

# Chronic kidney disease-induced mineral and bone disorders



Fabrice Mac-Way, MD  
CHU de Québec  
Hôtel-Dieu de Québec



# Conflicts of interest

- Research funds and Advisory Board
  - Amgen, Sanofi, Baxter, Astra Zeneca

# Objectives

- Highlight the particularities of bone disease in CKD
- Discuss how should we assess bone disease in CKD
- Review the evidence on the prevention and treatment of CKD-induced bone disease

# Typical case

71 years-old CKD stage 4 patient with diabete, hypertension...

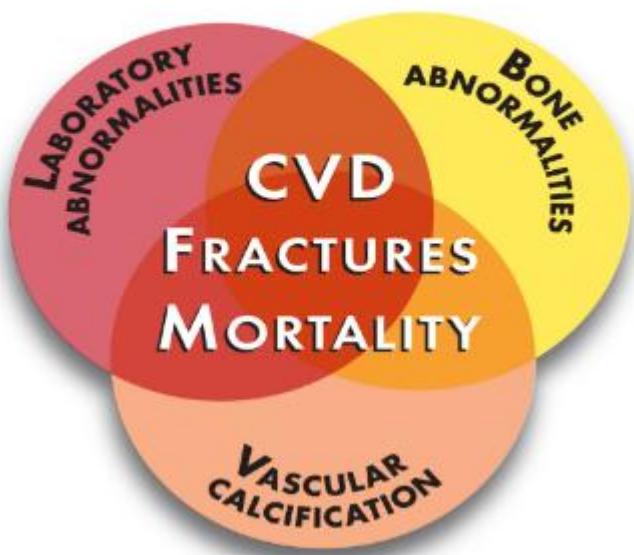
Recent hip fracture

PTH 300-400 pg/mL, calcium 2.10 mmol/L, phosphate 1.5 mmol/L,  
vitamin D 40 nmol/L, Bicarbonate 19-20 mEq/L

- A) Mineralisation defect
- B) ABD disease since she has diabetes
- C) Hyperparathyroidism bone disease
- D) Mixed osteodystrophy
- E) Post-menopausal osteoporosis
- F) I don't know

# CKD-MBD

## CHRONIC KIDNEY DISEASE— MINERAL AND BONE DISORDER

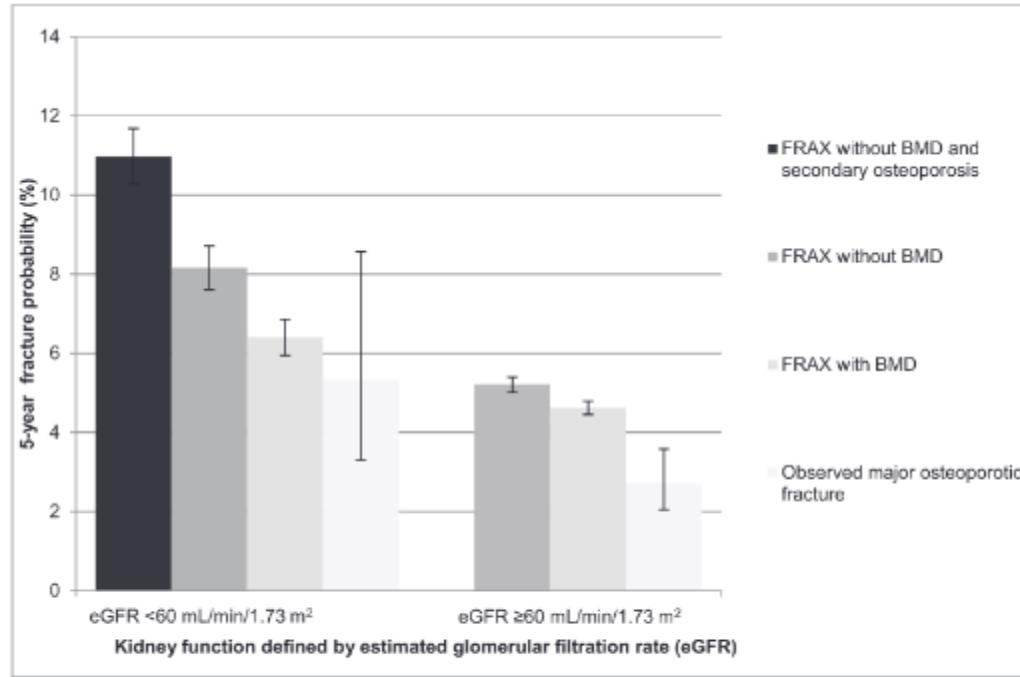


eGFR	RELATIVE RISK OF FRACTURE	
< 65 ml/min/1,73m <sup>2</sup>	VERTEBRA	1,13
	HIP	1,57
	WRIST	1,79
< 55 ml/min/1,73m <sup>2</sup>	VERTEBRA	2,32
	HIP	2,5
< 15 ml/min/1,73m <sup>2</sup>	HIP	4,0

# Fracture in CKD stage 5D

Authors	HD	General population	Relative risk
<b>Incidence per 1,000 person-years</b>			
Alem 2000, United States	13.6	7.4	4.4
Tentori 2000, Multicenter	7.6	0.51	6.2
Wakasugi 2013, Japan	17.4	1.8	4.9

# Higher fracture risk even in CKD stage 3



**Figure 2.** | Mean predicted 5-year fracture risk from the Canadian FRAZ tool (with and without BMD) and observed 5-year major osteoporotic fracture risk (Kaplan–Meier) according to eGFR. Error bars are 95% confidence intervals. BMD, bone mineral density; FRAZ, Fracture Risk Assessment Tool.

# Higher fracture risk even in CKD stage 3

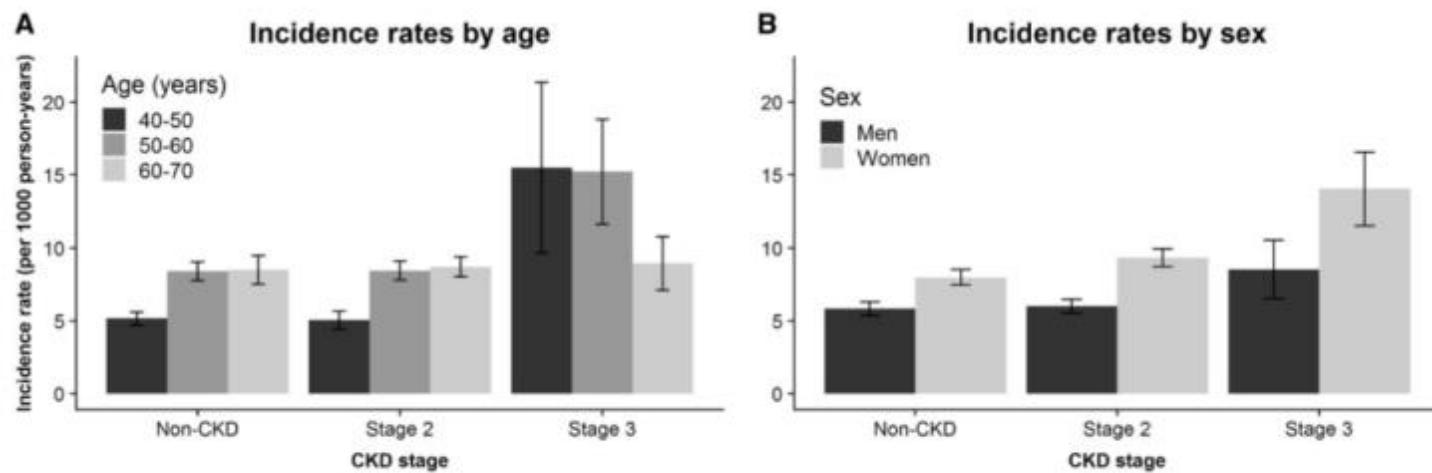
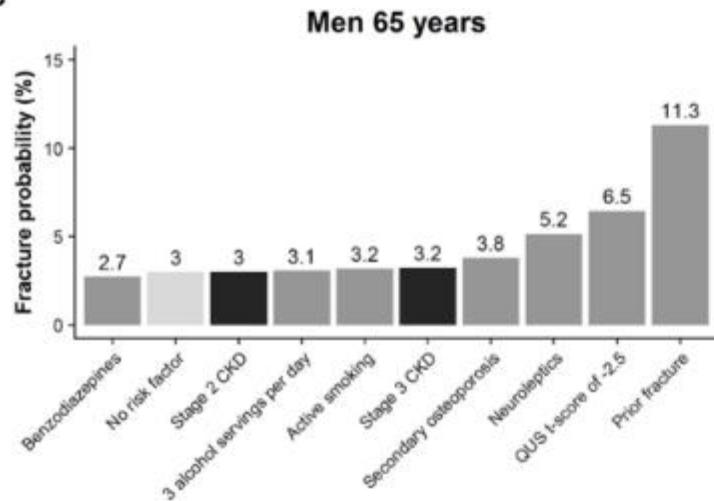


