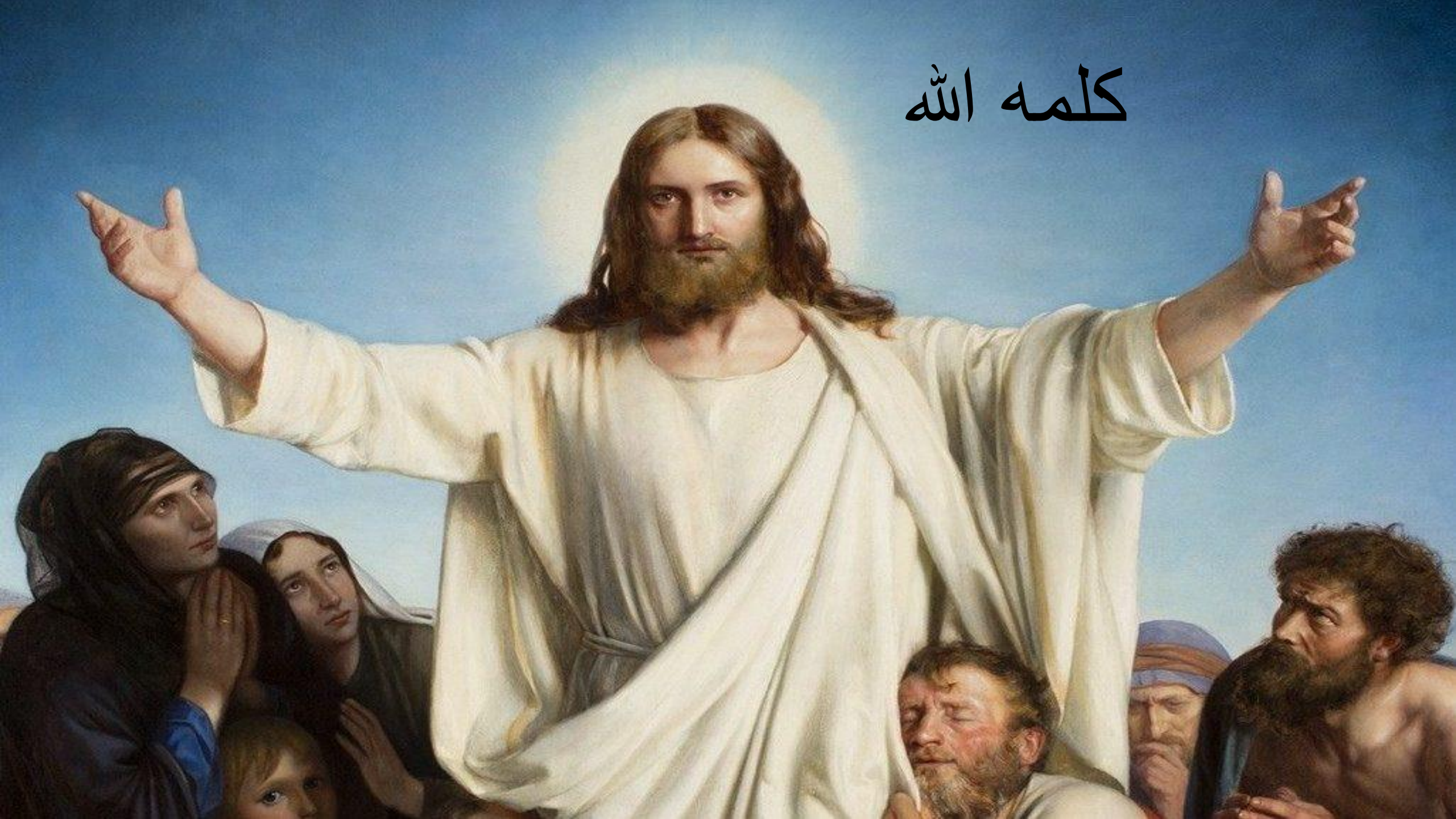
Importance of Inter-disciplinary Conferences

- Holistic Approach to pt care
- More Accurate & Safer Clinical Decision-Making
- Deep & Practical Learning
- Reduce Medical Errors & Complications
- Improve Diagnostic & Therapeutic Quality
- Essential for Complex & High-Risk Pts
- Strenghten Teamwork & Care Coordination


کلمه الله

I Have No Conflict of Interest

Travel Grant (Orchid Pharmed)

Osteoporosis & Kidney Disease

Amir A. Nassiri, MD,DIU

SBUMS

Yazd, 2025 Dec 25th

Why Do We Worry About Bone in CKD ?

Amir A. Nassiri, MD,DIU

SBUMS

Yazd, 2025 Dec 25th

Epidemiology of chronic kidney disease: an update 2022

kidney INTERNATIONAL supplements

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Extremely common

843,6 Million in 2017

Approximately 1 in 10

Increasing death rate

+41.5% 1990 to 2017

Rank in cause of death

Large burden in low- and middle-income countries

Among the **top 10 causes** of death in Singapore, Greece, and Israel

Kovesdy, 2022

CONCLUSION

Chronic kidney disease (CKD) occurs frequently and has devastating consequences. This should prompt major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016

Incidence
↑ 89%
to 21 million

Prevalence
↑ 87%
to 276 million

Death due to CKD
↑ 98%
to 1.2 million

Disability Adjusted Life Years (DALYs)
↑ 63%
to 35 million

Drivers of ☒ DALYs

Population Growth

Aging

Diabetes

Age-standardized DALYs rate

63%
of burden in low and low-middle income countries

Conclusion: The global toll of CKD is significant, rising, and unevenly distributed; it is primarily driven by demographic expansion and in some regions significant tide of diabetes epidemic.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Xie et al. Kidney International, 2018

AN ENORMOUS BURDEN WORLDWIDE

1/3

1/5

GLOBALLY OVER 50 WILL SUFFER AN OSTEOPOROTIC FRACTURE

+8.9 MILLION FRACTURES ANNUALLY

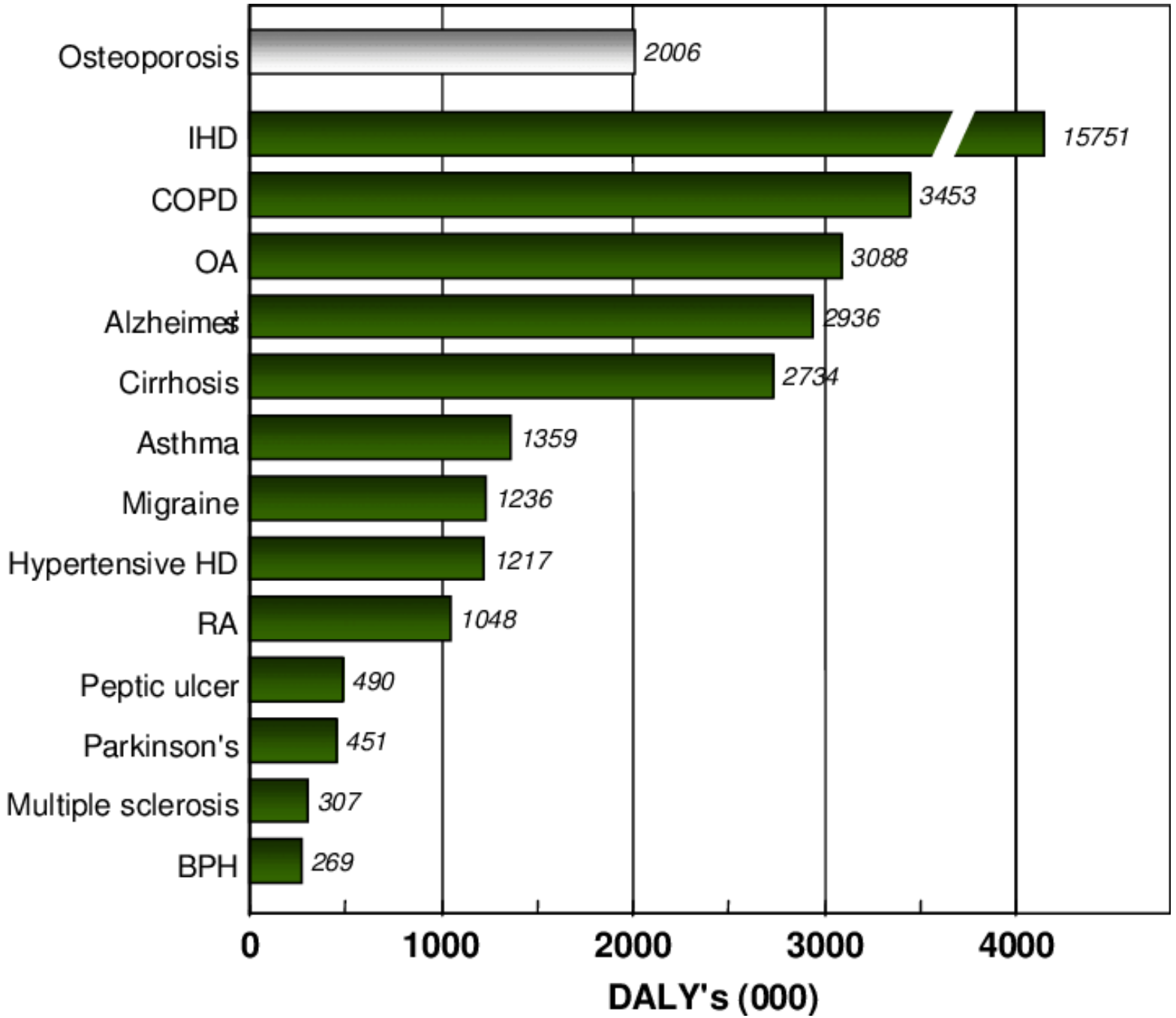
1 fracture **every 3 sec**

HIP FRACTURE INCREASE

1990 → 2050

+310%

+240%


Osteoporosis
2006
IHD
15751
COPD
3453
OA
3088
Alzheimers
2936
Cirrhosis
2734
Asthma
1359
Migraine
1236
Hypertensive HD
1217
RA
1048
Peptic ulcer
490
Parkinson's
451
Multiple sclerosis
307
BPH
269
0
1000
2000
3000
4000
DALY's (000)

Hip fracture

LOSS OF FUNCTION AND INDEPENDENCE AMONG SURVIVORS

40% UNABLE TO WALK INDEPENDENTLY

60% REQUIRE ASSISTANCE A YEAR LATER

33% DEPENDENT OR IN A NURSING HOME IN THE YEAR FOLLOWING A HIP FRACTURE

Mortality UP TO 20-24% IN THE FIRST YEAR AFTER A HIP FRACTURE

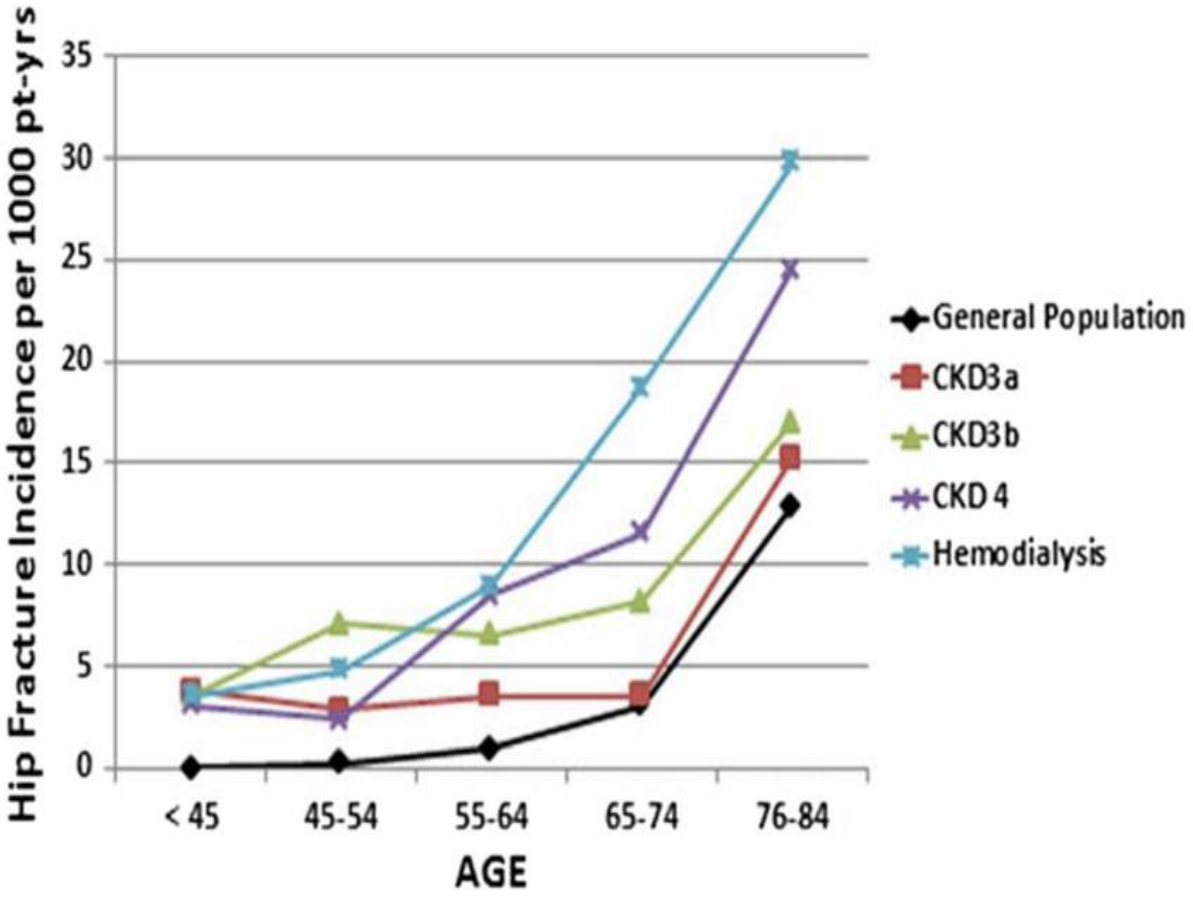
In ESRD pts there is 50% rate of mortality after the 1st year.

