*

- BPs increase BMD to a greater extent when baseline BTM are higher,
- BPs increase BMD in patients with baseline BTM in the normal range.
- Anti vertebral fracture efficacy is not affected by BTM pre treatment levels
  (Bauer DC et al J Bone Miner Res 2006;21:292–299.)

- Teriparatide prevents vertebral fractures in PM osteoporosis (increased turnover) Bisphosphonates prevent fractures in glucocorticoid induced osteoporosis in which bone formation is low

Is bone biopsy always necessary?

- Is bone biopsy popular?



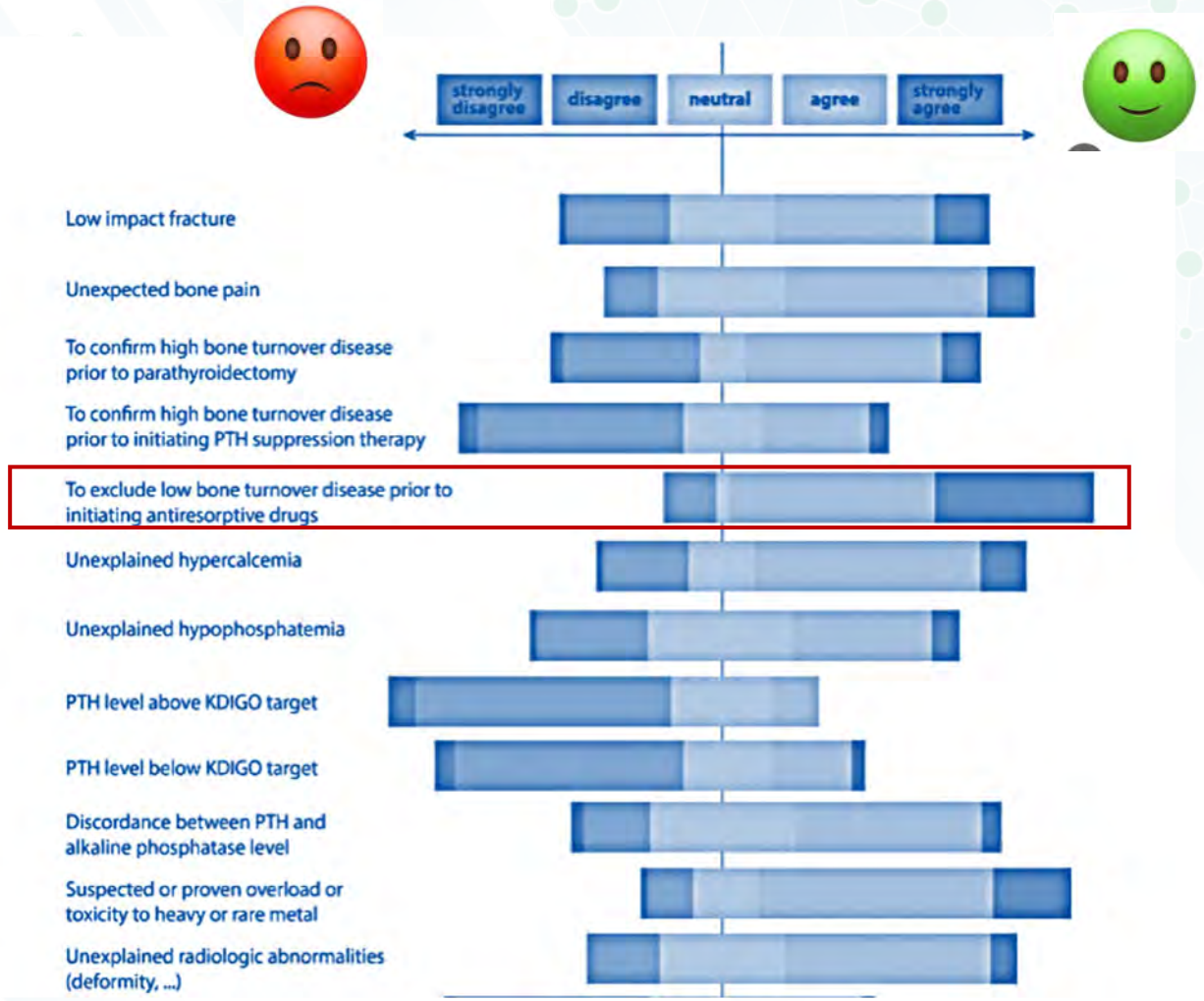
Evenepoel et al Nephrol Dial Transplant (2017) 32: 1608–1613 , on 68

- Should we simplify the procedure?

- Change trephine?
- Get rid of tetracycline labeling ?
- Ask radiologists to perform the biopsy?
- Replace biopsy with BTM?

Novel-Catin E, et al Bone. 2020 ;138:11589
Jorgensen HS et al. Bone. 2021;152: 115460:/ Salam S et al Bone 142 (2021) 115689
Lavigne F, et al J Nephrol. 2021;34(3):901-906.
Jorgensen et al Am J Kidney Dis 2021 .79(5):667-676., Salam S et al JASN.2018;29(5):1557-1565

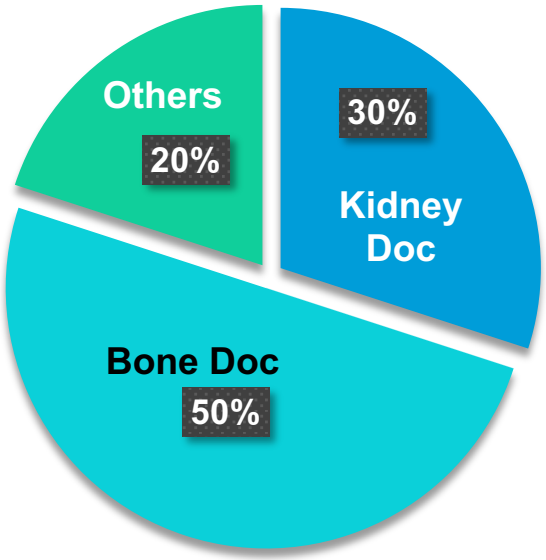
Is bone biopsy always necessary before anti OP treatment?