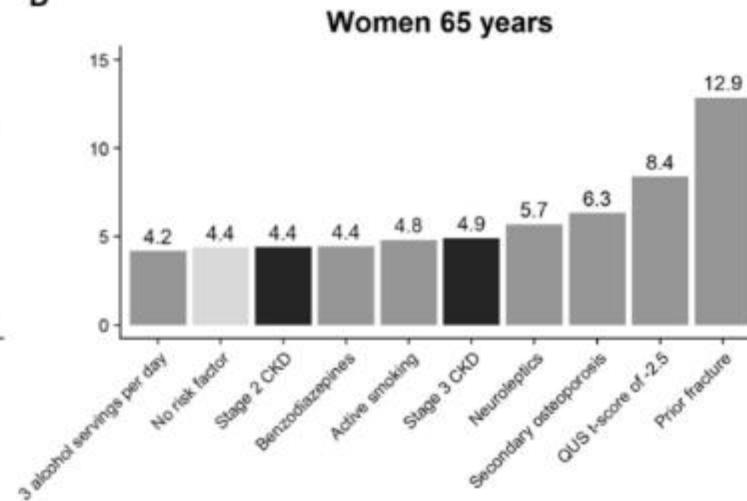
FIGURE 2: Age- and sex-stratified fracture incidence rates by CKD stage. This figure displays the fracture incidence rates (and corresponding confidence intervals) for each CKD stage after stratification for (A) age or (B) sex.

# CKD stage 3 is associated with high fracture risk

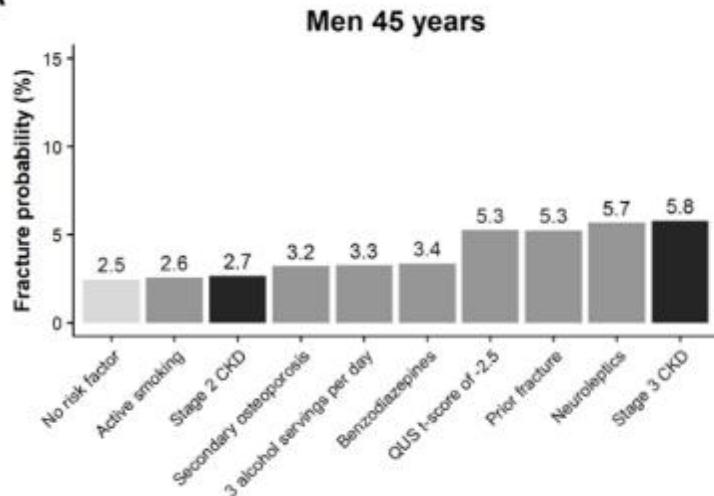
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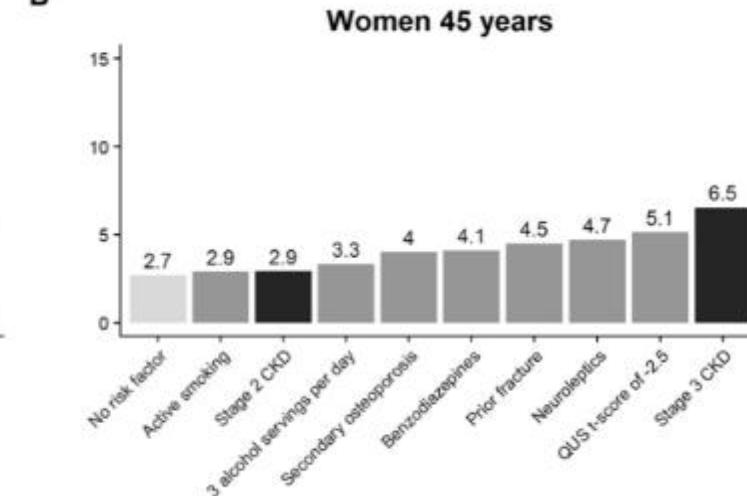
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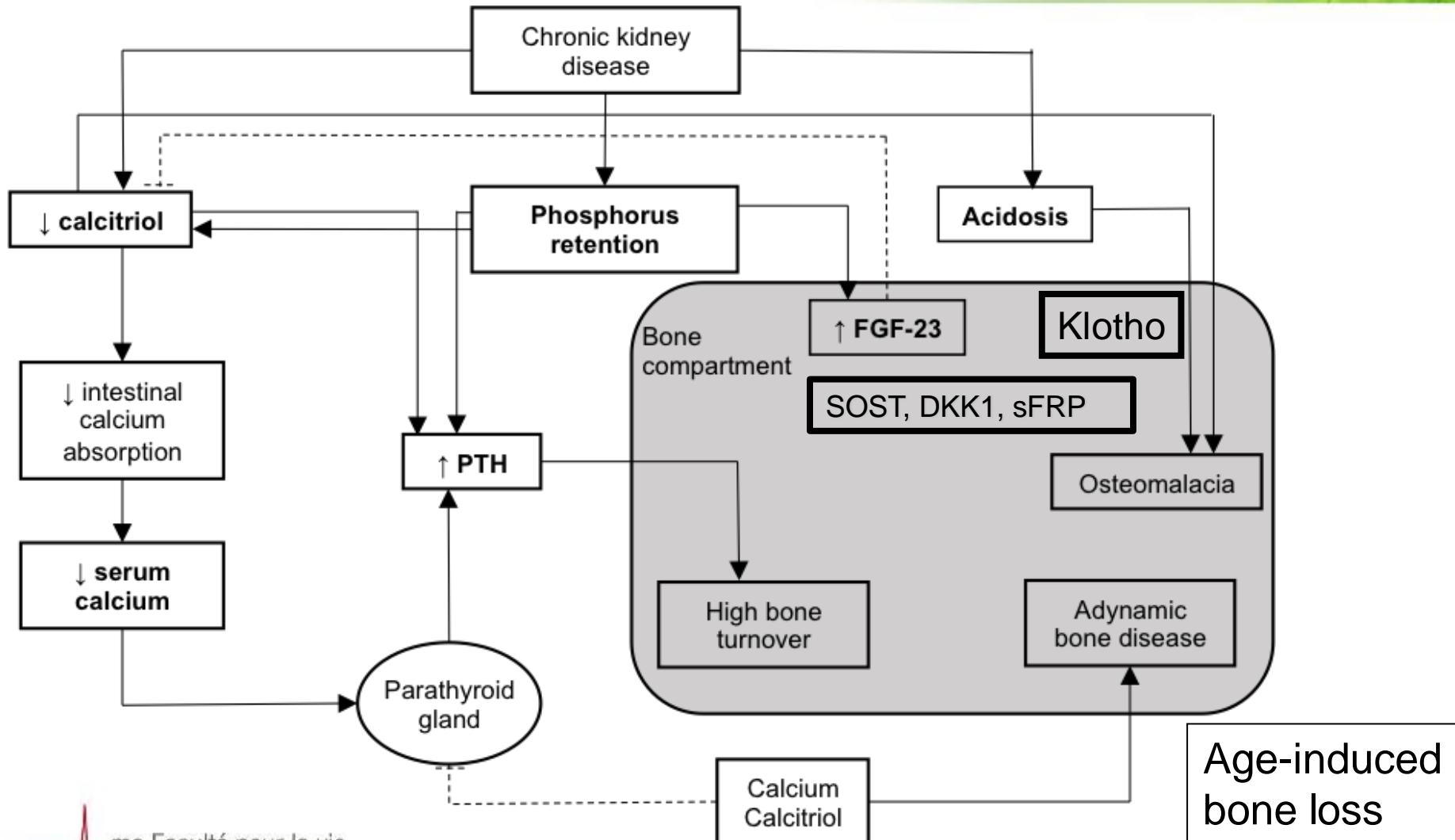
A