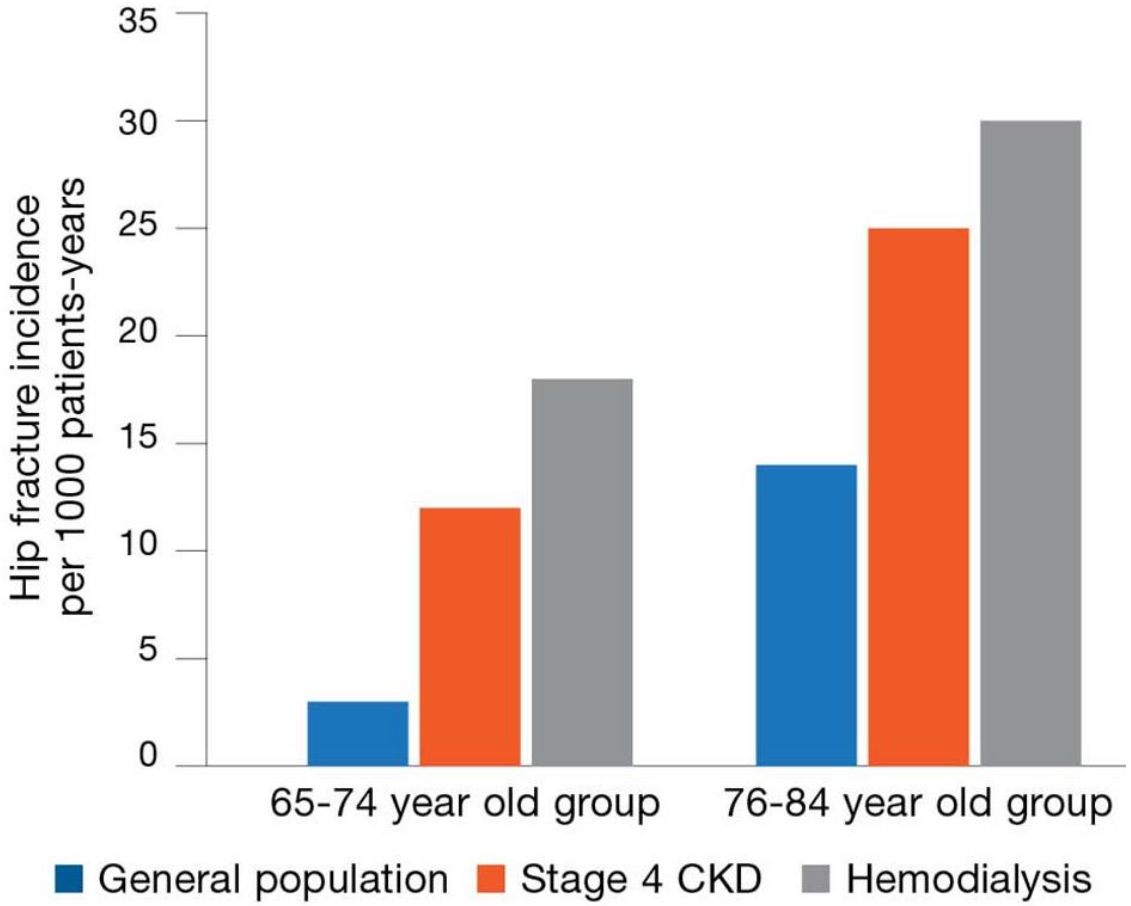
50% OF PEOPLE WITH ONE OSTEOPOROTIC FRACTURE WILL HAVE ANOTHER

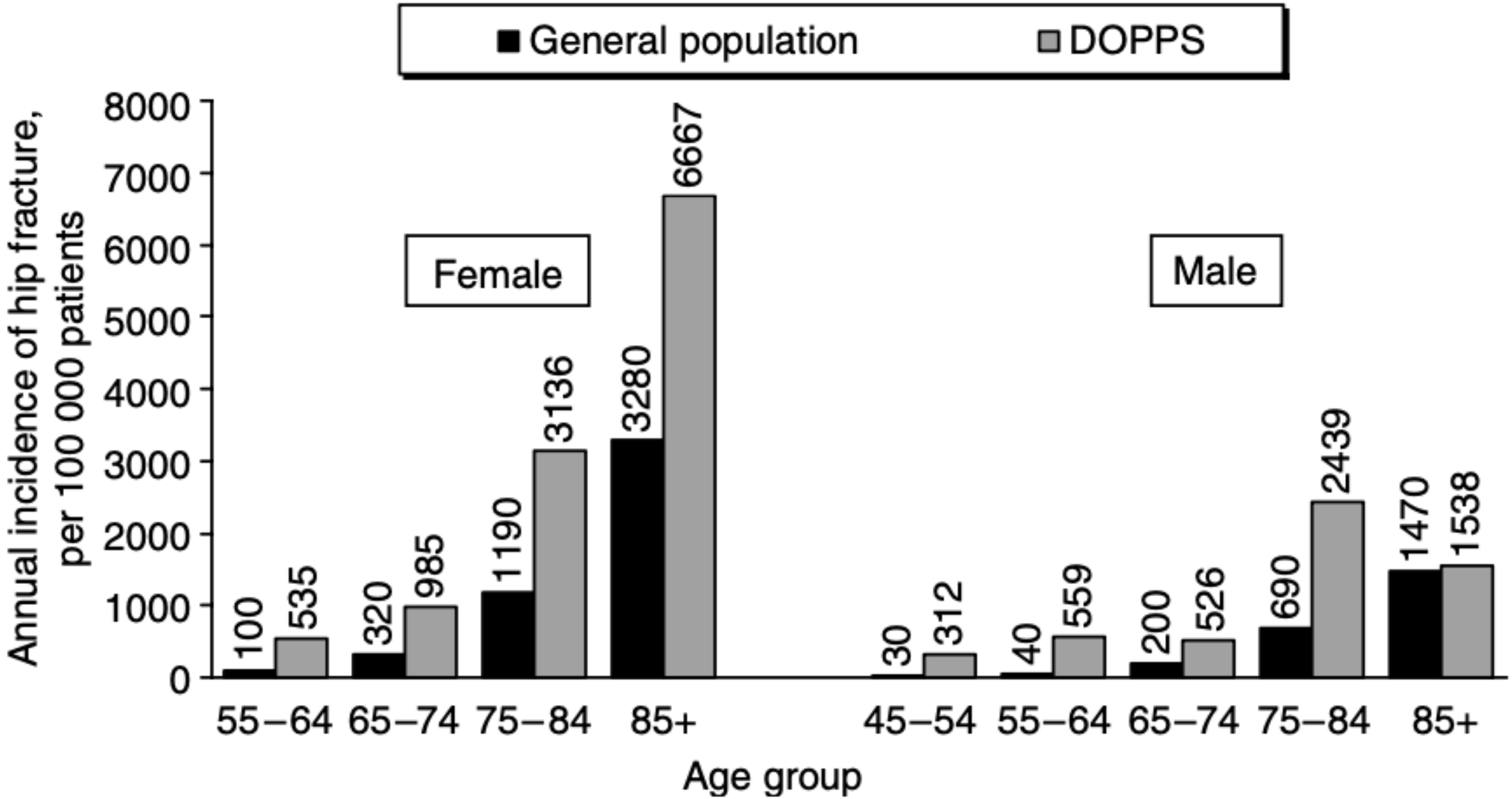
Why OP is Important in CKD ?

- Pt w/eGFR<60 have at lease x2 higher risk of OP
- ESRD have x4-6 folds of Fx risk vs to matched population