Evenepoel et al Nephrol Dial Transplant (2017) 32: 1608–1613 , on 68

What is normal in bone histomorphometry?:
different reference ranges among study groups impacts results

Bone histomorphometry Working group



Literature survey → identification of european HM users/ experts → Mailing survey → Bone histomorphometry Working group →Delphi methodology (Estimate-Talk-Estimate)→

- Biopsy Procedure
- Sample processing
- Quantification methods
- Diagnosis criteria
- Final report

AUSTRIA	– Pr Astrid Fahrleitner-Pammer
BELGIUM	– Pr. Patrick d'Haese
	– Geert Behets, PhD
	– Pr Pieter Evenepoel
DENMARK	– Dr. Ditte Hansen
	- Dr. Hanne Skou Jørgensen
FINLAND	– Pr Heikki Kröger
	– Pr Eero Honkanen
	– Dr. Xiaoyu Tong
FRANCE	– Pr. Justine Bacchetta
	– Pr MH Lafage-Proust
	– Pr. Martine Cohen-Solal
	– Dr. Pablo Ureña-Torres
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	– Dr. Neveen Hamdy
	– Dr. Renate de Jongh
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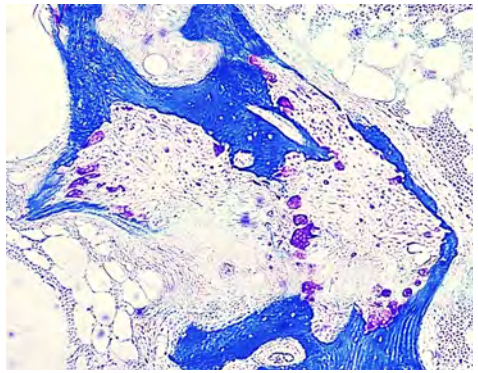
SWITZERLAND	– Pr Andrea Thrombetti
	– Dr. Maude Gerbaix
	– Dr. Marie-Josée Begin
UK	– Dr. Alex D Lalayiannis
	– Dr. Rukshana Shroff
	– Dr. Syazrah Salam

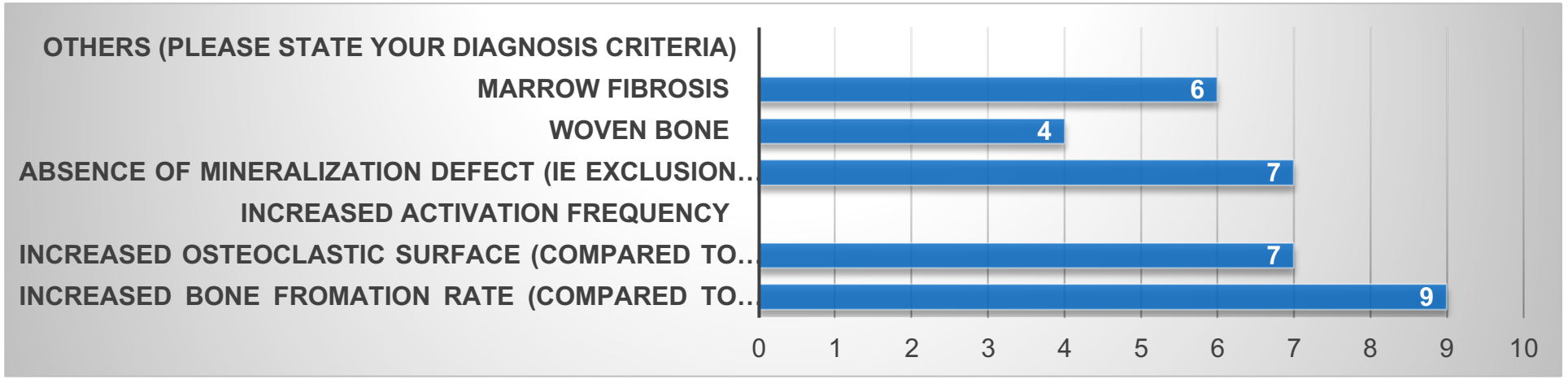
era edta LEADING EUROPEAN NEPHROLOGY

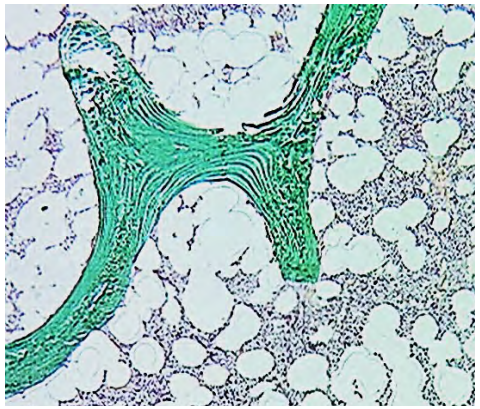
KDIGO KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

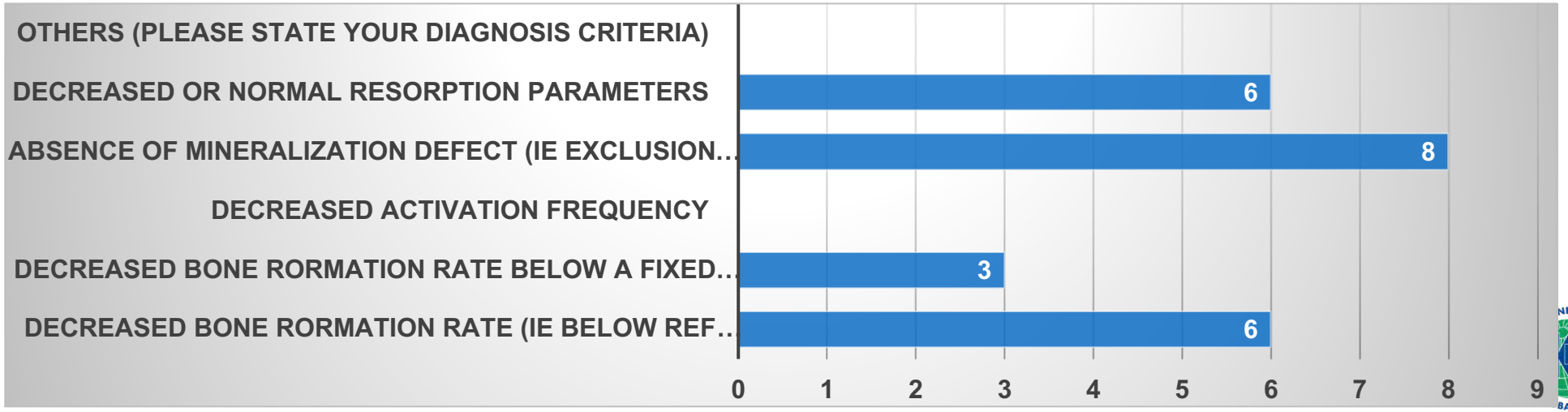
Agreement: Diagnosis criteria: low and high bone turnover