B



# Pathophysiology of renal osteodystrophy



# Types of bone disease in CKD

## Turnover

Low

Normal

High

## Mineralization

Normal

Abnormal (osteomalacia)

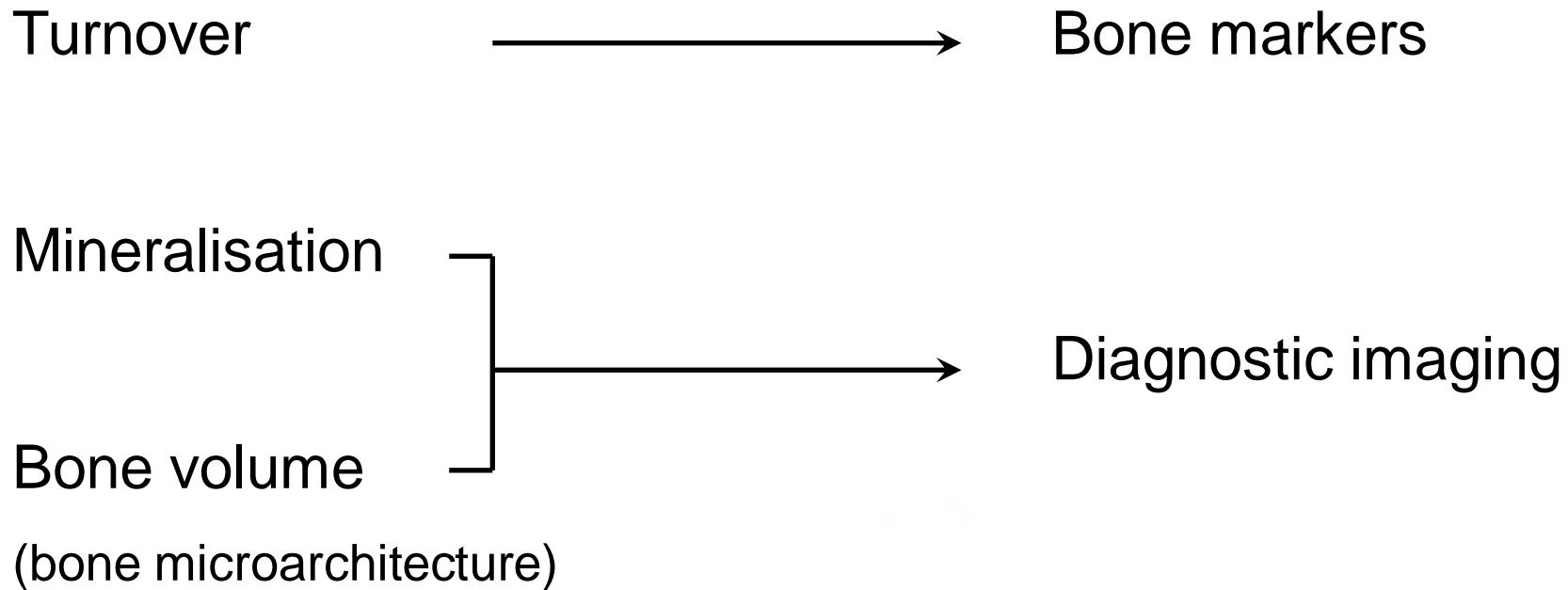
## Volume/Mass

Low

Normal

High

# How to diagnose the type of bone disease in CKD?



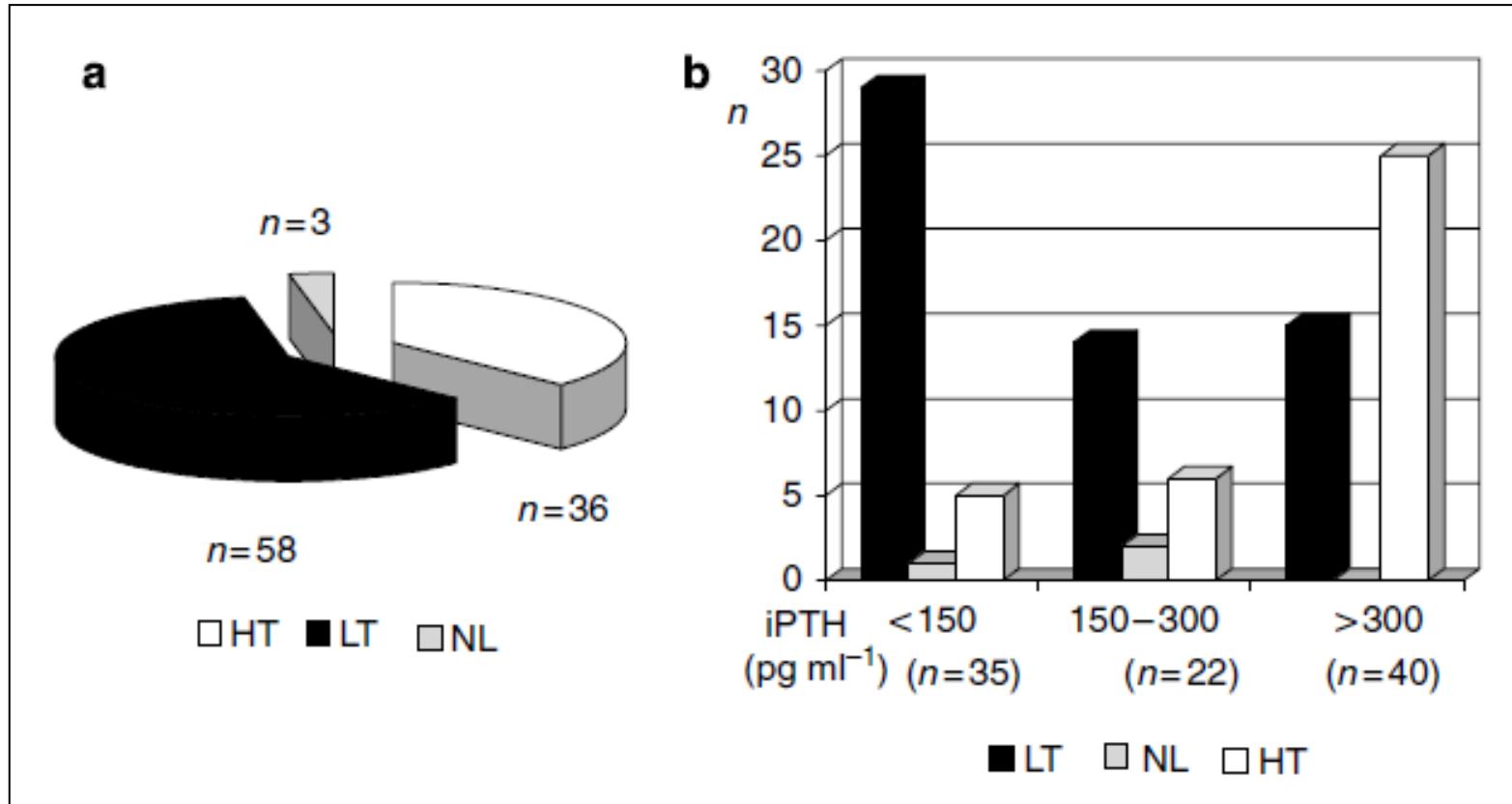
# PTH, AP and Bone Formation Rate

**Table 2.** Correlation matrix of humoral and bone histomorphometric parameters

Parameters	Intact PTH	BGP	AP	BALP
Intact PTH	1.0000			
BGP	0.6177 (0.666)	1.0000		
AP	0.8043 (0.885)	0.4334 (0.564)	1.0000	
BALP	0.7674 (0.871)	0.2611 (0.576)	0.9174 (0.953)	1.0000
TRAP	0.4009 (0.352)	0.2311 (0.370)	0.5702 (0.447)	0.4671 (0.419)
ICTP	0.7891 (0.742)	0.3285 (0.592)	0.8485 (0.785)	0.9388 (0.804)
DPD	0.7565 (0.730)	0.5708 (0.548)	0.6394 (0.830)	0.5641 (0.773)
BV/TV	0.3830 (0.299)	0.4402 (0.384)	0.3935 (0.331)	0.4124 (0.393)
OV/BV	0.8218 (0.787)	0.5215 (0.691)	0.7448 (0.820)	0.8019 (0.832)
O.Th	0.7625 (0.723)	0.3757 (0.557)	0.7624 (0.793)	0.8328 (0.850)
OS/BS	0.7473 (0.767)	0.6941 (0.733)	0.6484 (0.788)	0.5497 (0.810)
ObS/BS	0.8825 (0.886)	0.6341 (0.686)	0.7648 (0.921)	0.6746 (0.930)