Hip Fx risk & incidence in CKD



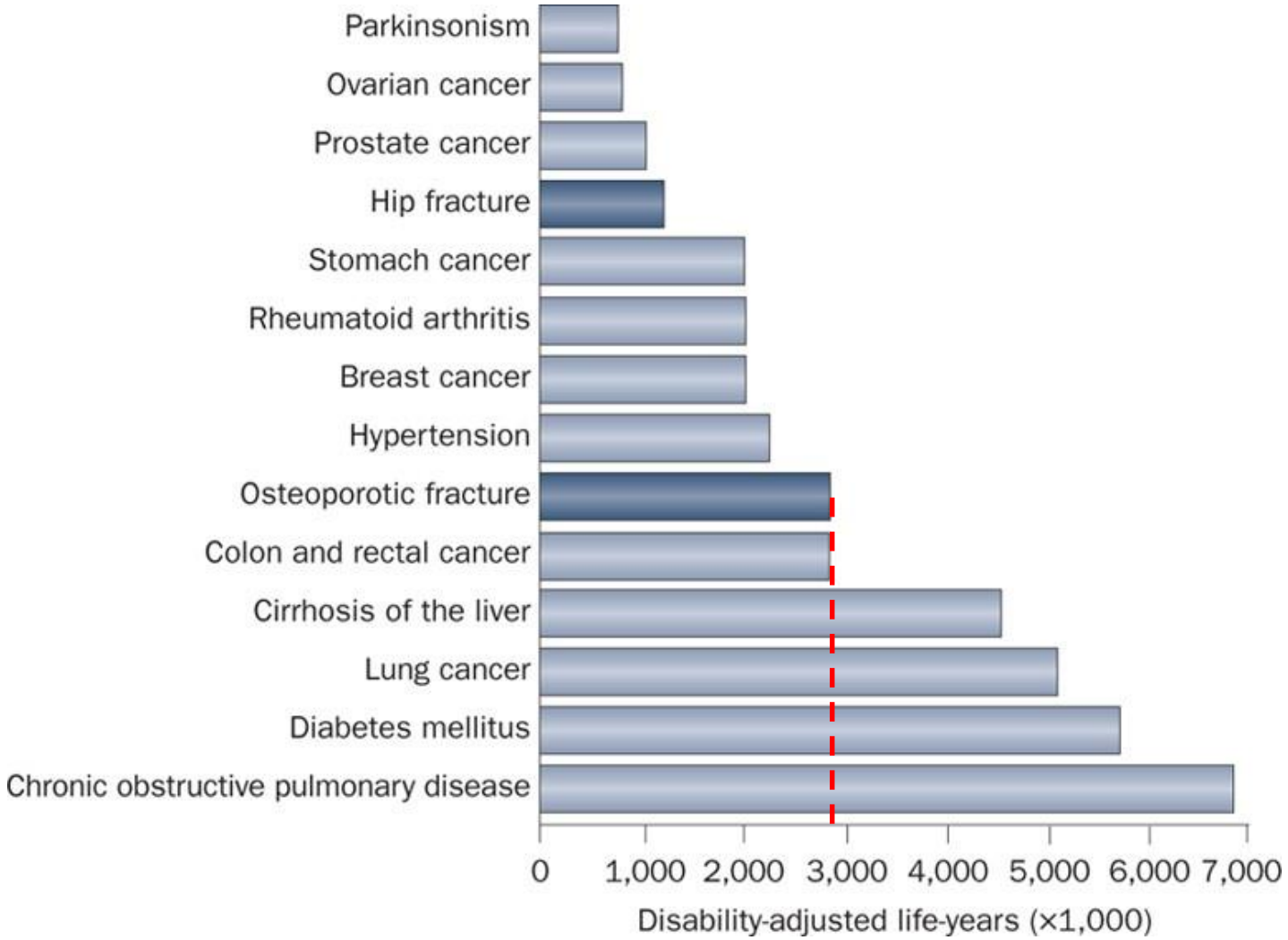


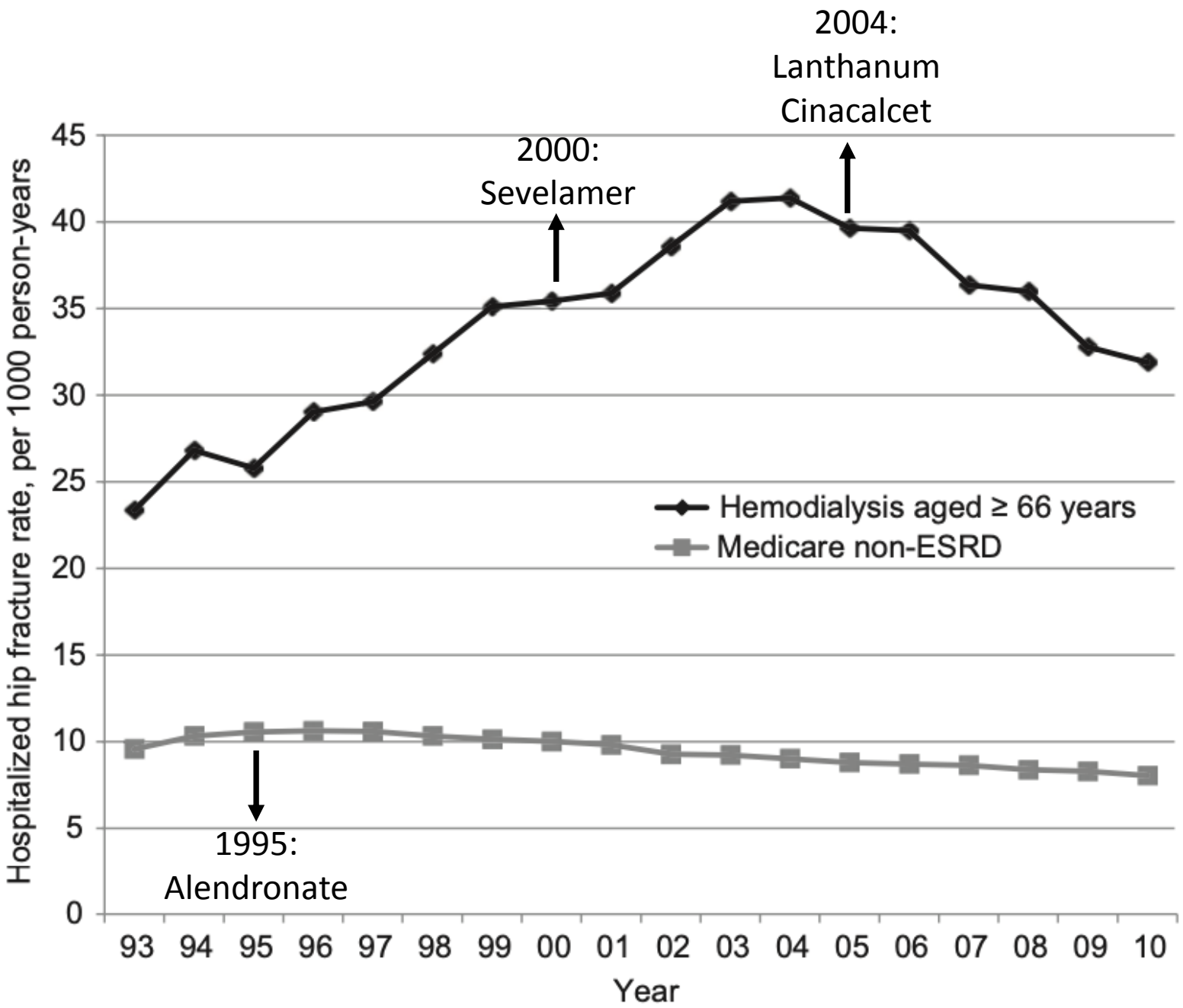

General population
DOPPS
Annual incidence of hip fracture, per 100 000 patients
8000
7000
6000
5000
4000
3000
2000
1000
0
Female
Male
100
535
320
985
1190
3136
3280
6667
30
312
40
559
200
526
690
2439
1470
1538
55–64
65–74
75–84
85+
45–54
55–64
65–74
75–84
85+
Age group

Outcome of Hip Fx

	Normal kidney function	Non-dialysis-requiring CKD	ESRD	*p* Value
Mortality, *n* (%)	3826 (1.6)	1259 (3.7)	285 (5.9)	<0.001
LOS, days, median (10th, 90th percentile)	5 (3, 10)	5 (3, 11)	7 (4, 16)	<0.001[a]
Costs, dollars, median (10th, 90th percentile)	13,314 (8206, 25,483)	14,807 (9194, 28,467)	17,875 (10,203, 39,525)	<0.001[a]
Disposition of survivors, *n* (%)				
No. of survivors	235,260	32,838	4551	
Home	17,739 (7.5)	780 (2.4)	173 (3.8)	<0.001
Nursing home	193,595 (82.3)	30,025 (91.4)	4024 (88.4)	<0.001
Home care	20,235 (8.6)	1648 (5.0)	234 (5.1)	<0.001
Other hospital	3403 (1.4)	361 (1.1)	112 (3.5)	0.846
Others	289 (0.1)	25 (0.1)	10 (0.2)	0.768

DALY in Fx due to OP

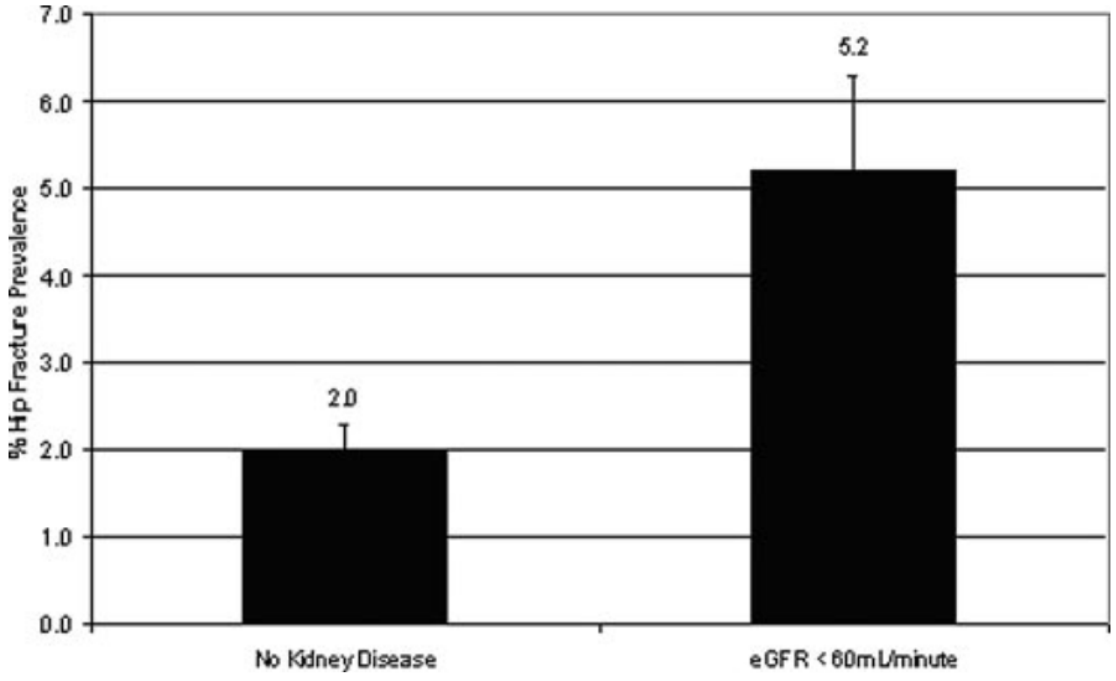


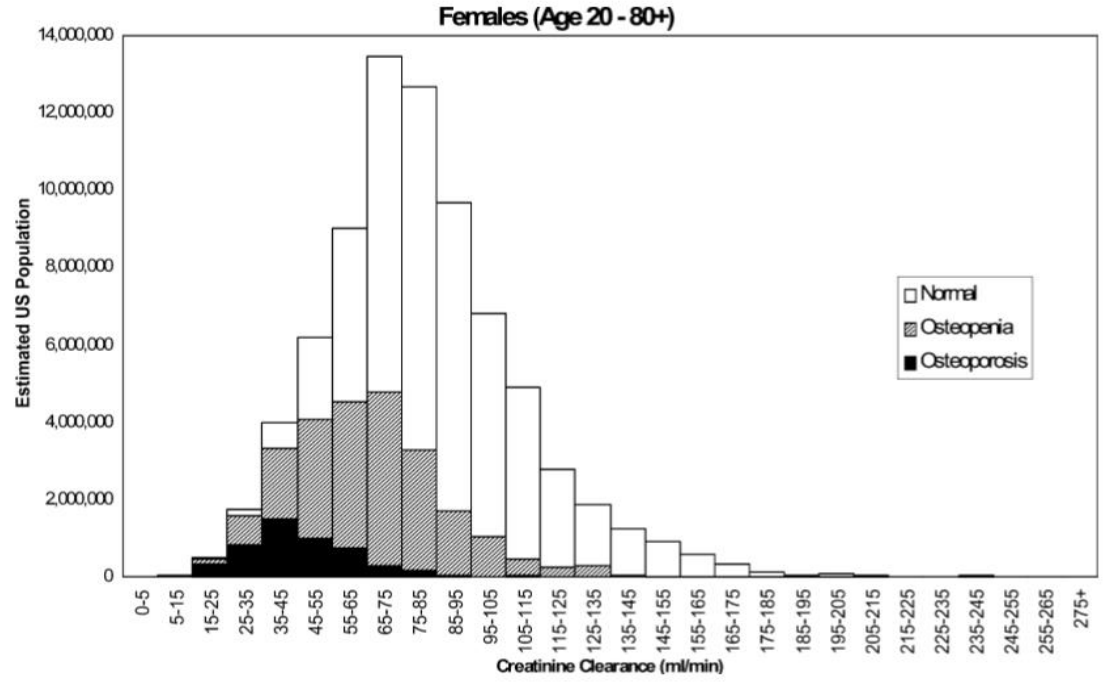

2004:
Lanthanum
Cinacalcet
2000:
Sevelamer
1995:
Alendronate
Hemodialysis aged ≥ 66 years
Medicare non-ESRD
Hospitalized hip fracture rate, per 1000 person-years
0
5
10
15
20
25
30
35
40
45
93
94
95
96
97
98
99
00
01
02
03
04
05
06
07
08
09
10
Year

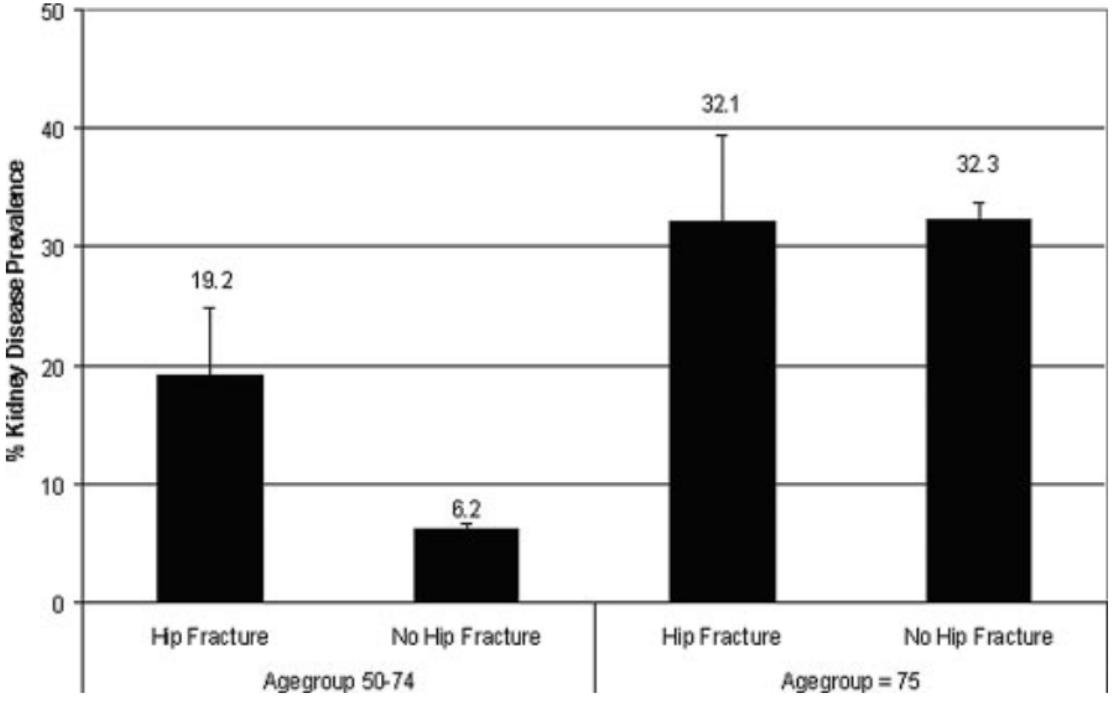
Relationship between Moderate to Severe Kidney Disease and Hip Fracture in the United States

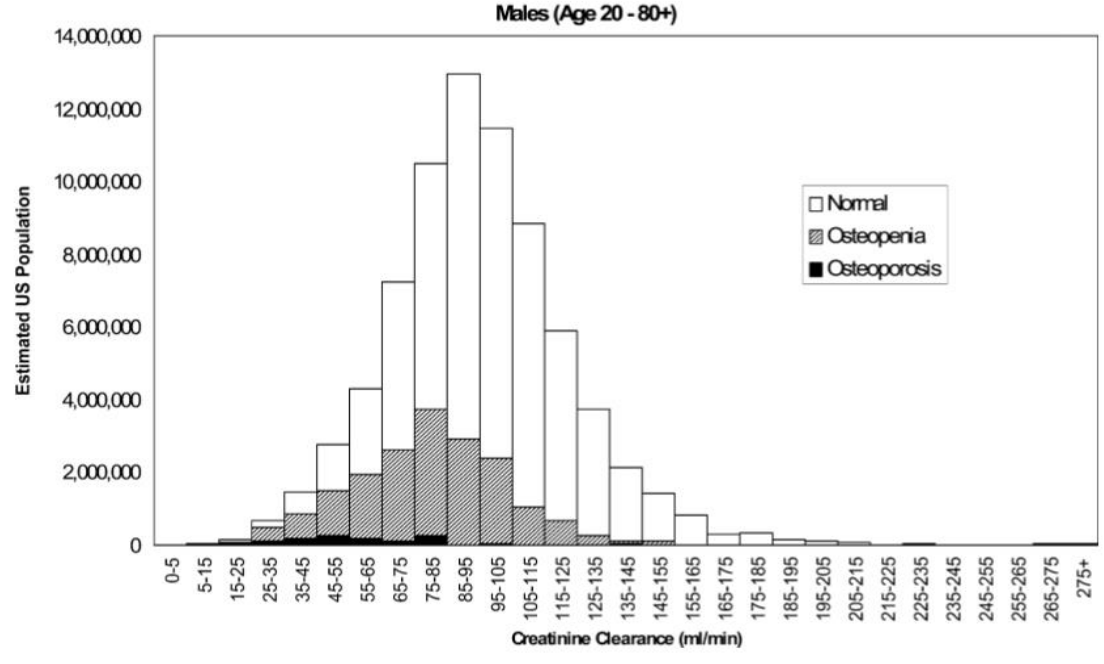
Thomas L. Nickolas,* Donald J. McMahon,† and Elizabeth Shane†