- We agreed on the type of lesion
- High Bone TO: high bone formation + no mineralization defect + other features
- Low Bone TO : low bone formation + no mineralization defect + other features



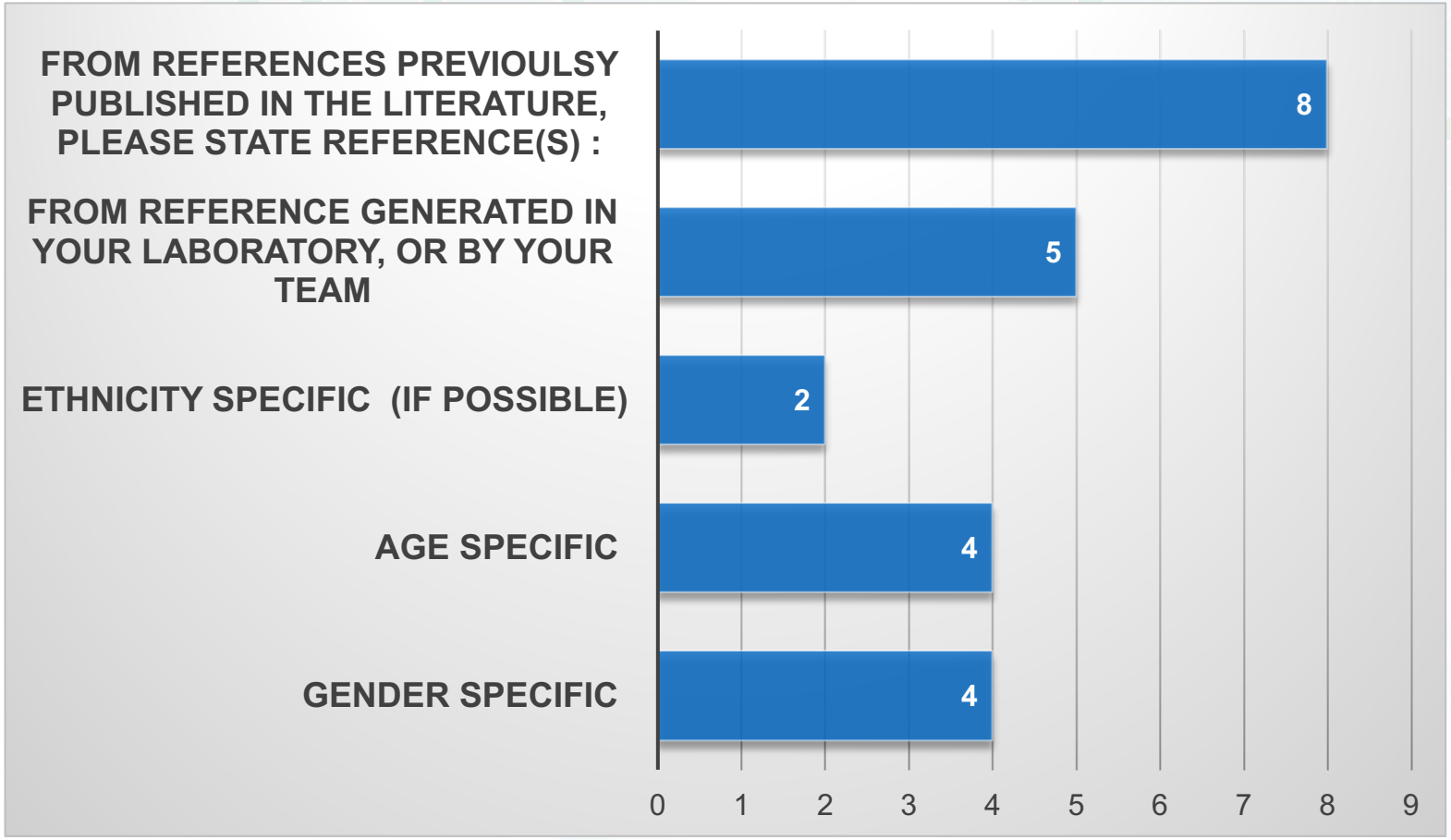






Disagreement: Normal Population references

- Reference Values Condition diagnosis results



- Thomsen J.S., Osteopoross Int, 2015
- Bach-Gansmo F.L., Bone, 2016
- Melsen F., Acta Path. Microbiol., 1978
- Melsen F, Mosekilde L (1978) Calcif. Tissue Res 26:99–102
- Rehman M. T. A., J Clin Pathol, 1994
- For children: Glorieux et al, Bone 2000
- Luciene M at al: J Bone Miner Metab 2007; 25(6):400-6
- S.Vedi et al Metabolic Bone Disease and Rel Res 4, 4, 1982: 231-236