ES/BS	0.6401 (0.683)	0.4720 (0.515)	0.4945 (0.739)	0.4419 (0.770)
OcS/BS	0.6554 (0.724)	0.3417 (0.502)	0.5815 (0.796)	0.5651 (0.818)
sLS/BS	0.6811 (0.818)	0.5583 (0.655)	0.5147 (0.803)	0.5045 (0.854)
dLS/BS	0.7537 (0.756)	0.6576 (0.648)	0.7579 (0.849)	0.7698 (0.849)
MS/OS	0.3459 (0.588)	0.2156 (0.373)	0.2847 (0.633)	0.2914 (0.654)
MAR	0.8192 (0.819)	0.6056 (0.656)	0.7789 (0.841)	0.7678 (0.845)
BFR/BS	0.7984 (0.848)	0.6238 (0.710)	0.9009 (0.887)	0.8917 (0.896)
Aj.AR	0.6786 (0.732)	0.4804 (0.499)	0.6949 (0.761)	0.6890 (0.772)
Mlt	-0.1877 (-0.615)	-0.1652 (-0.412)	-0.1264 (-0.614)	-0.1142 (-0.613)

Spearman correlation coefficients in parentheses.

# PTH and bone turnover



# Measurement of BMD in CKD?

## **2009 KDIGO CKD-MBD Recommendations**

3.2.2. In patients with CKD stages 3–5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

# Does BMD predicts fracture?

## Bone Mineral Density and Fracture Risk in Older Individuals with CKD

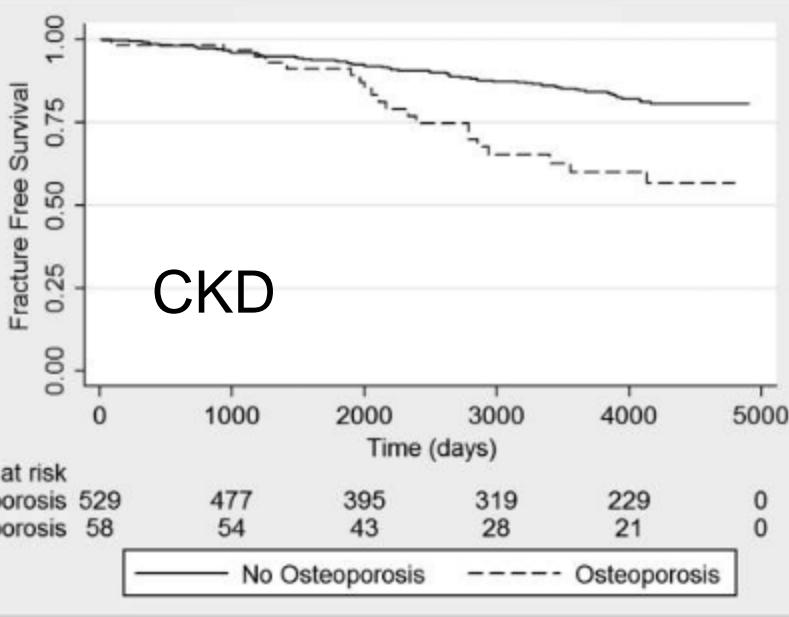
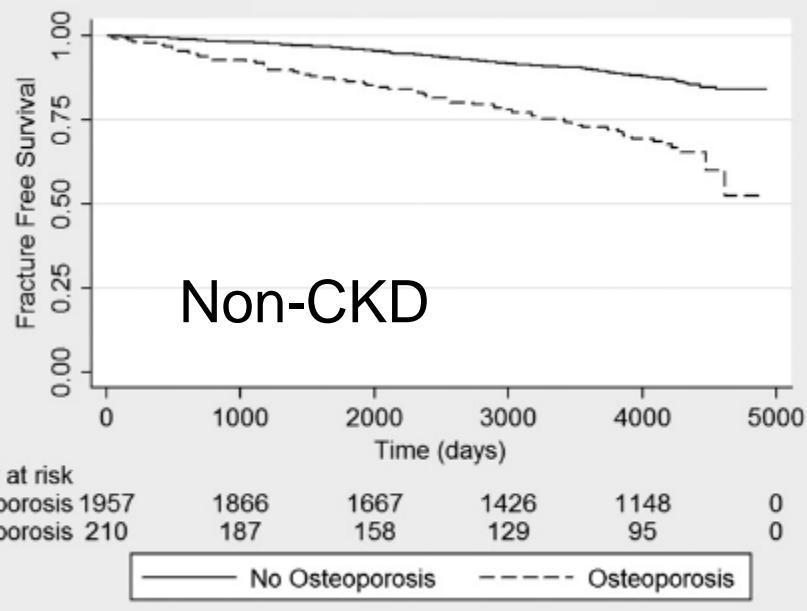
Robert H. Yenck, Joachim H. Ix, [...], and for the Health,  
Aging, and Body Composition Study