Division of Nephrology and †Division of Endocrinology, Department of Medicine, Columbia University Medical Center, New York, New York


% Hip Fracture Prevalence
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
2.0
5.2
No Kidney Disease
eGFR < 60mL/minute


Females (Age 20 - 80+)
Estimated US Population
14,000,000
12,000,000
10,000,000
8,000,000
6,000,000
4,000,000
2,000,000
0
Normal
Osteopenia
Osteoporosis
0-5
5-15
15-25
25-35
35-45
45-55
55-65
65-75
75-85
85-95
95-105
105-115
115-125
125-135
135-145
145-155
155-165
165-175
175-185
185-195
195-205
205-215
215-225
225-235
235-245
245-255
255-265
275+
Creatinine Clearance (ml/min)

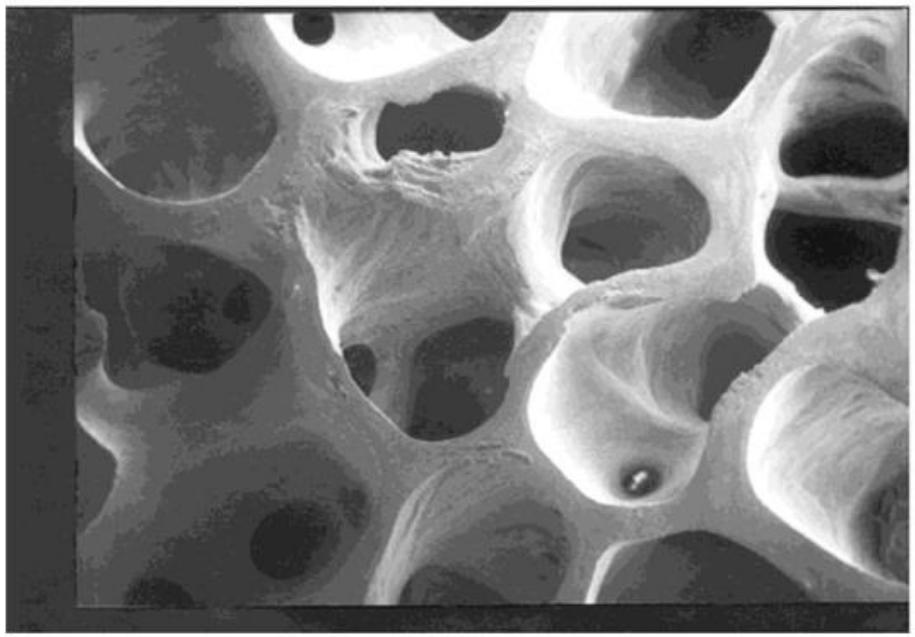

% Kidney Disease Prevalence
50
40
30
20
10
0
19.2
6.2
32.1
32.3
Hip Fracture
No Hip Fracture
Hip Fracture
No Hip Fracture
Agegroup 50-74
Agegroup = 75


Males (Age 20 - 80+)
Estimated US Population
14,000,000
12,000,000
10,000,000
8,000,000
6,000,000
4,000,000
2,000,000
0
Normal
Osteopenia
Osteoporosis
0-5
5-15
15-25
25-35
35-45
45-55
55-65
65-75
75-85
85-95
95-105
105-115
115-125
125-135
135-145
145-155
155-165
165-175
175-185
185-195
195-205
205-215
215-225
225-235
235-245
245-255
255-265
265-275
275+
Creatinine Clearance (ml/min)

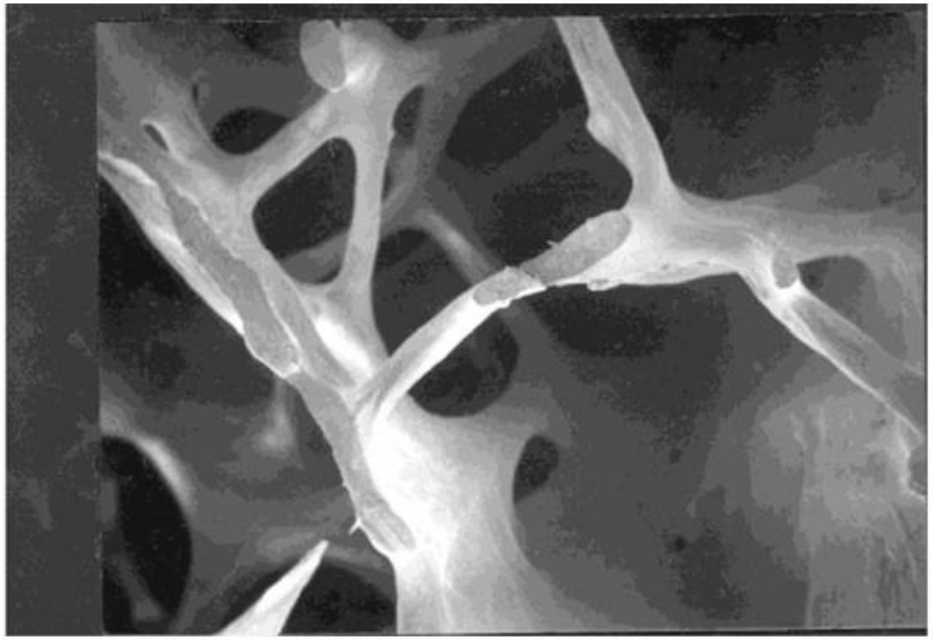
Definitions

- Bone deficiency
- Bone thinning
- Bone loss
- Bone weakening

Osteoporosis



Normal bone



Osteoporotic bone

Bone Mass Through Life

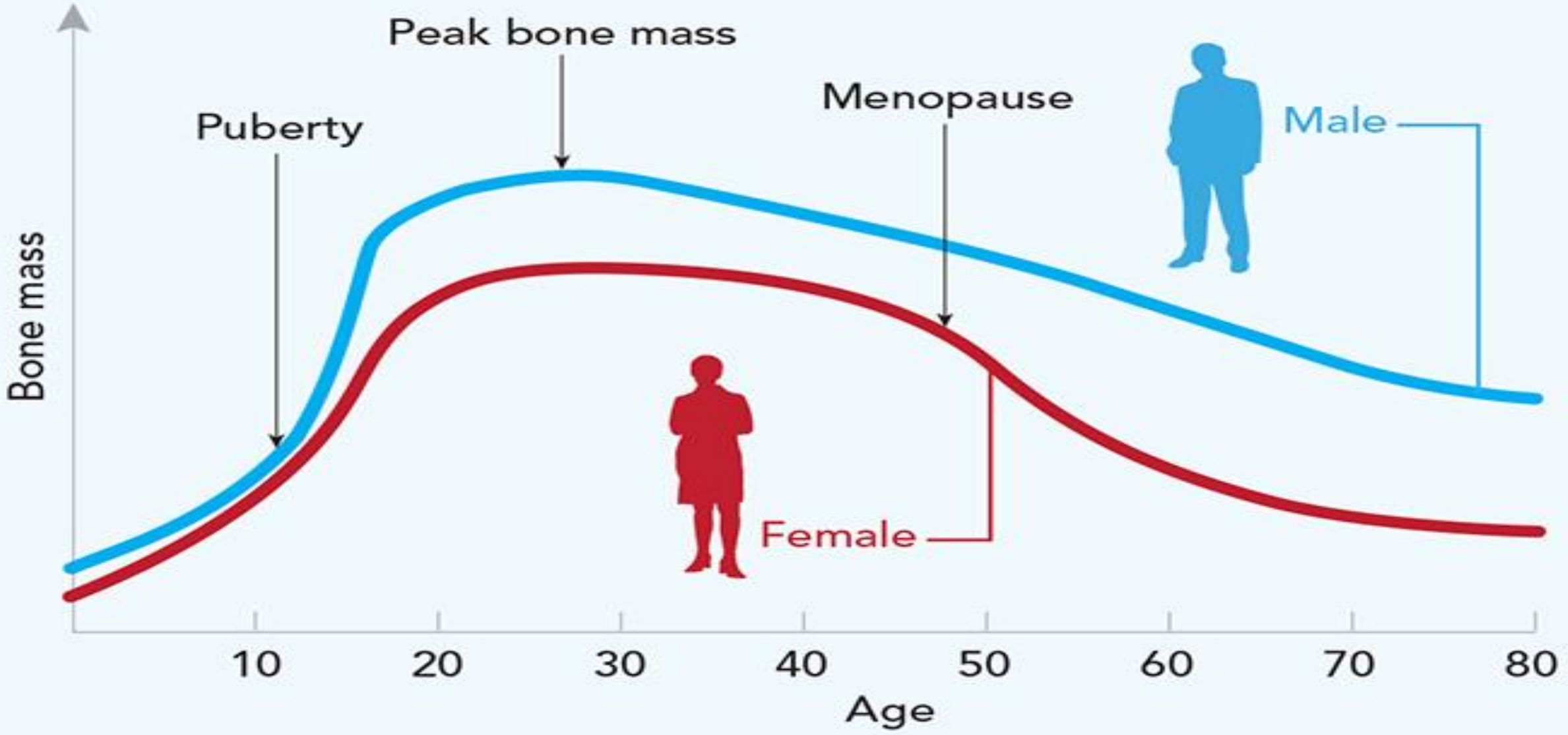
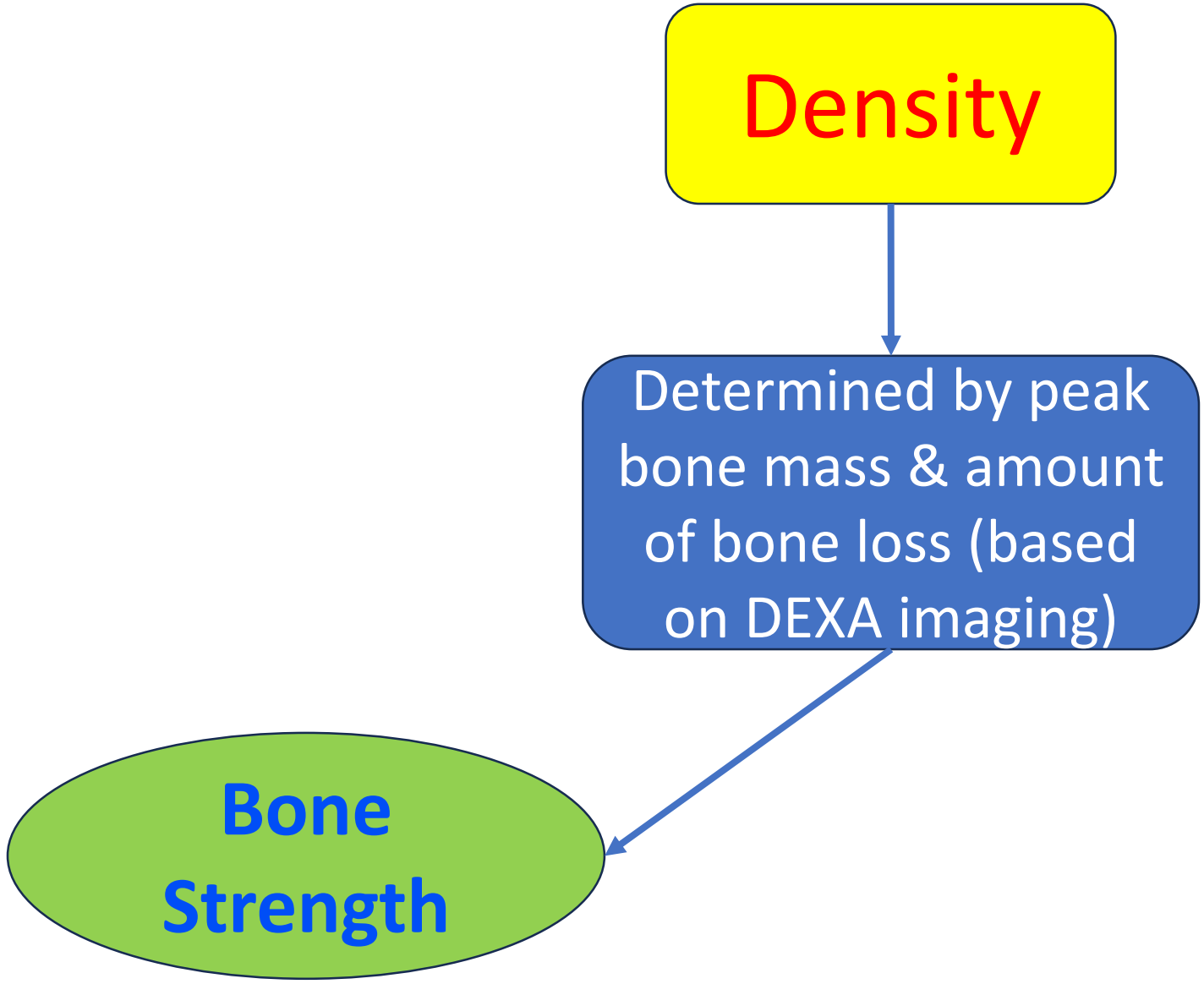
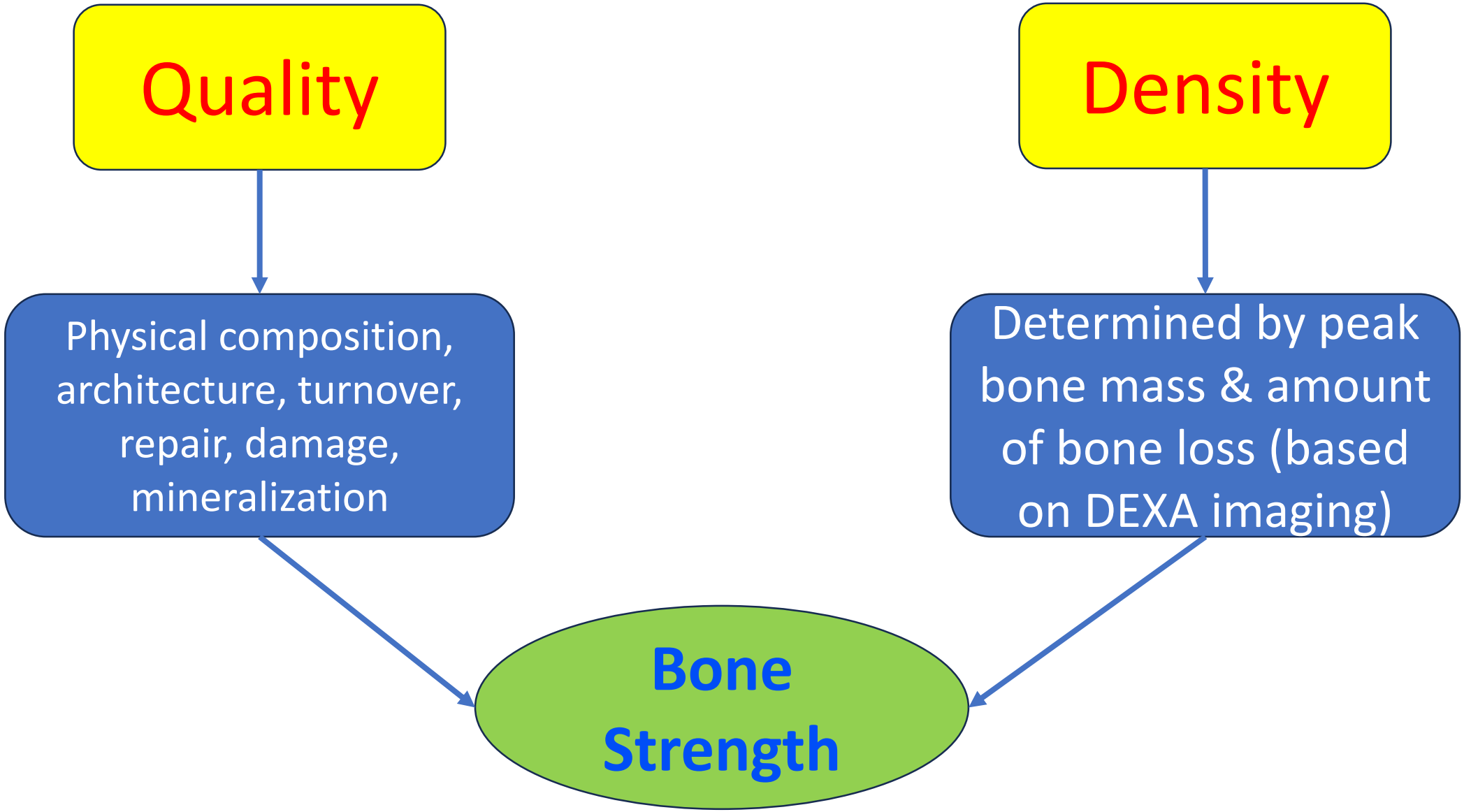
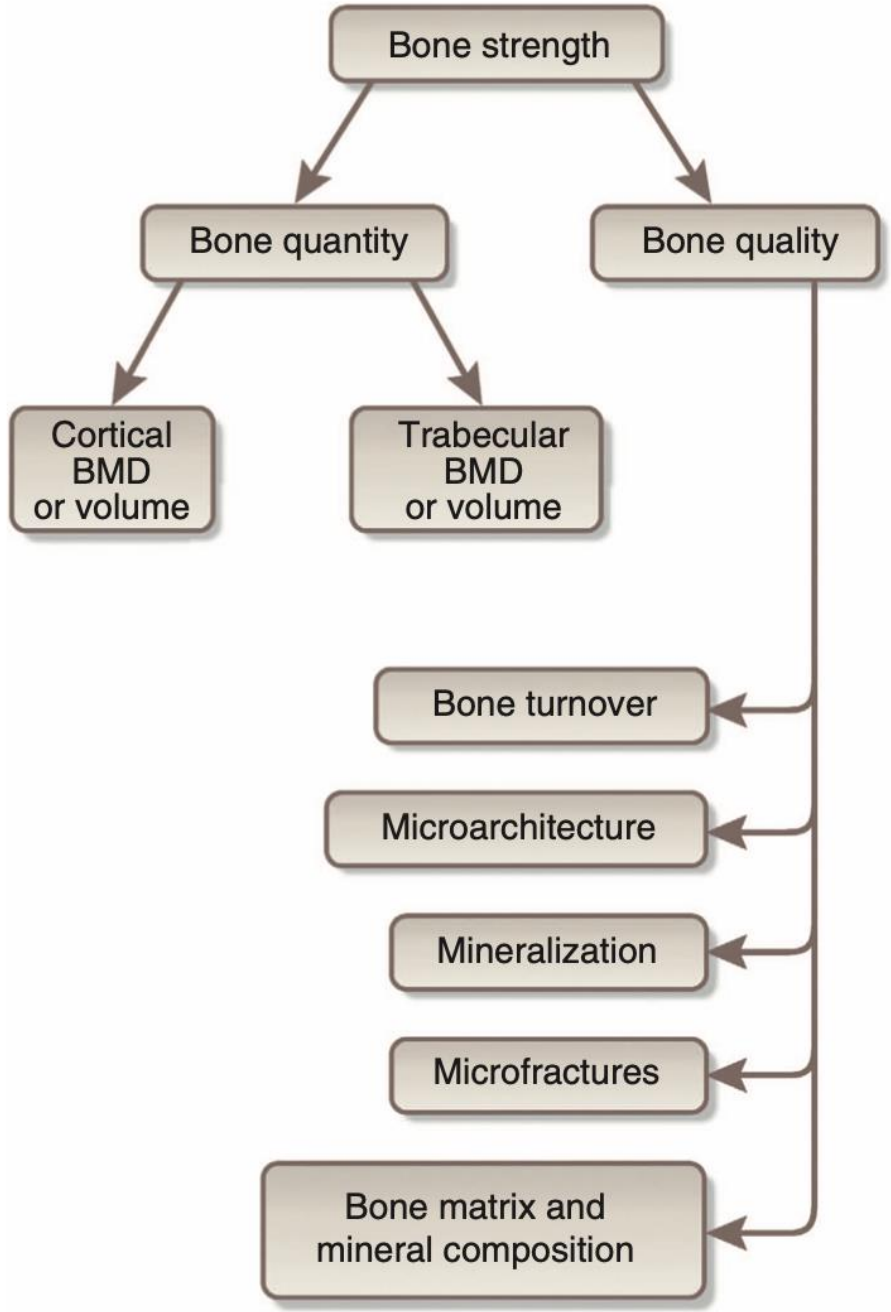