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- -
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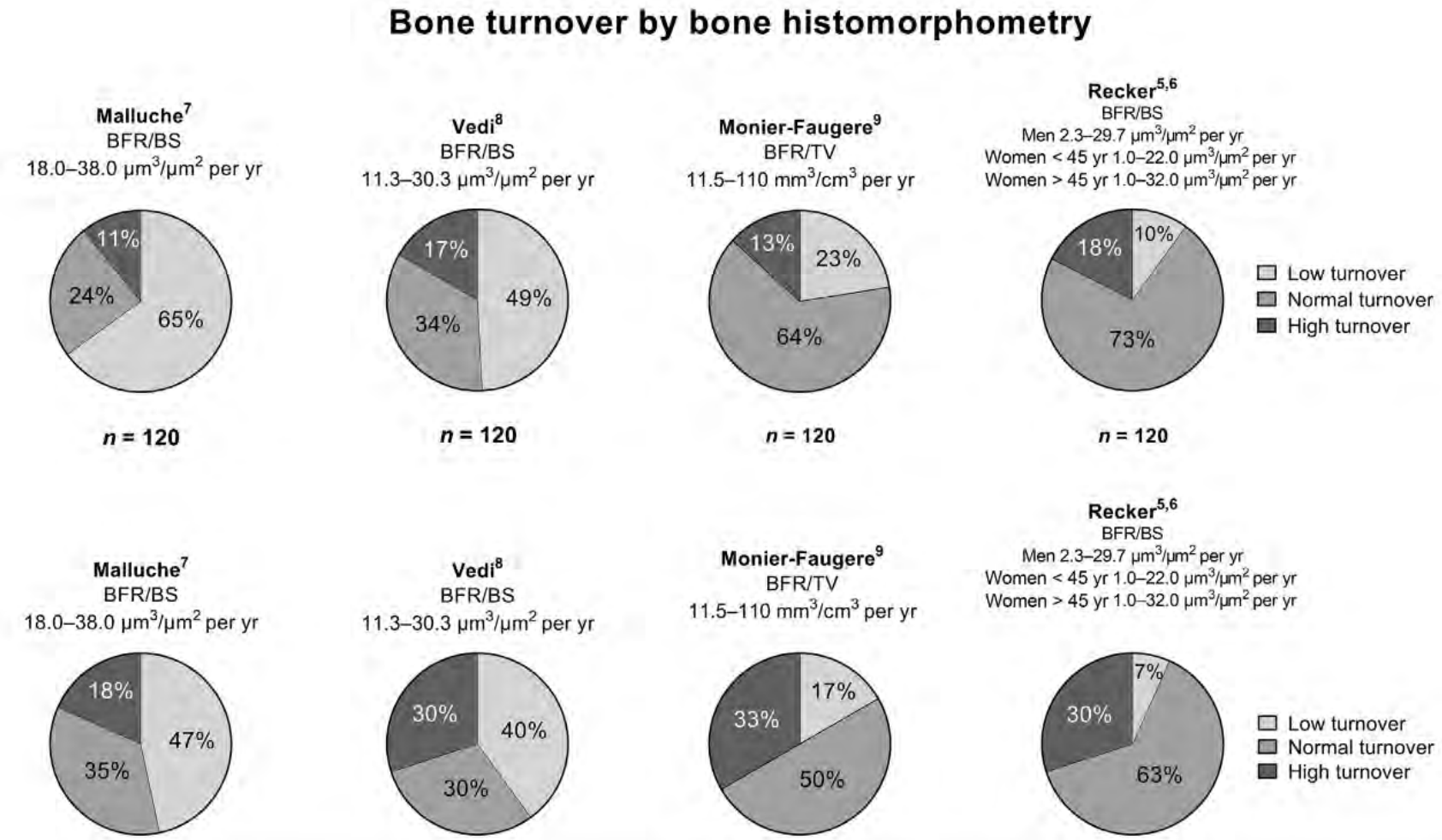
- ……

HM diagnosis of renal osteodystrophy: a call for harmonization of reference ranges

- *Jorgensen S H et al , EUROD group, Kidney International (2022) 102, 431–434*

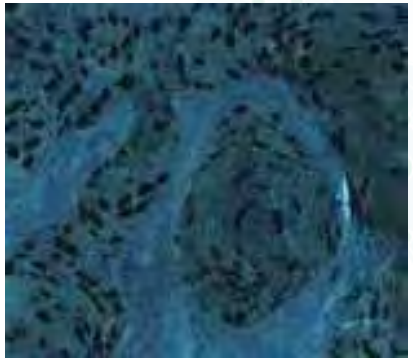


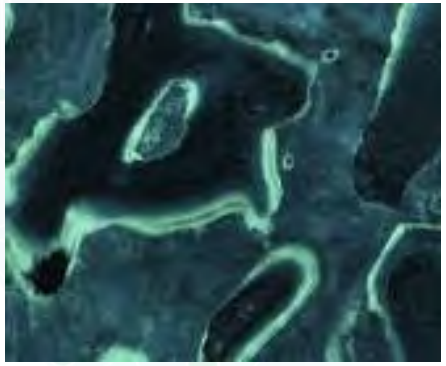
ROD and Osteoporosis in CKD

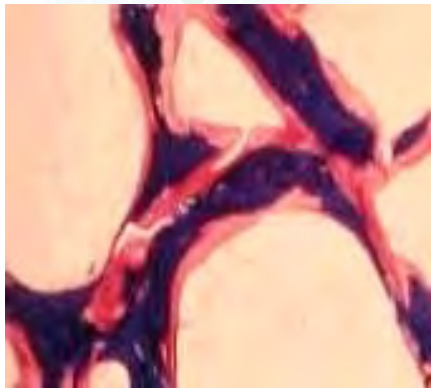
ROD physiopathology: recent advances

ROD physiopathology: current knowledge

- ROD is defined by lesions that affect bone turnover & primary mineralisation
- = what happens at the bone surface



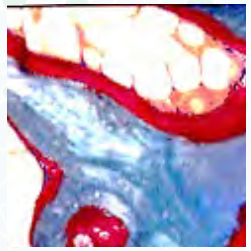




- What if what is below the surface also matters?

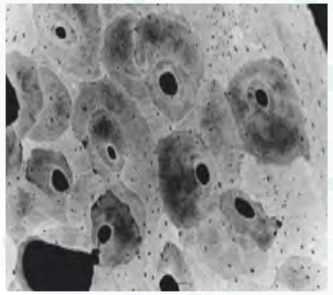
ROD physiopathology: recent advances

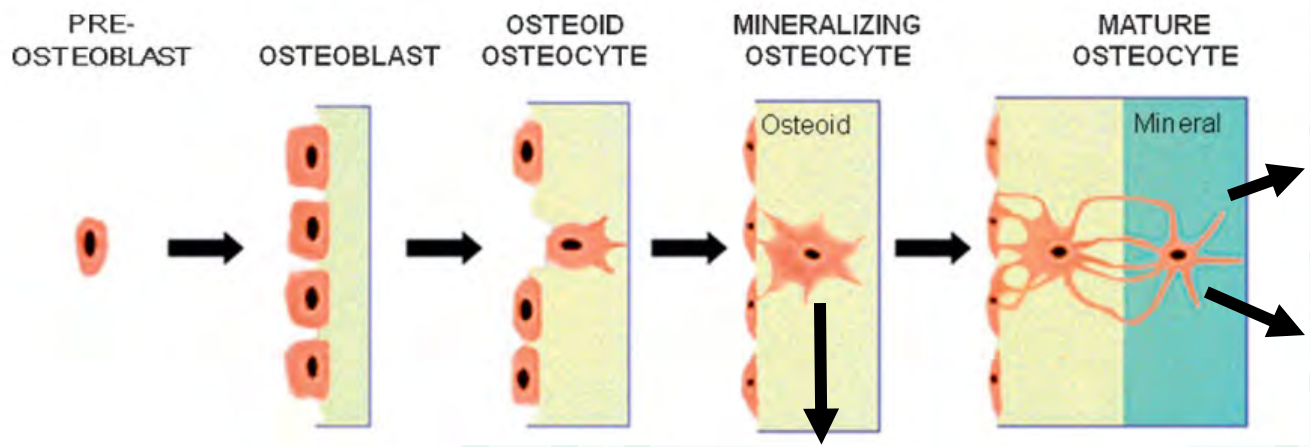
- Why Osteocyte dysfunction(s) could be a target in CKD-MBD?