Prospective study, n=2754

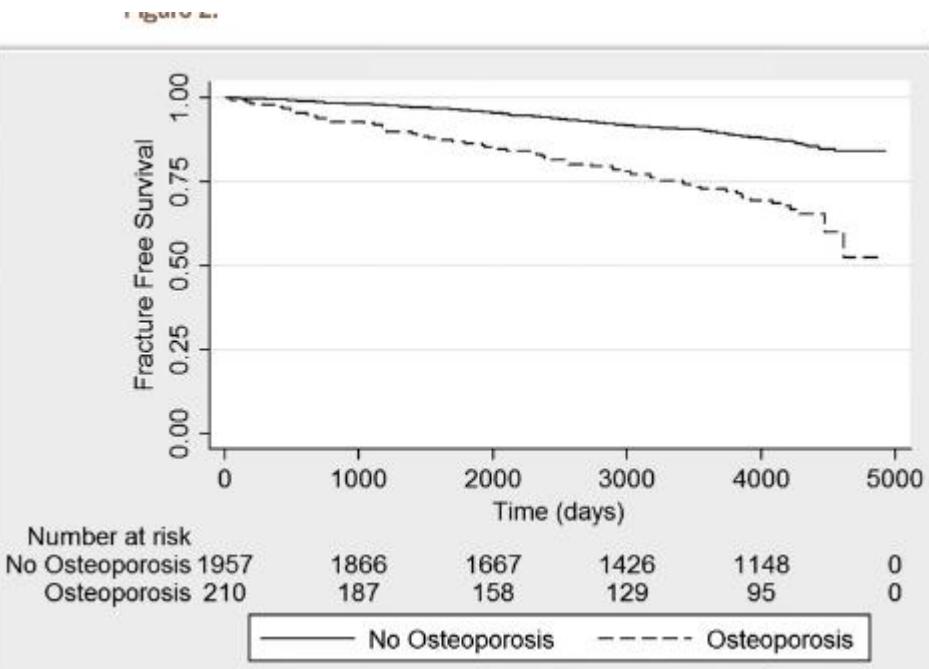
Mean age of 73 years

CKD 3-5

Does BMD predict fracture?



## CKD with or without OP



# KDIGO 2017

## 2009 KDIGO CKD-MBD Recommendations

3.2.2. In patients with CKD stages 3–5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

DXA BMD measurement does not indicate the type of bone disease in CKD

## 2016 REVISED KDIGO CKD-MBD Recommendations

3.2.1. In patients with CKD Stages 3a-5D 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. (2B)

### Brief rationale for updating

Multiple new prospective studies have documented that lower DXA BMD predicts incident fractures in patients with CKD Stages 3a-5D. The order of these first two recommendations was changed since a DXA BMD result might impact the decision to do a bone biopsy.

# What to do?

71 years-old CKD stage 4 patient with diabete, hypertension...

Recent hip fracture

PTH 300-400 pg/mL, calcium 2.10 mmol/L, phosphate 1.5 mmol/L,  
vitamin D 40 nmol/L, Bicarbonate 19-20 mEq/L

- A) Mineralisation defect (since calcium, vitamin D and bicarbonate are low)
- B) ABD disease since she has diabetes
- C) Hyperparathyroidism bone disease (even if PTH is not that high)
- D) Mixed osteodystrophy
- E) Post-menopausal osteoporosis
- F) I don't know

# Barriers to bone biopsy

- 1) Invasive procedure
- 2) I don't know how to do it
- 3) Lack of bone histomorphometry specialist

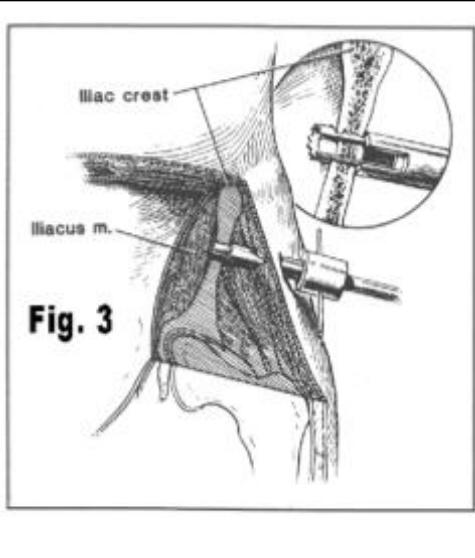
# Complications rate of bone biopsy

	Survey of 18 centers*	%
# of cases	9 030	100
Haematoma	21	0,23
Pain >7days	17	0,19
Neuropathy	11	0,12
Skin infection	6	0,07
Fracture	1	0,01
Osteomyelitis	1	0,01
Total	57	0,63

▪ Duncan et al, MBDRR 1980

▪ Simard-Meilleur et al, Nephron Extra 2017

# Bone biopsy (blind technique)



Performed by the  
clinicians



# Iliac crest bone biopsy by radiologist

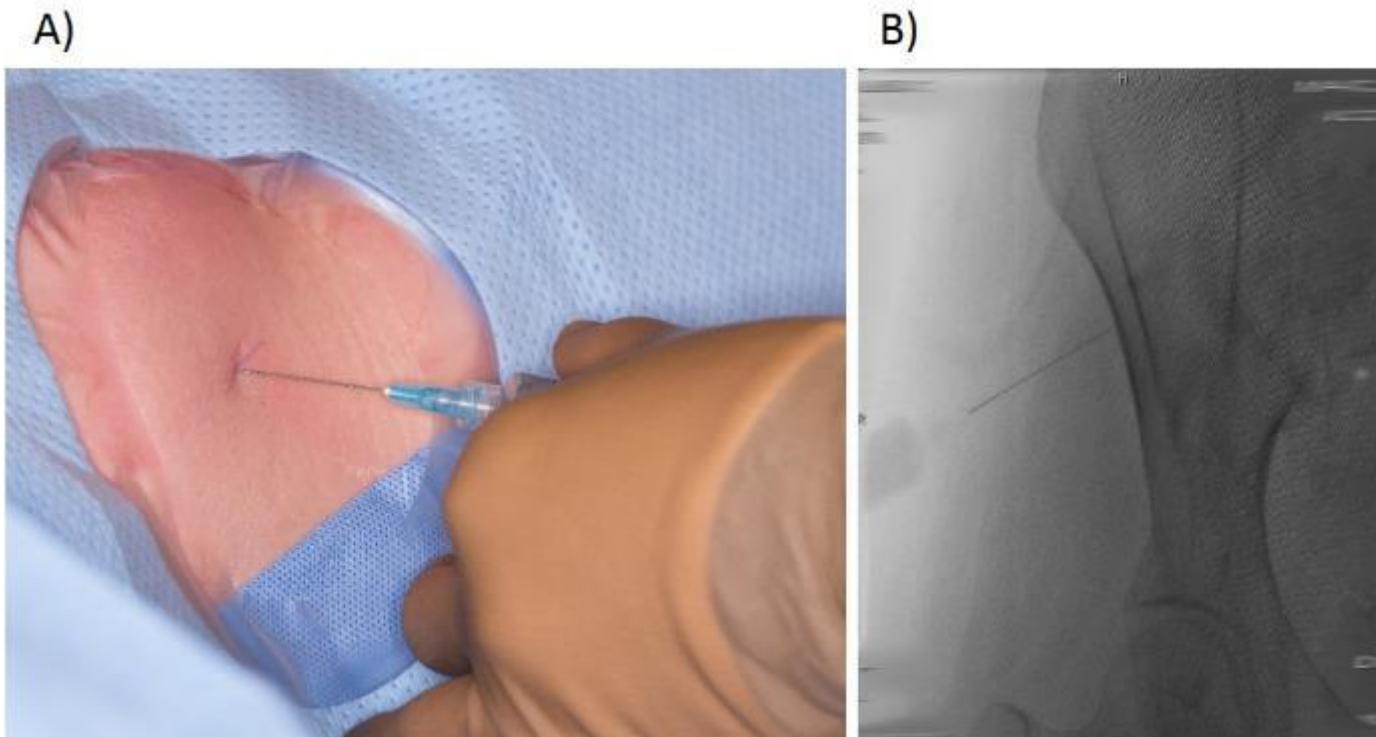
Allowing direct visualisation of the outer and inner cortical bone