Table 5 Defining osteoporosis by BMD

WHO definition of osteoporosis based on BMD		
Classification	BMD	T-score
Normal	Within 1 SD of the mean level for a young-adult reference population	T-score at −1.0 and above
Low bone mass (osteopenia)	Between 1.0 and 2.5 SD below that of the mean l evel for a young-adult reference population	T-score between −1.0 and −2.5
Osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population	T-score at or below −2.5
Severe or established osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population with fractures	T-score at or below −2.5 with one or more fractures


Density
Determined by peak bone mass & amount of bone loss (based on DEXA imaging)
Bone Strength


Quality
Density
Physical composition, architecture, turnover, repair, damage, mineralization
Determined by peak bone mass & amount of bone loss (based on DEXA imaging)
Bone Strength


Bone strength
Bone quantity
Bone quality
Cortical BMD or volume
Trabecular BMD or volume
Bone turnover
Microarchitecture
Mineralization
Microfractures
Bone matrix and mineral composition

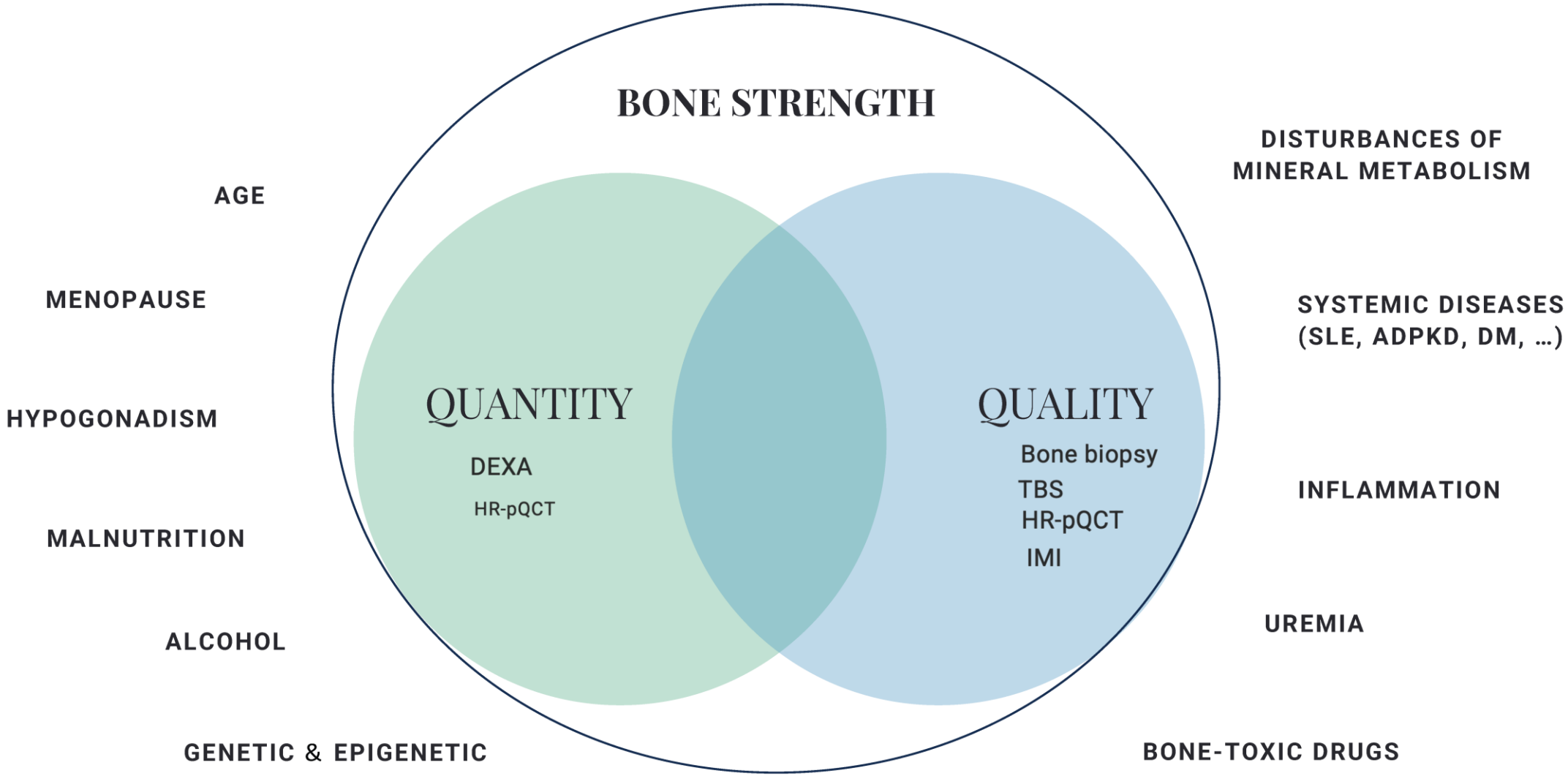
NIH definition

- NJE define OP as =

  skeletal disorder characterized by

  “compromised bone strength (Q&Q)”

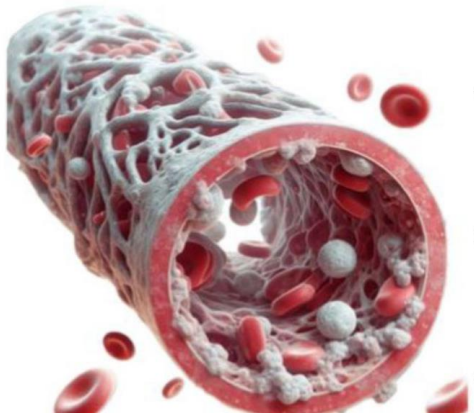
  predisposing to “increased Fx” risk.