Primary mineralization

Secondary mineralization





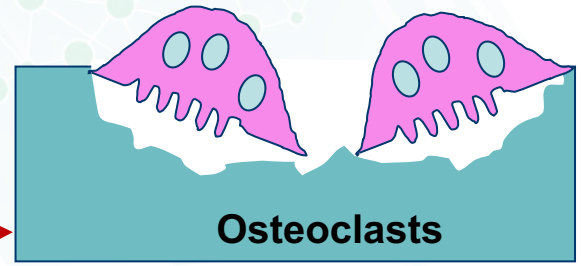
Podoplanin
MT1-MMP

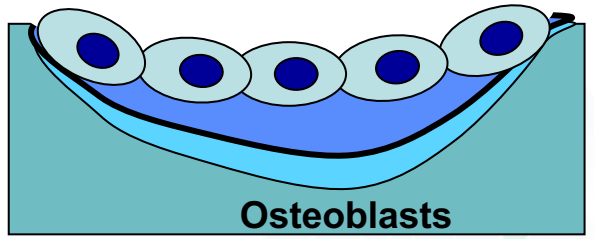
DMP1

FGF23

RANKL

Sclerostin





Mineral release (?)

- Carb Anhydrase, TRAP, Cathepsin K

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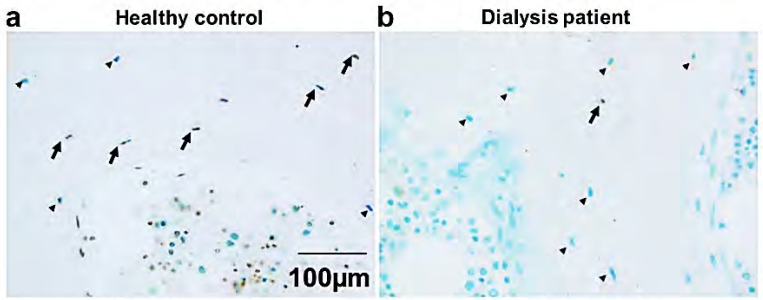
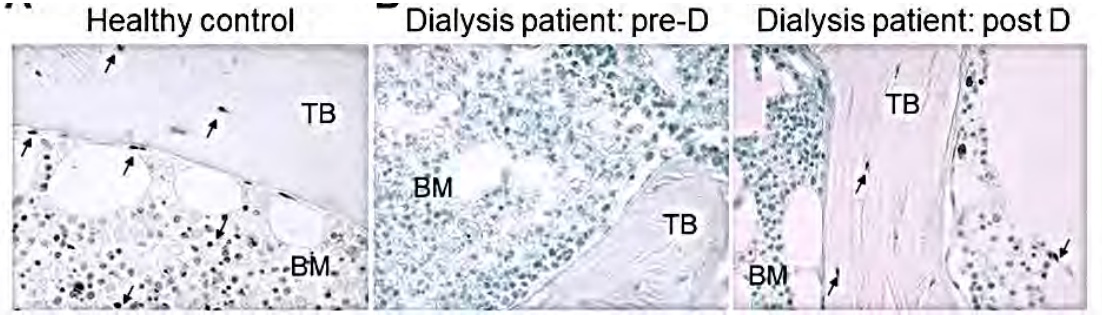
Osteocytes death in the context of CKD

- Osteocytes apoptosis is ***decreased*** in young CKD patients , associated with defect in Ocy maturation and increased by Vit D derivatives





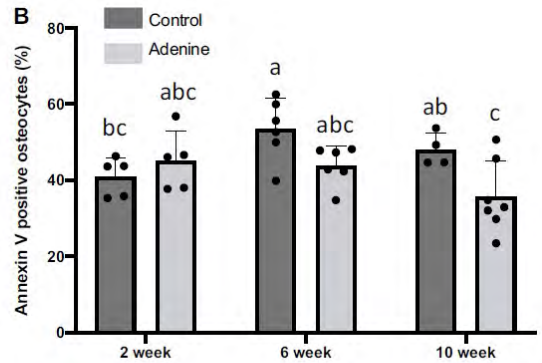
- Osteoblast apoptosis is ***increased*** by dietary Phosphate load in CKD rats with low turnover

Table 4. Osteoblastic and osteocytic apoptotic rates (%).

	Sham	Nx+PTx 0.6%	Nx+PTx 1.2%
	(n=10)	(n=9)	(n=9)
Osteoblast apoptosis, %	1.2 (0.9-1.8)	0.4 (0.3-0.8) [a,b]	1.3 (0.9-1.5)
Osteocyte apoptosis, %	0.5 (0.3-1.0)	0.2 (0.15-0.25) [a,b]	0.4 (0.3-0.5)

Nx+PTx: 5/6 nephrectomy and total parathyroidectomy a: $p < 0.05$ vs. sham; b: $p < 0.05$ vs. Nx+PTx 1.2%.