- Perfect specimen
- Even less complications

The technique can be performed in every centers where there is a interventional radiologist

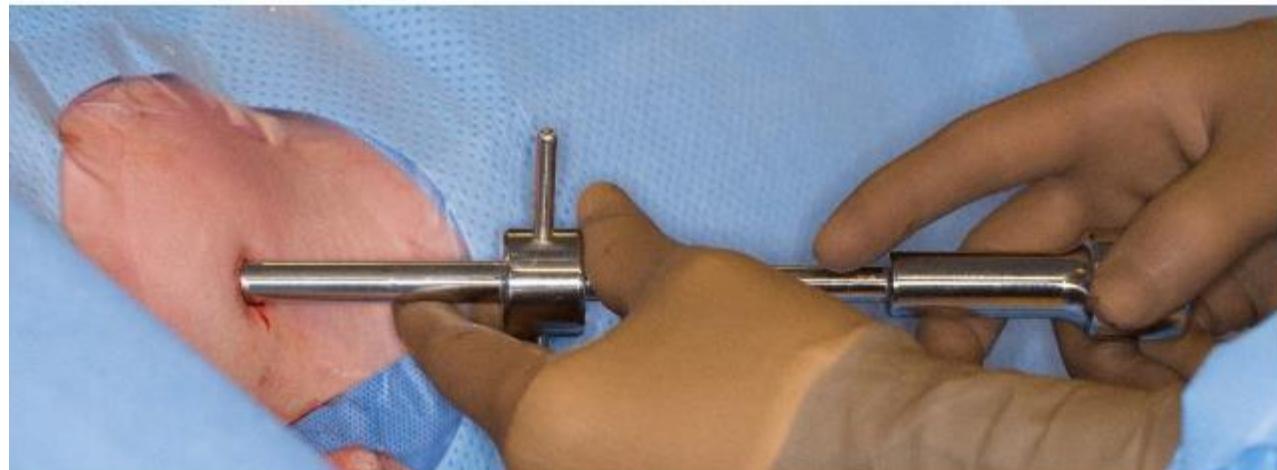
Allows access to bone biopsy

# Iliac crest bone biopsy by radiologist



# Iliac crest bone biopsy by radiologist

A)



B)



ma Faculté pour la vie

Lavigne et al, J Nephrol 2020

# Bone biopsy in radiology

## Clinical utility

- Diagnosis of type of bone disease in CKD
- Guide treatment

## Research

- Evaluate the effects of current treatments on bone turnover and mineralisation
- Translational and mechanistic studies

# Half bone biopsy with smaller kit?

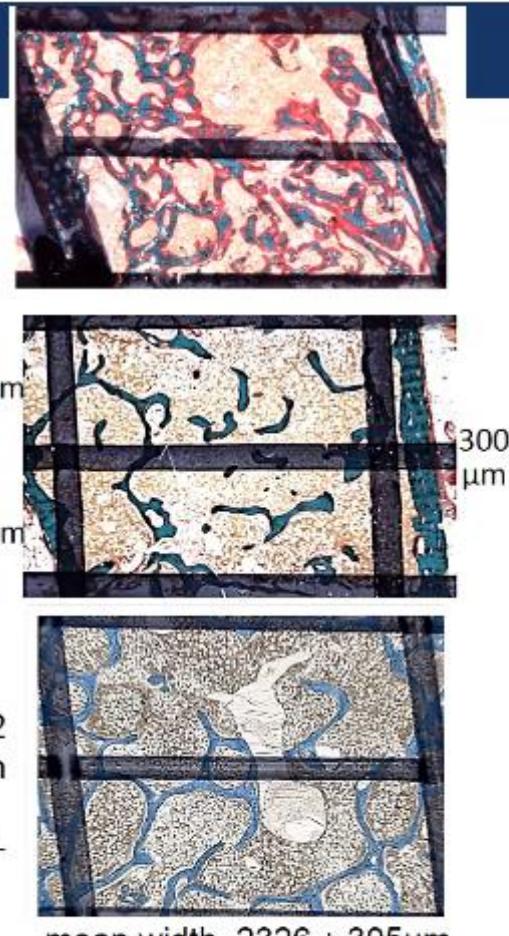
## METHODS-1

68 iliac bone biopsies performed with a Bordier/Meunier trephine (7.5mm internal Ø) in CKD patients were included\*:

\*St Etienne, Lyon- R Chapurlat, P D'Haese

Diagnosis	# of samples (%)
Osteitis Fibrosa	31 (45%)
Adynamic Bone Disease	8 (12%)
Osteomalacia	7 (10%)
Mixed Uremic Disease	14 (21%)
Other	8 (12%)

- Histological sections were divided lengthwise to define 2 hemi-biopsies to simulate samples that would have been obtained with a smaller needle such as a Jamshidi needle.
- Histological sections were then oriented to define two hemi-biopsies arbitrarily called hemi-biopsy 1 and 2.



# EUROD Working group

*Full Review*

## Position paper

### Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative—a position paper

Pieter Evenepoel<sup>1</sup>, Patrick D'Haese<sup>2</sup>, Justine Bacchetta<sup>3</sup>, Jorge Cannata-Andia<sup>4</sup>, Anibal Ferreira<sup>5</sup>,  
Mathias Haarhaus<sup>6</sup>, Sandro Mazzaferro<sup>7</sup>, Marie-Helene Lafage Proust<sup>8</sup>, Syazrah Salam<sup>9</sup>, Goce Spasovski<sup>10</sup>,  
Mario Cozzolino<sup>11</sup> on behalf of the ERA-EDTA Working Group on CKD-MBD\*

1. To revitalize bone biopsy as a clinically useful tool in daily practice. Bone biopsies should regain a prominent place in daily practice to help tailor CKD-MBD therapy for individual patients, a relevant goal in an era favouring person-

3.2.1. In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (*not graded*).

## 2009 KDIGO

## 2016 KDIGO

3.2.2. In patients with CKD Stages 3a-5, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions.  
*(Not Graded)*

### 2016 REVISED KDIGO CKD-MBD Recommendations

3.2.1. In patients with CKD Stages 3a-5D 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. (2B)

The primary motivation for this revision was the growing experience with osteoporosis medications in patients with CKD, low BMD and a high risk of fracture. The lack of ability to perform a bone biopsy may not justify withholding antiresorptive therapy to patients at high risk of fracture.