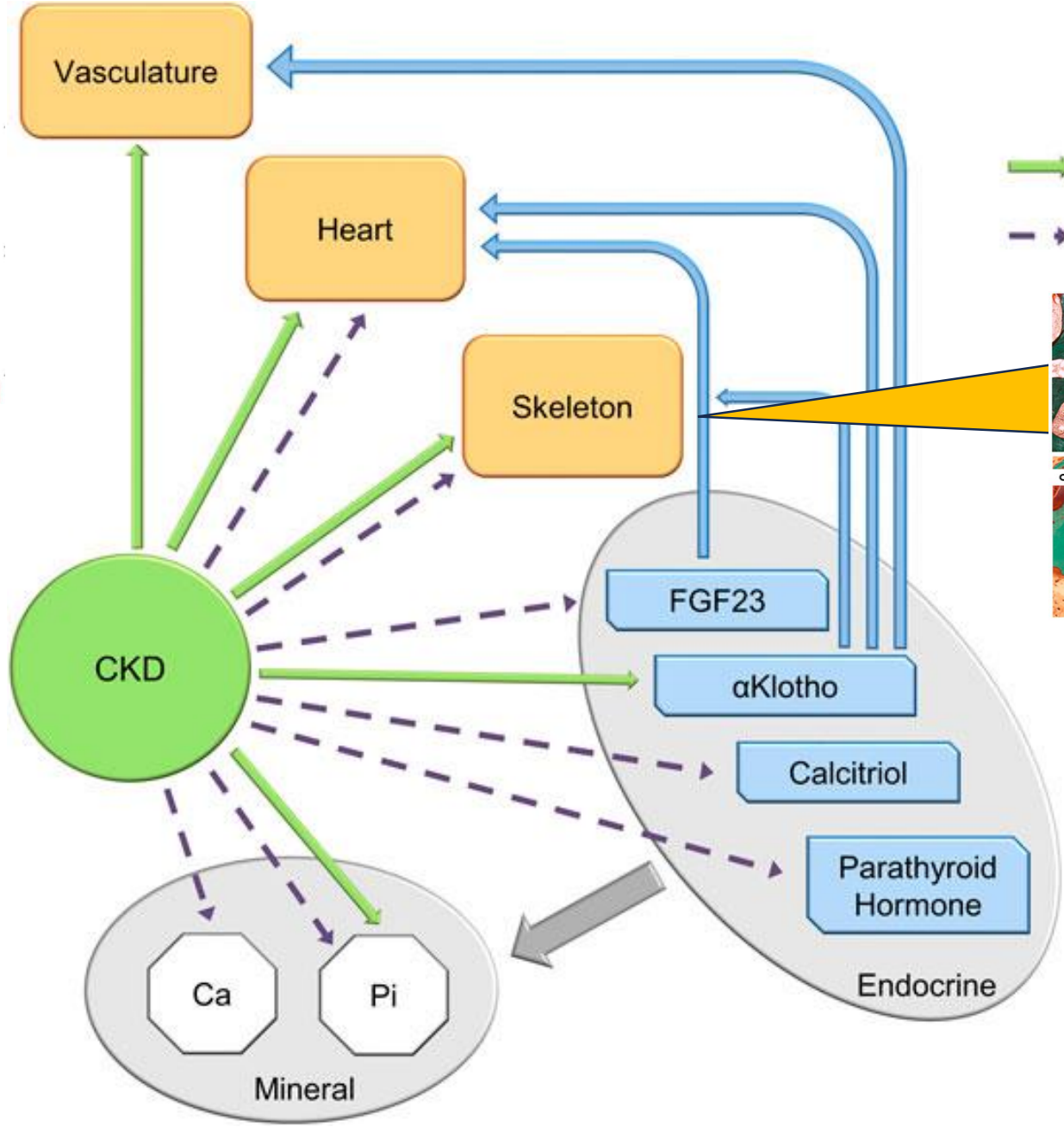

BONE STRENGTH
QUANTITY
DEXA
HR-pQCT
QUALITY
Bone biopsy
TBS
HR-pQCT
IMI
AGE
MENOPAUSE
HYPOGONADISM
MALNUTRITION
ALCOHOL
GENETIC & EPIGENETIC
DISTURBANCES OF MINERAL METABOLISM
SYSTEMIC DISEASES (SLE, ADPKD, DM, …)
INFLAMMATION
UREMIA
BONE-TOXIC DRUGS

Screening

Table 3. General and CKD-Specific Risk Factors for Bone Loss and Fractures

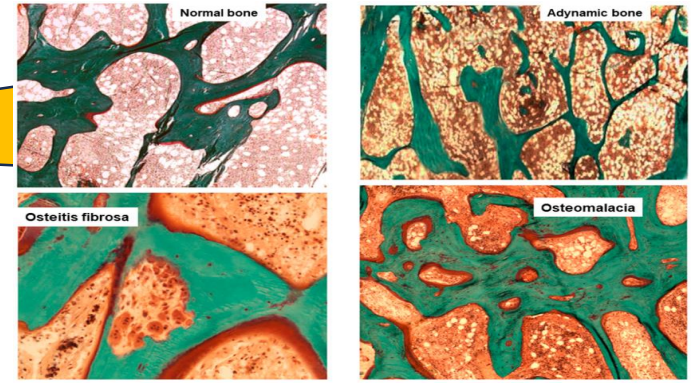
General risk factors	CKD-specific
Patient-related (non-modifiable) • Age • Sex • Ethnicity • Past history of fracture General (modifiable) • Low physical activity • Smoking • Alcohol • Medications (eg, streoids) • Diabetes • Sarcopenia • Chronic inflammatory disorders	• Hyperparathyrodism • Low nutritional 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 • Higher prevalence of general risk factors for osteoporosis