- Osteocyte apoptosis is ***decreased*** in the adenine CKD model



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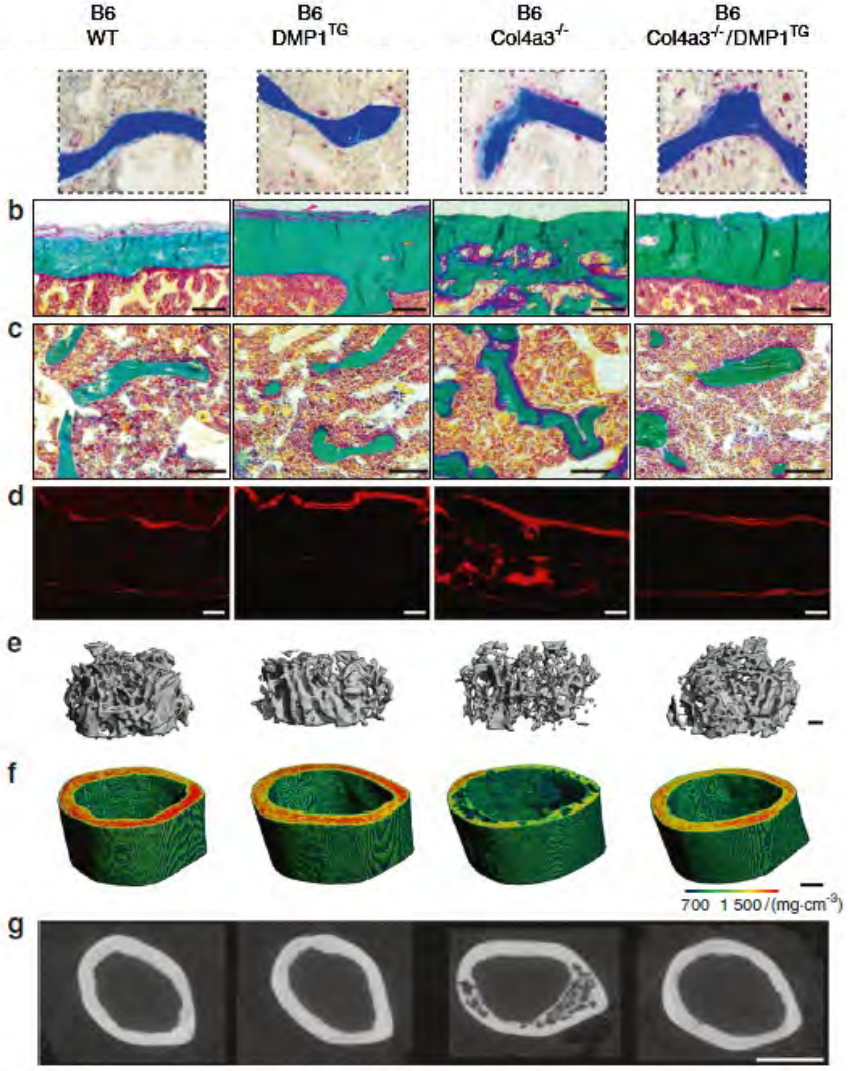
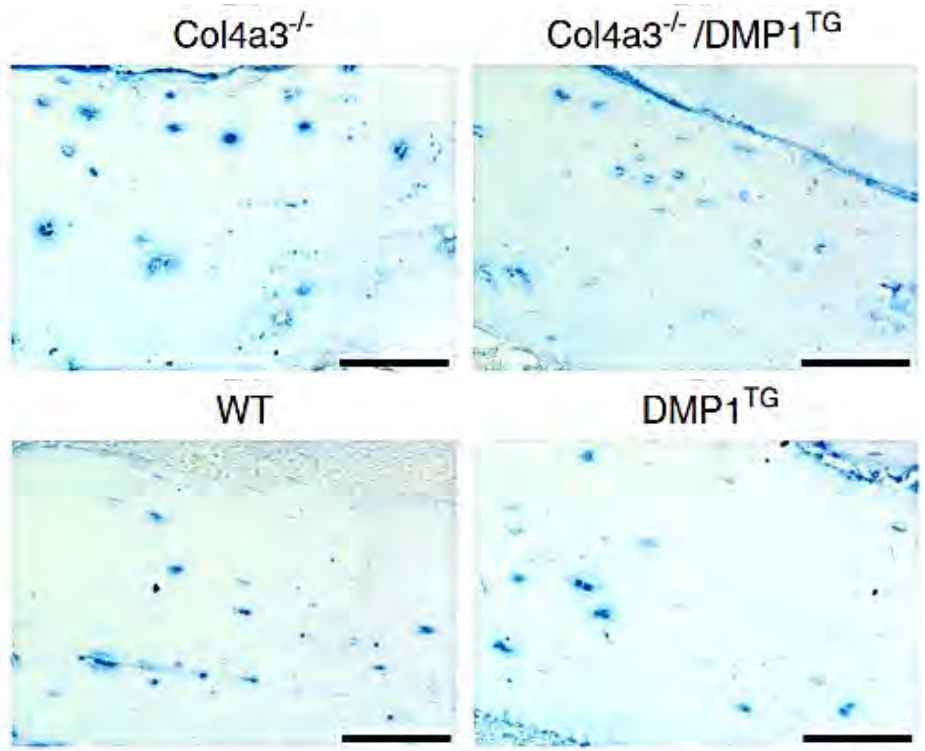
Rojas E, et al. Kidney Int. 2003;63:1915–1923
Tan SD. et al. J Dent. Res. 85, 905–909 (2006).

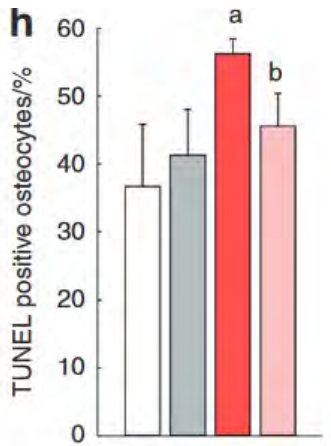
Osteocytes death in the context of renal osteodystrophy

- DMP1 overexpression in late osteoblasts/ osteocytes improves bone health in the Col4a3 $^{-/-}$ Mouse model of CKD



- CKD (High bone turnover) →increase in osteocyte apoptosis decreased by DMP1 overexpression in late Ob/Ocy