## Rationale

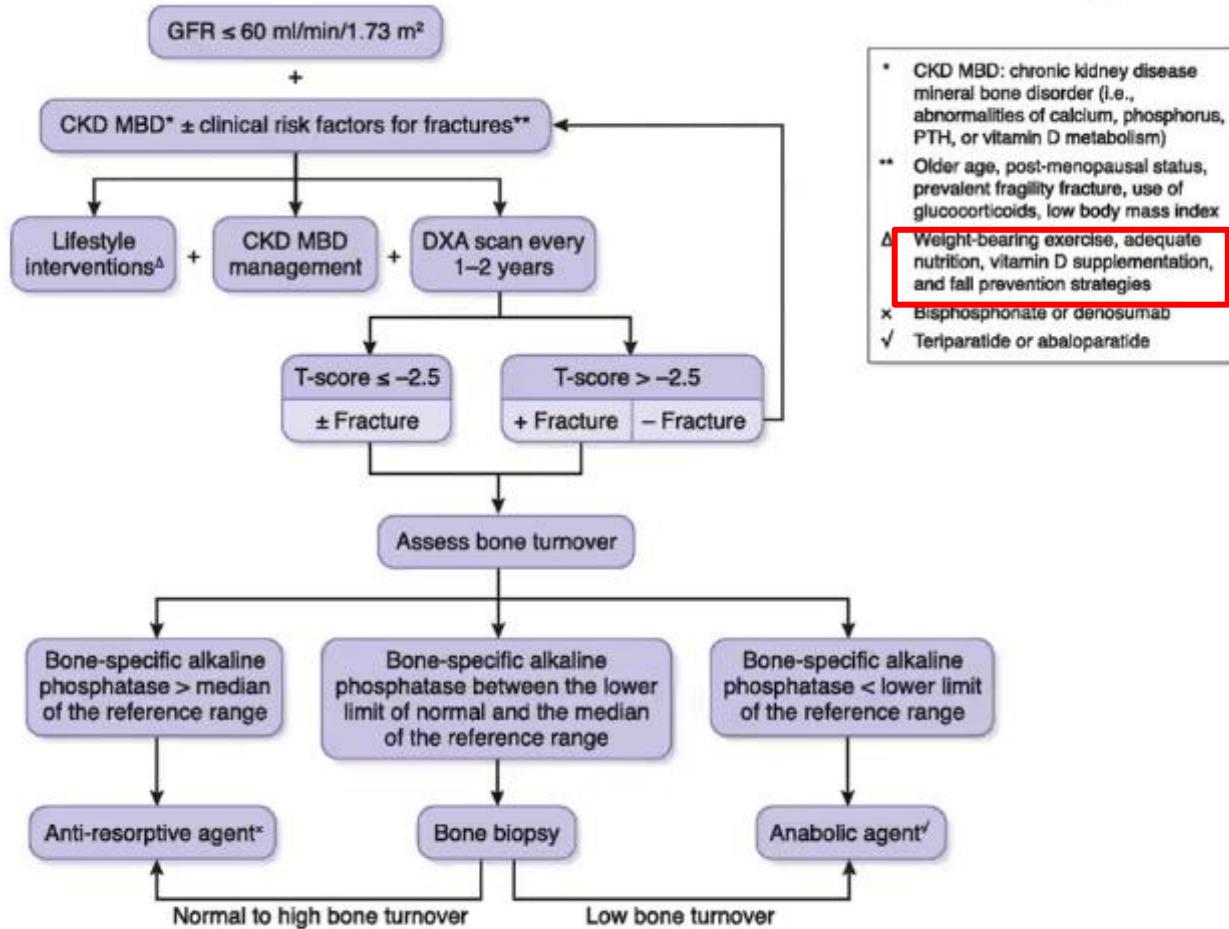
# Anti-osteoporotic treatment in CKD?

Table 2. Efficacy and safety of common osteoporosis drugs in the setting of CKD

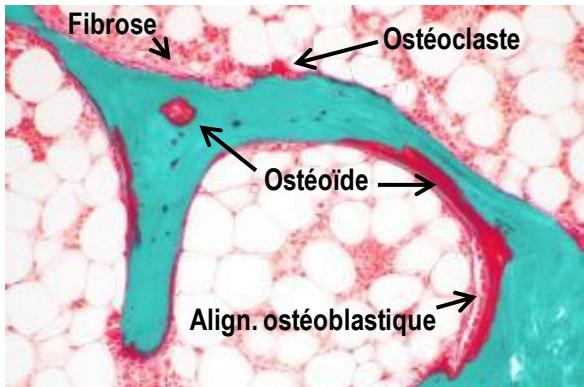
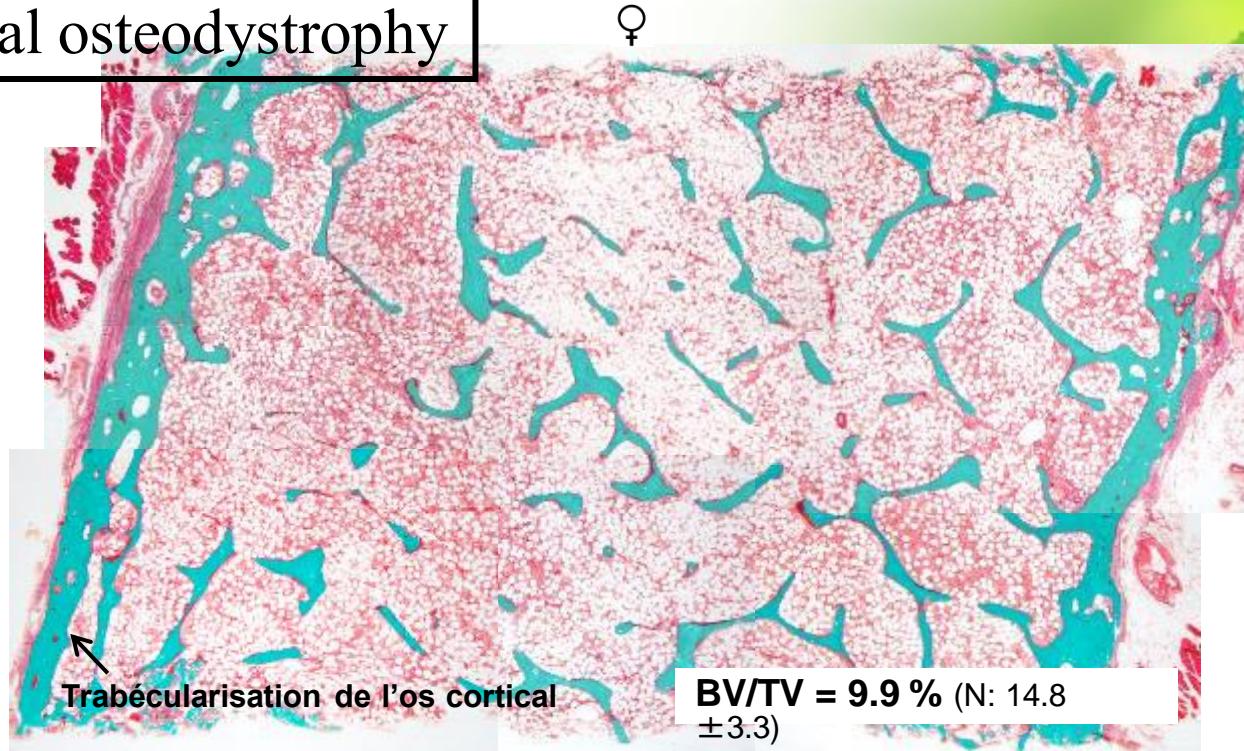
Drugs	Renal retention	Efficacy Preclinical	Post hoc (postmenopausal women)	Clinical trial (ad- vanced CKD)	Safety (postmeno- pausal women)	Comments
Nitrogen-containing bisphosphonates (alendronate, ibandro- nate, risedronate and zoledronic acid)	Yes [115, 116]	Yes [117, 118] ↳	Fracture ↓ [119–121]	BMD (↑) [122–126]	Atypical fracture, ONJ, oesophagitis, (hypocalcemia, re- nal dysfunction) [127, 128–130]	Dose adjustments?
Denosumab	No [131]	Yes [132]	Fracture ↓ [133]	BMD ↑ [125, 134, 135, 136, 137]	Atypical fracture, ONJ, hypocalcae- mia [129, 134]	Beware: offset of effect [138]
PTH analogues (teripara- tide, abaloparatide)	No	Yes [118]	Fracture ↓ [139, 140]	BMD ↑, in patients with ABD or hyoparathyroidism	Hypotension [141]	Dose adjust- ments? Therapy to be limited to a maximum of 2 years
Romosozumab	Unlikely	Yes, low PTH only [142]	No data	No data	Cardiovascular ad- verse events ↑ [143] (hypocalcaemia)	Beware: offset of effect

# Fracture in CKD: my approach

- Assess fracture risk (BMD and FRAX)
- Anti-resorptive therapy if no ABD and no mineralisation defect
- Be extremely careful with denosumab in advanced CKD because of hypocalcemia
- Teriparatide if ABD (revealed by bone biopsy)