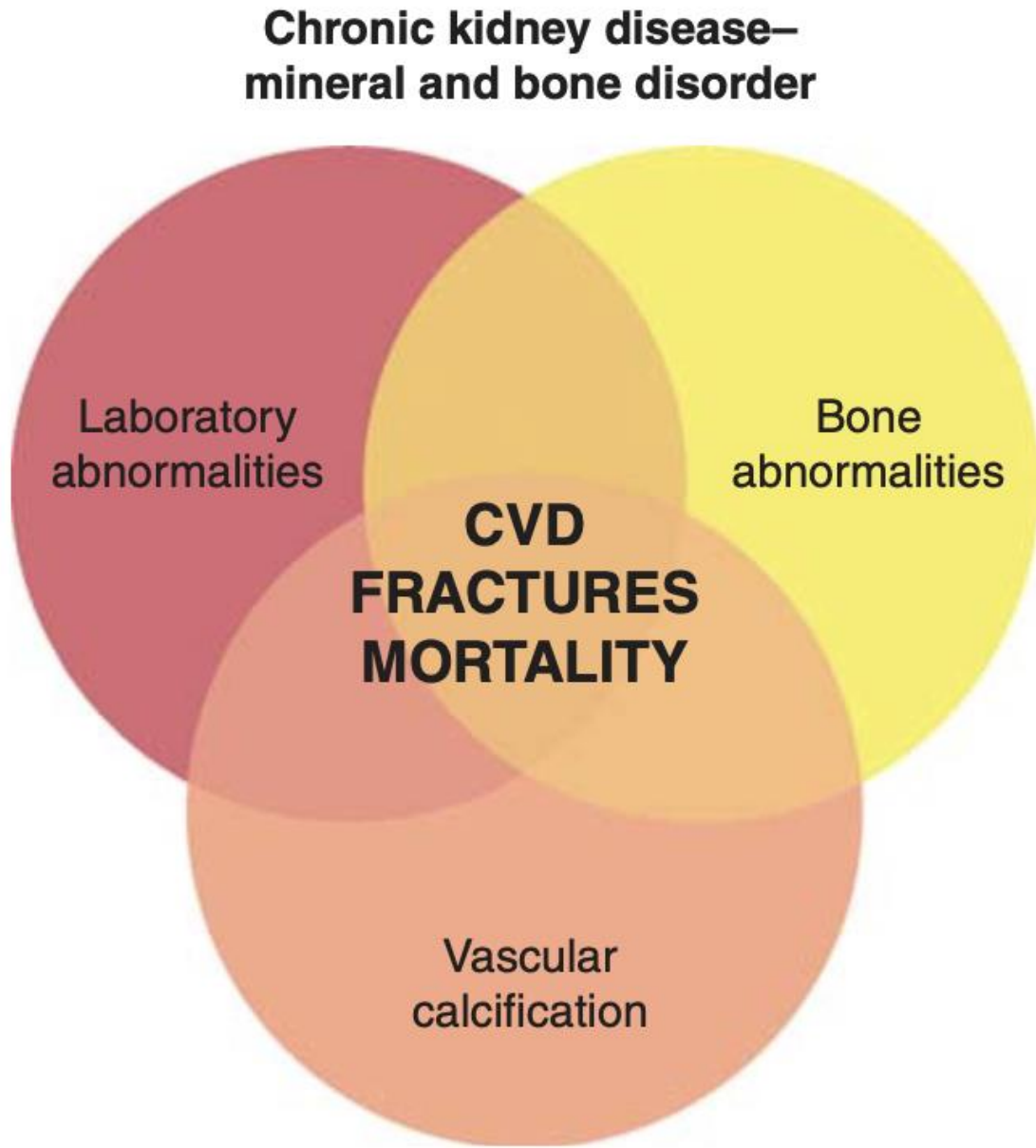


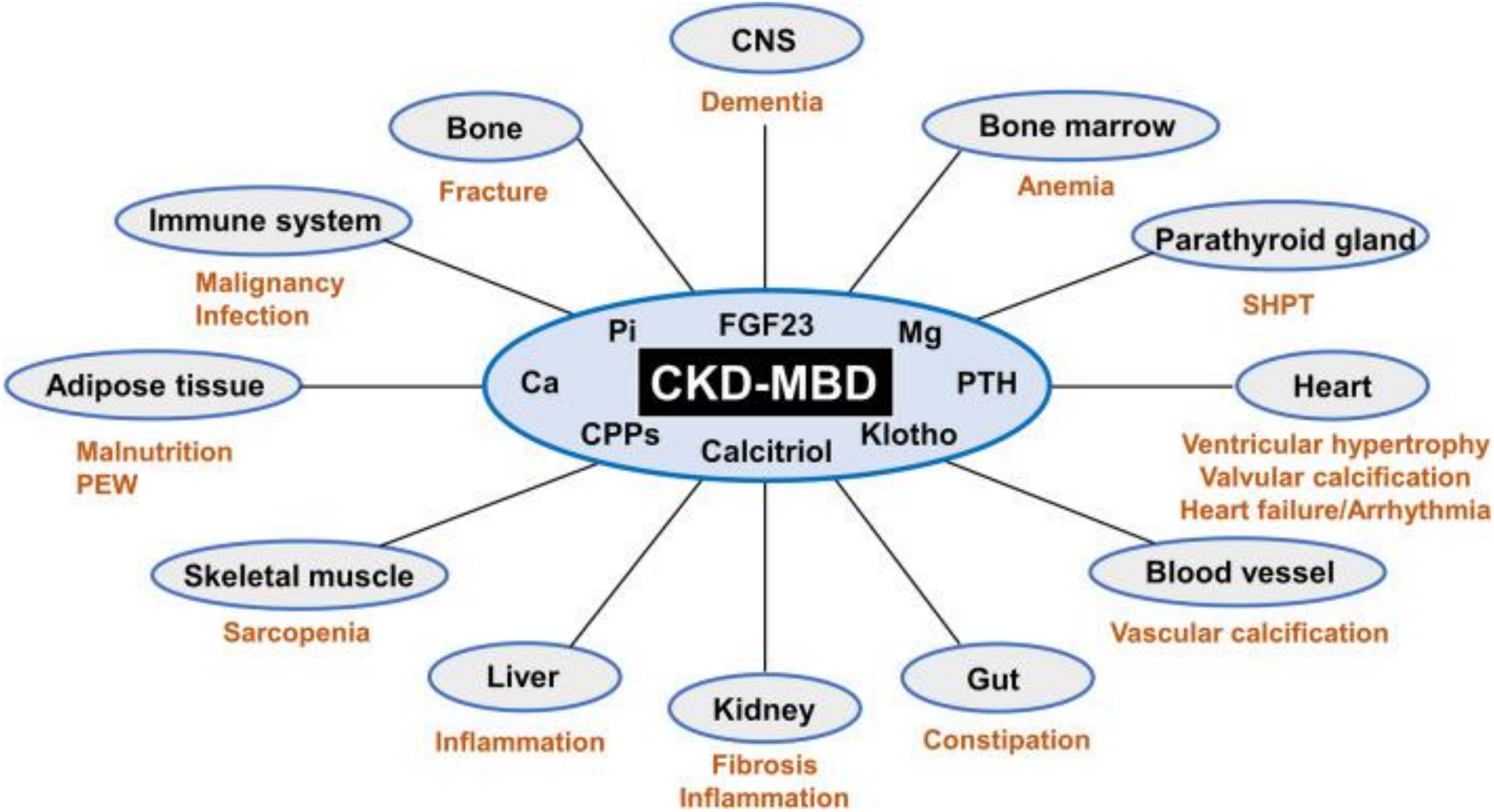
Direct effects of renal injury

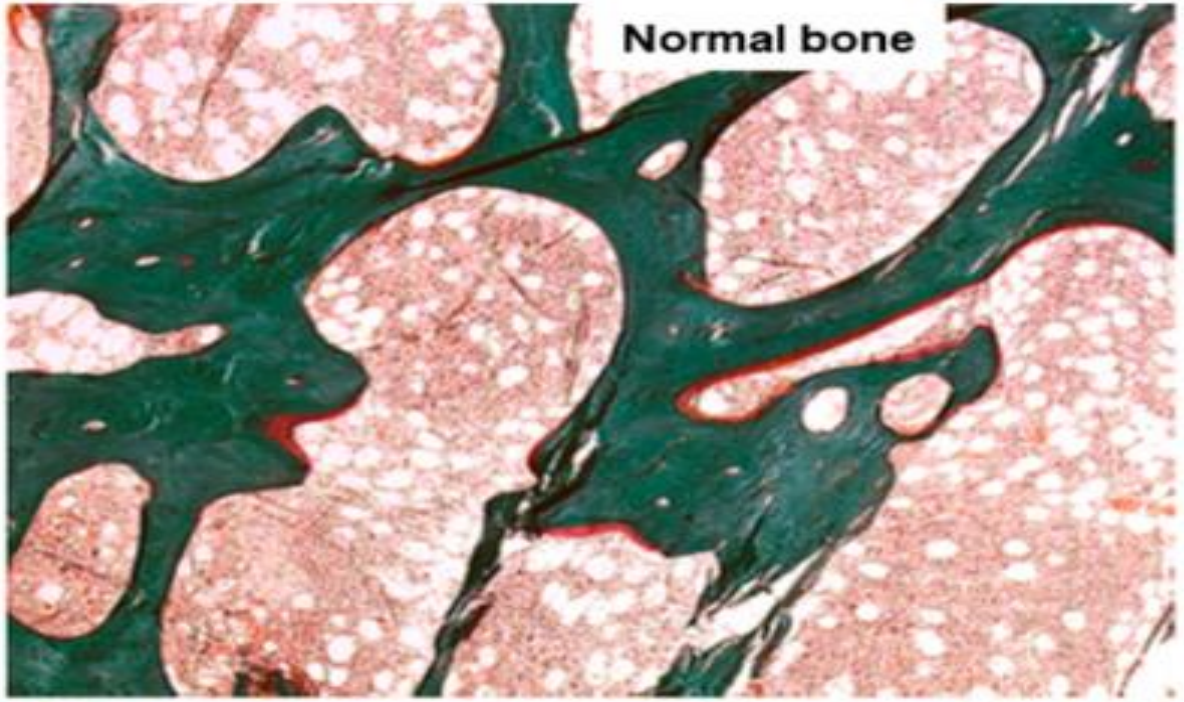
Indirect effects

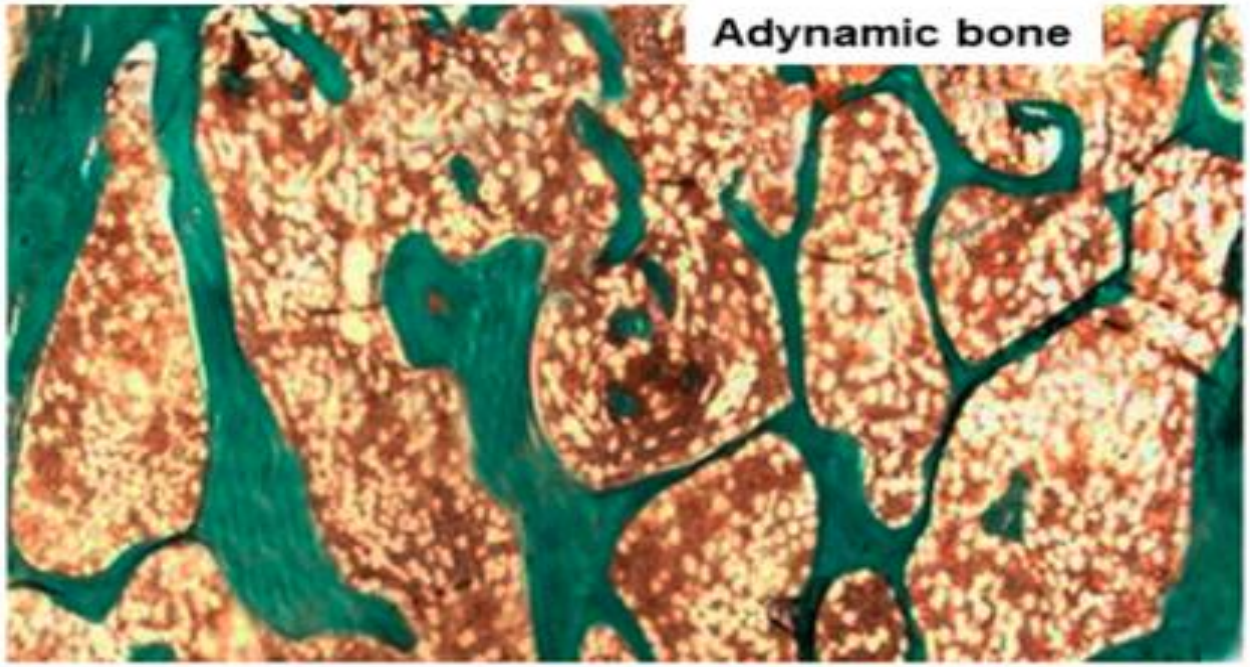


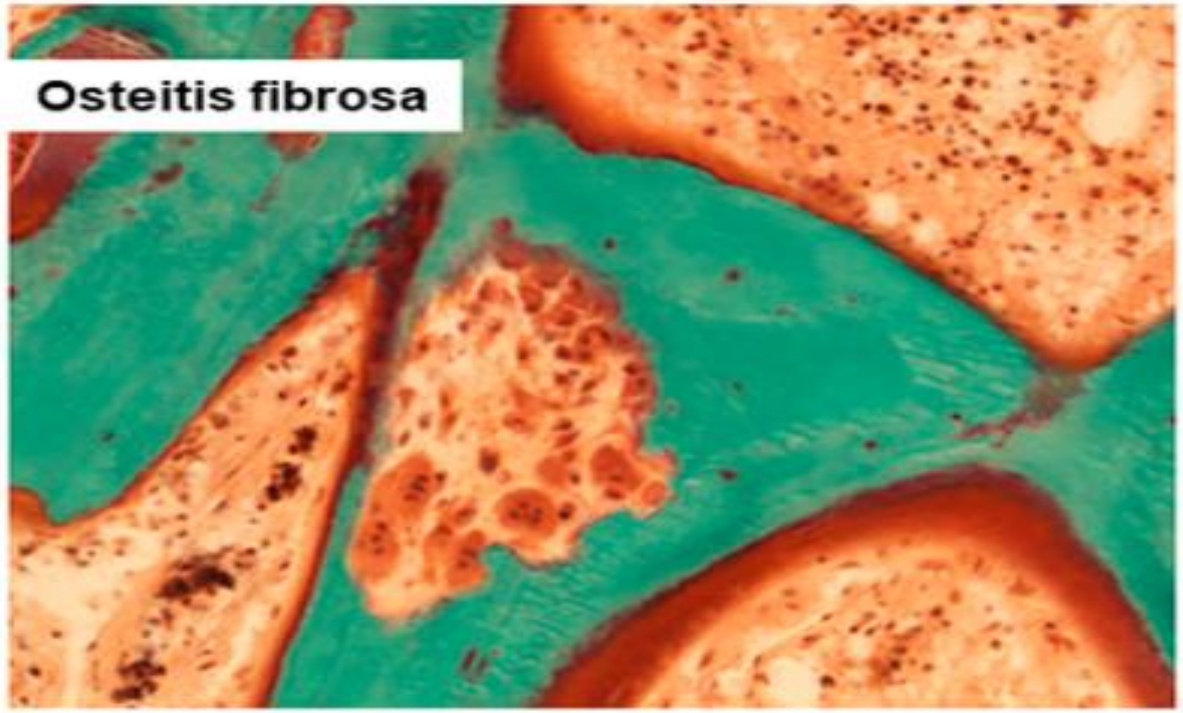
CKD-MBD

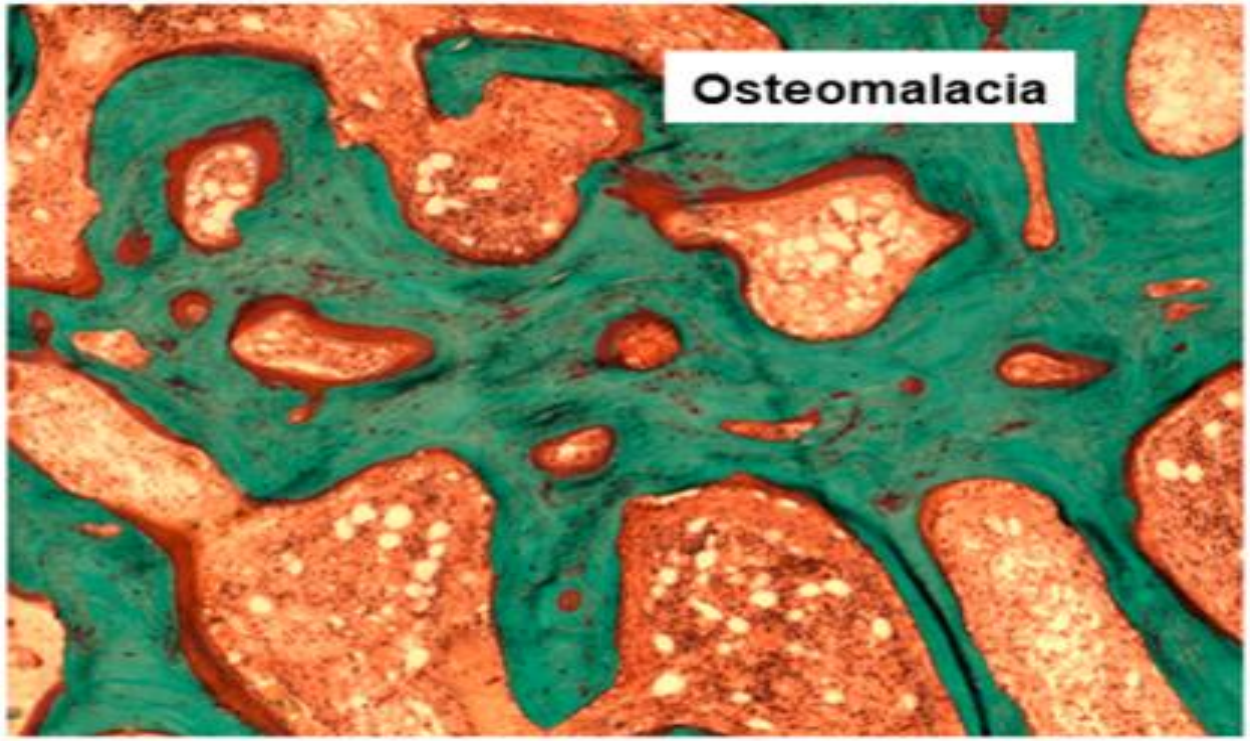

Chronic kidney disease–
mineral and bone disorder
Laboratory
abnormalities
Bone
abnormalities
CVD
FRACTURES
MORTALITY
Vascular
calcification

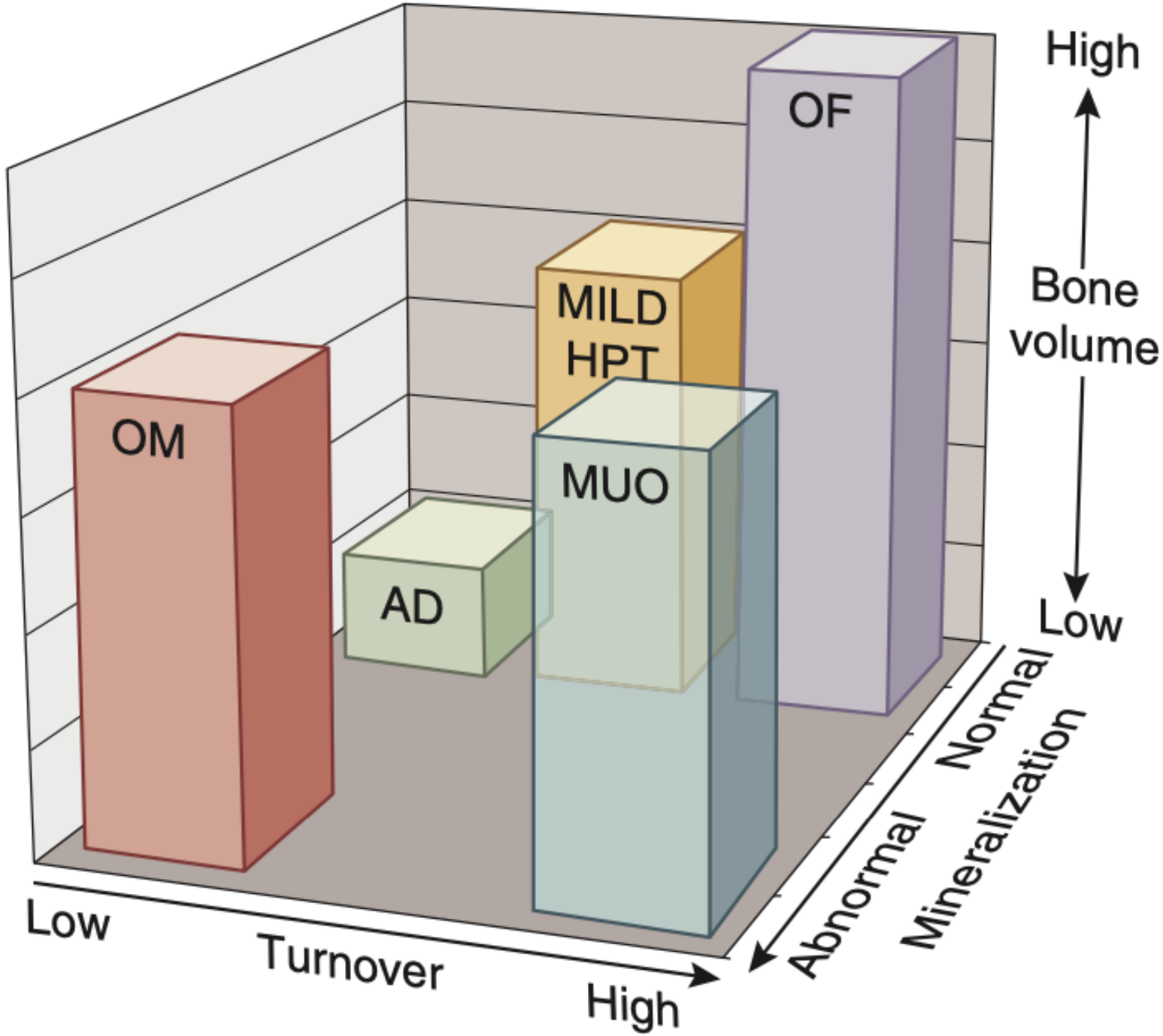

CNS
Dementia
Bone
Fracture
Bone marrow
Anemia
Immune system
Malignancy
Infection
Parathyroid gland
SHPT
Pi
FGF23
Mg
Ca
CKD-MBD
PTH
CPPs
Calcitriol
Klotho
Adipose tissue
Malnutrition
PEW
Heart
Ventricular hypertrophy
Valvular calcification
Heart failure/Arrhythmia
Skeletal muscle
Sarcopenia
Blood vessel
Vascular calcification
Liver
Inflammation
Kidney
Fibrosis
Inflammation
Gut
Constipation