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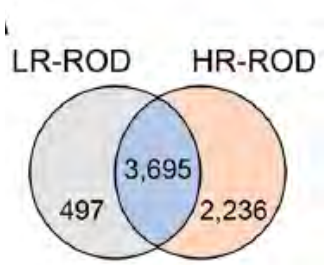
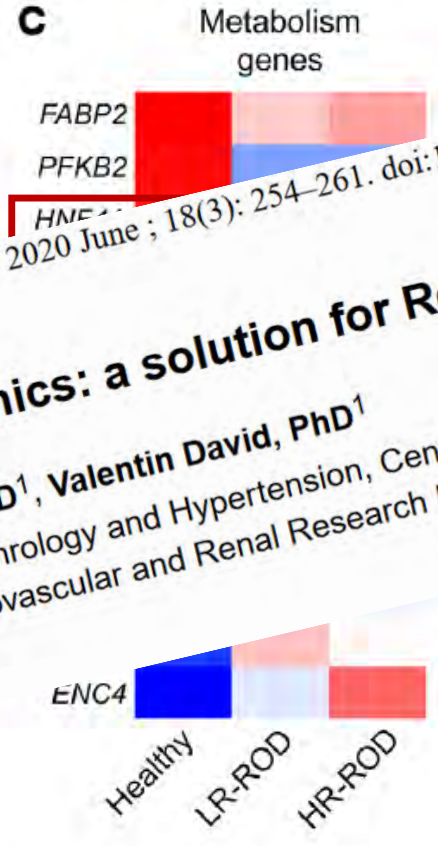
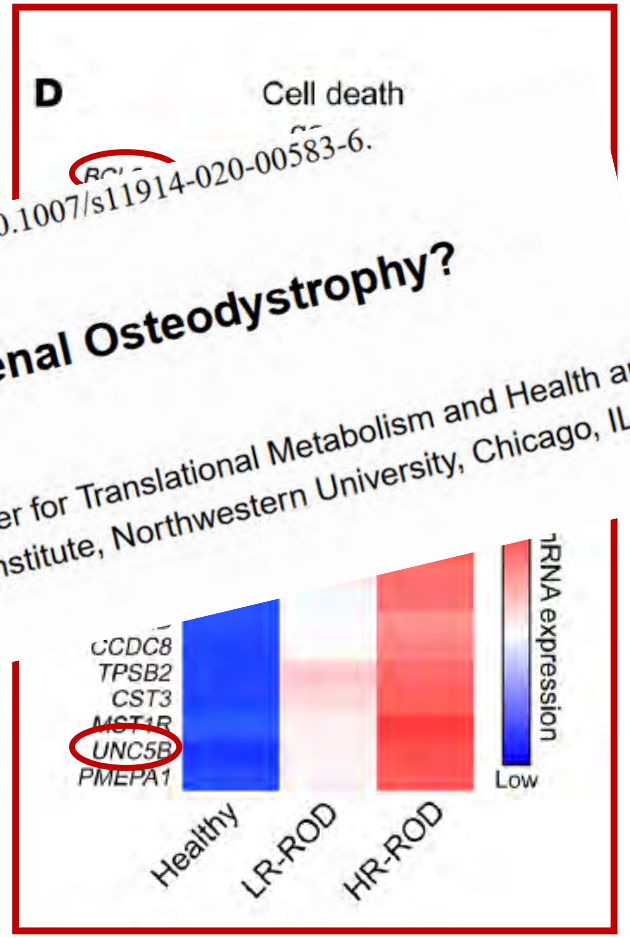
RNA seq on human bone biopsies in CKD according to Turnover







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Transcriptomics: a solution for Renal Osteodystrophy?

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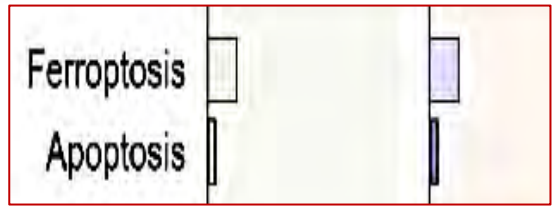