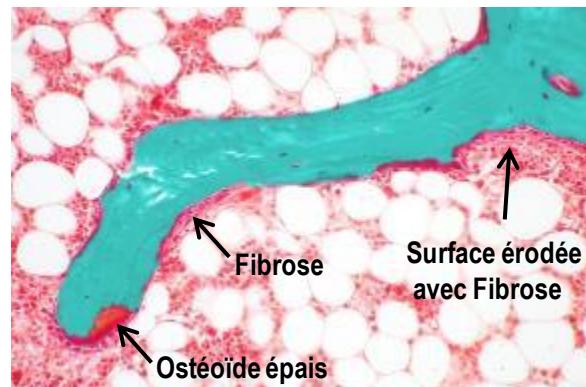


# Mixed renal osteodystrophy



$OV/BV = 8.5 \% \text{ (N: } 2.2 \pm 1.4\text{)}$

$O.Th = 6.6 \mu m$

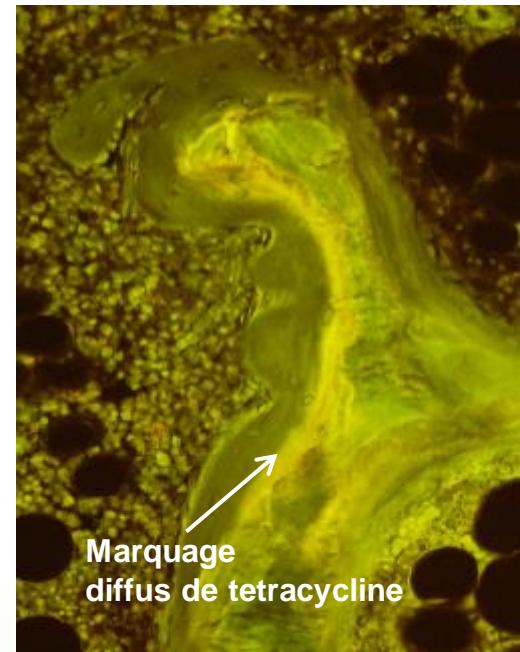
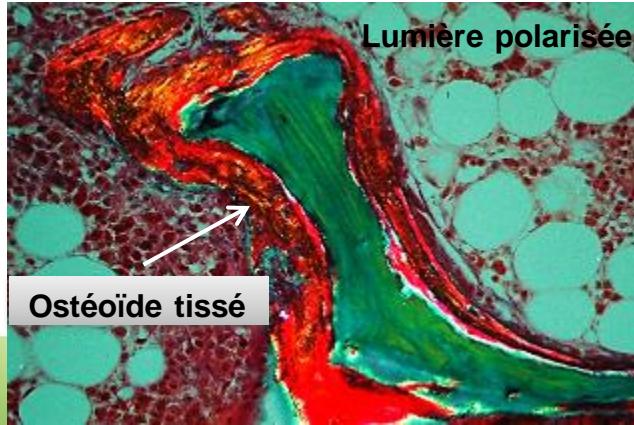


$OS/BS = 36.8 \% \text{ (N: } 12.1 \pm 7.5\text{)}$

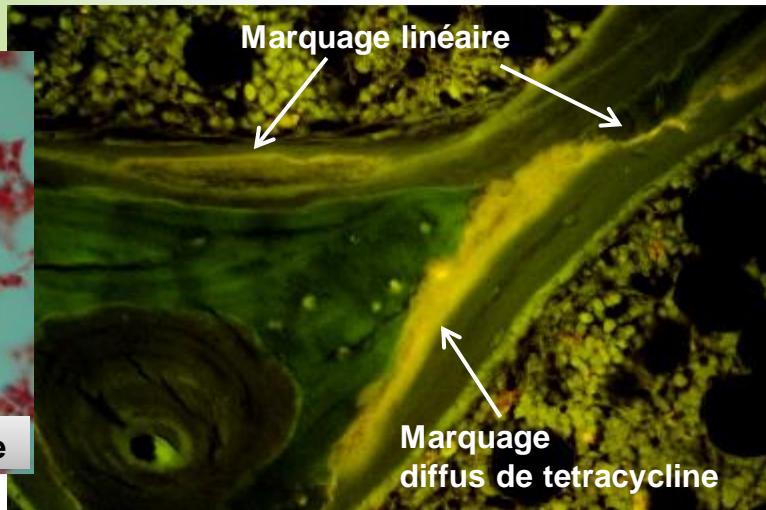
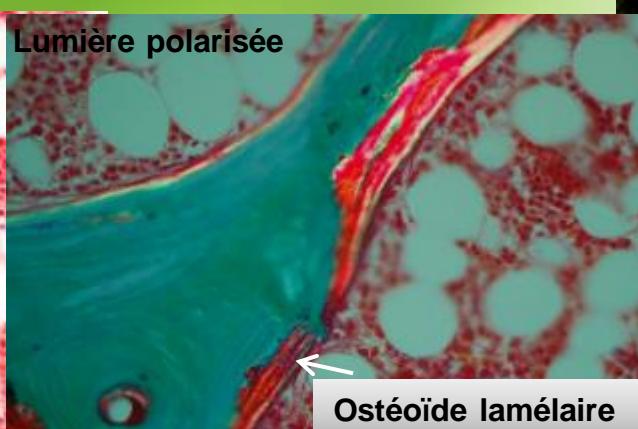
$\bar{E}S/BS = 8.2 \% \text{ (N: } 3.6 \pm 1.1\text{)}$

# Mixed renal osteodystrophy

♀



Foyers d'ostéoïde épais et parfois tissé, trouble de minéralisation focal

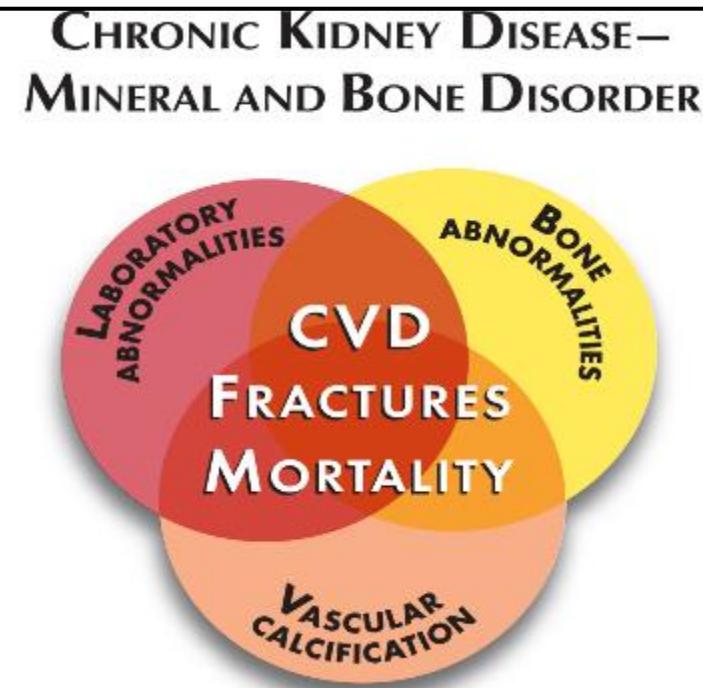


LAVAL

Dr Louis-Georges Ste-Marie MD



# CONCLUSION



- Fracture is a major health issue in CKD population
- Facilitate access to bone biopsy (radiology?)
- The causes and treatment of CKD-induced bone disease is unique and should be discussed with the nephrologist
- Translational research is needed to better understand the mechanisms of CKD-MBD in order to propose appropriate treatment



# Thank you!