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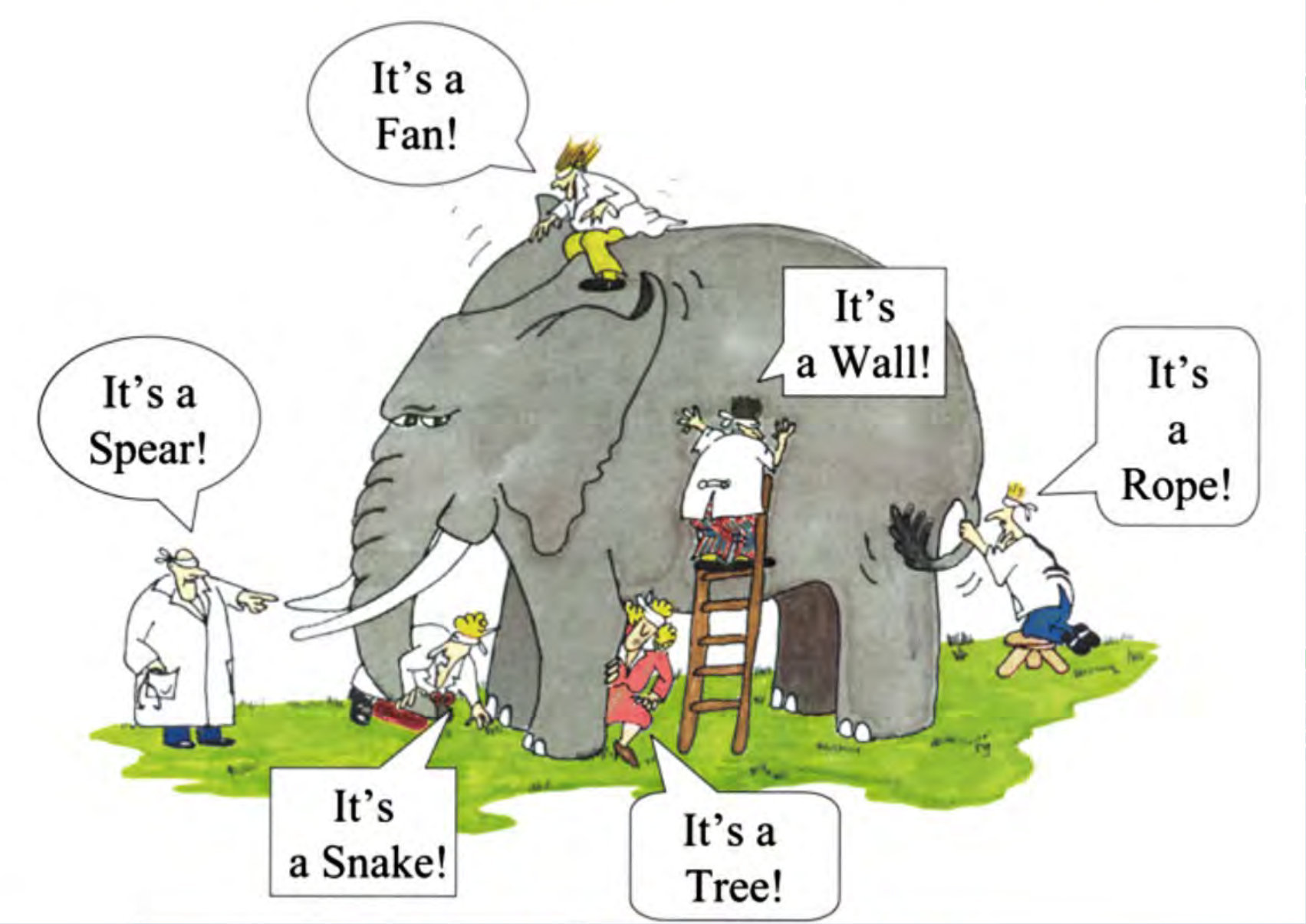
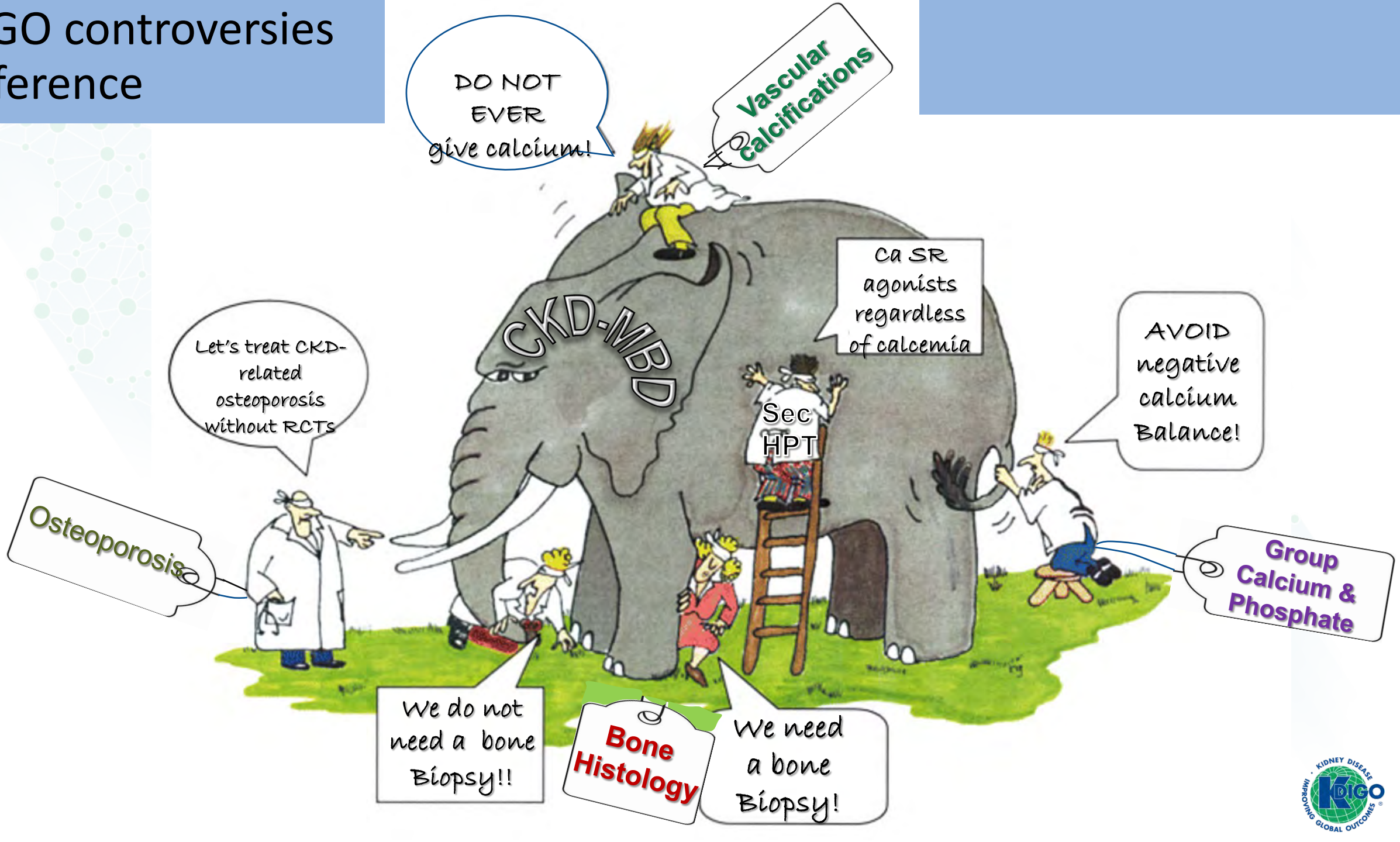
The tale of the 6 blind men and the elephant



https://emcrit.org/pulmcrit/the-tale-of-six-blind-physicians-and-the-elephant/

KDIGO controversies conference



The issue of normal reference values

Salusky et al., Kidney Int 33:975-982 (1988)

Biopsy in ten children, ages 2.5 to 17 years

	Osteitis Fibrosa	Mild lesions	ABD	OM	MUO	Normal
Osteoid area/V	<12%	<12%	<12%	>12%	>12%	<12%
BFR, µm2/mm2/day	>97	>613	<97	<97	<97	97<BFR<613
Fibrosis	+	0	0	0	+	0

Malluche HH . JBMR , 26, 6: 1368-1376, 2011, Malluche HH Calcif Tissue Int. 1982; 34: 449–455

	Low	High	Normal
Bone turnover	Activation frequency< 0.49/year ± BFR/BS< 1.80 mm^3/cm^2 /yr,	Ac.f. > 0.72/year ± BFR/BS > 3.80 mm3/cm2 /year	=0.49 <Ac.f.< 0.72/year ±1.80 <BFR/BS > 3.80 mm3/cm2 /year
Defective mineralization	Osteoid thickness> 20 µm + mineralization lag time > 50 d		

Table 1. Classification of 5 Histological Groups of ROD Dependent on Different Histomorphometric Ratios

	Normal Values	Mild Osteitis Fibrosa	Osteitis Fibrosa	Osteomalacia	Mixed Uremic Osteodystrophy	Adynamic Renal Bone Disease
Osteoid volume/bone volume (%)	4.0	<8	<8	>12	>12	
Osteoid surface/bone surface (%)	16.7	<22	>16.5	>33	>33	
Eroded surface/bone surface (%)	5.8	>11.6	>11.6	<11.6	>11.6	
Osteoblast-covered surface/bone surface (%)	3.2	<8	>8			<3.2
Osteoclast-covered surface/bone surface (%)	2.1	<2.5	>5.3			<2.1

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