Normal bone


Adynamic bone


Osteitis fibrosa

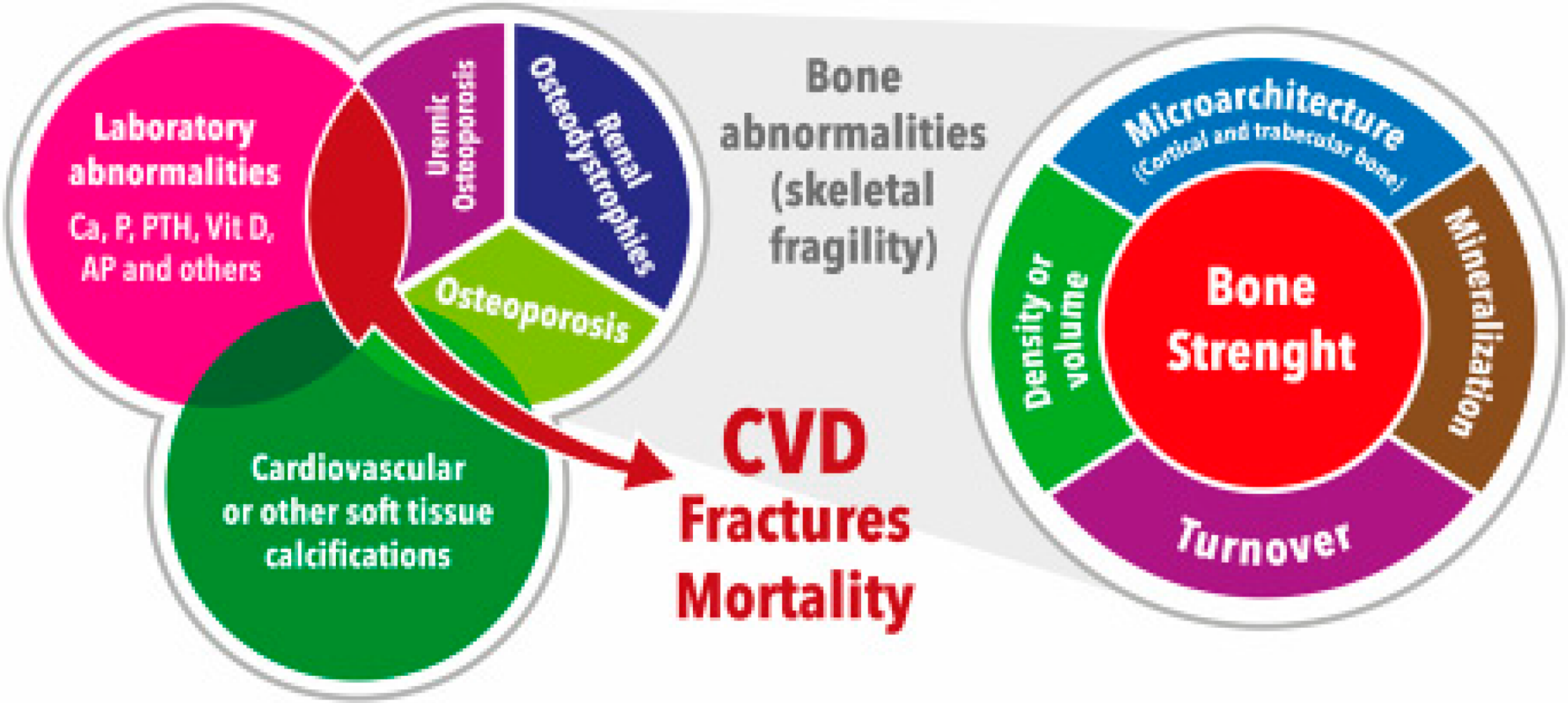

Osteomalacia

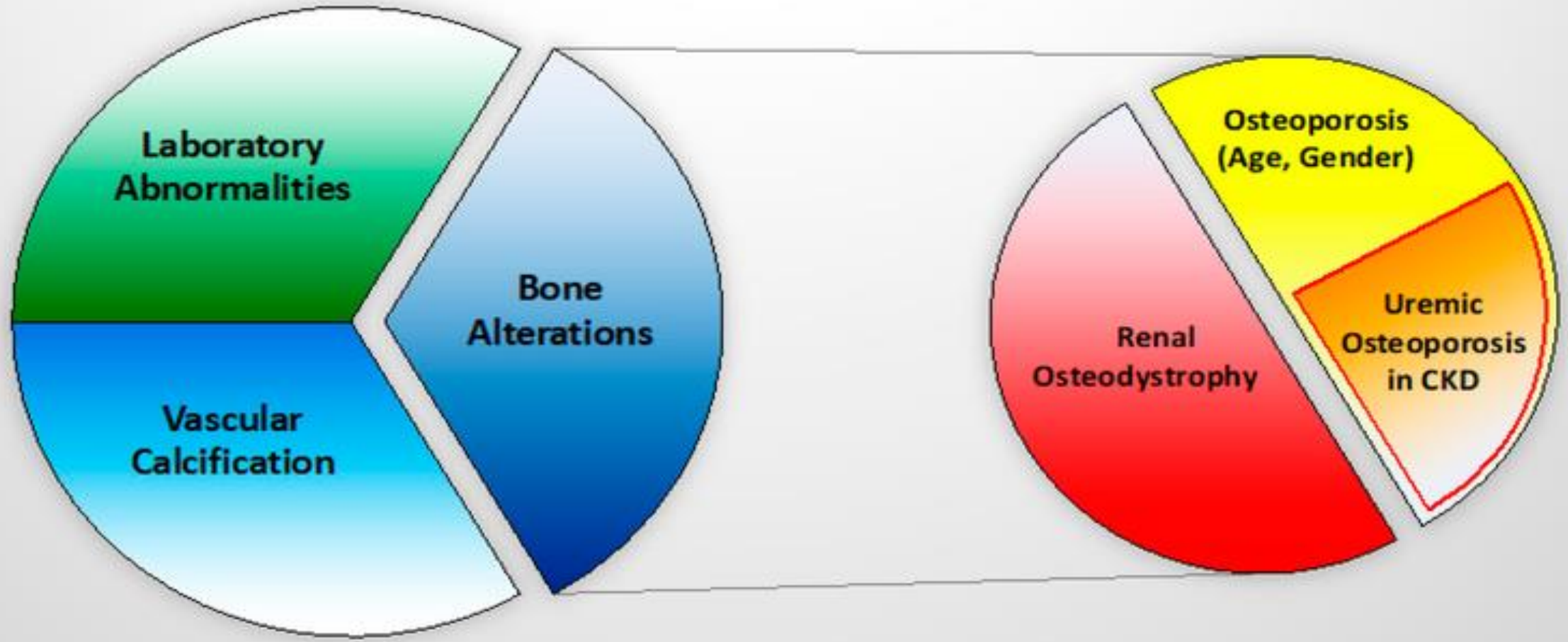

High
OF
MILD
HPT
MUO
OM
AD
Bone
volume
Low
Low
Turnover
High
Abnormal
Normal
Mineralization

ROD begin with eGFR 90-60 !

4 types of bone pathology & we get them “names” AND there is basically some combination with high or low bone turnover with or without mineralization defects

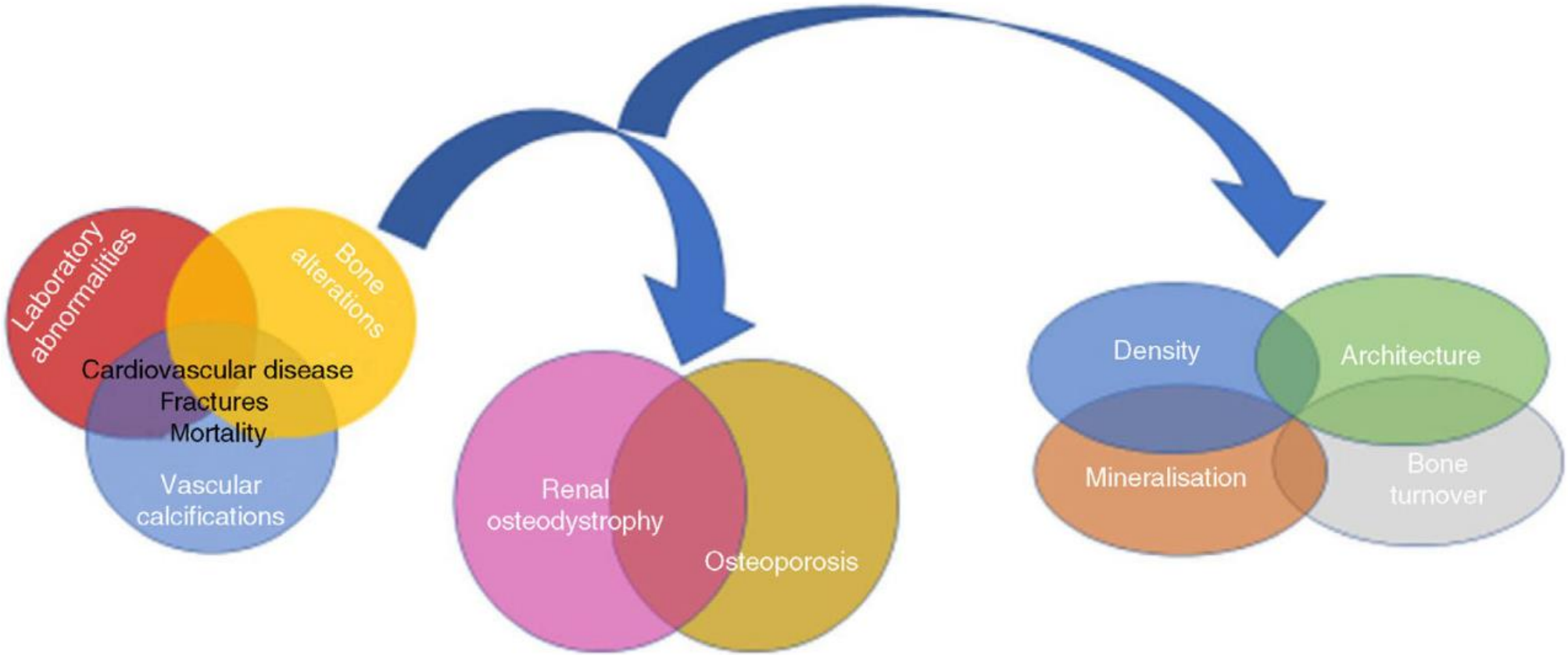
Type of ROD	Turnover	Mineralization	Volume
Osteomalacia	Low	Abnormal	Low to Medium
Osteitis Fibrosa	High	Normal	Normal to High
Adinamic Bone Disease	Low	Normal	Low to Normal
Mixed Osteopathy	Normal to High	Abnormal	Low to Normal
Osteoporosis	Normal	Normal	Low


Laboratory abnormalities
Ca, P, PTH, Vit D, AP and others
Uremic Osteoporosis
Renal Osteodystrophies
Osteoporosis
Cardiovascular or other soft tissue calcifications
Bone abnormalities (skeletal fragility)
CVD
Fractures
Mortality
Microarchitecture
(Cortical and trabecular bone)
Mineralization
Turnover
Density or volume
Bone Strenght



CKD-MBD

Histological Lesions in CKD

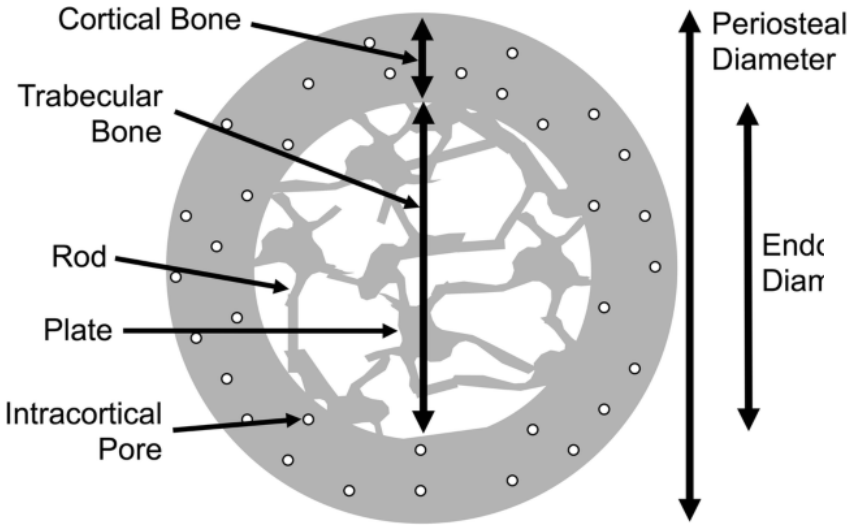


CKD-MBD

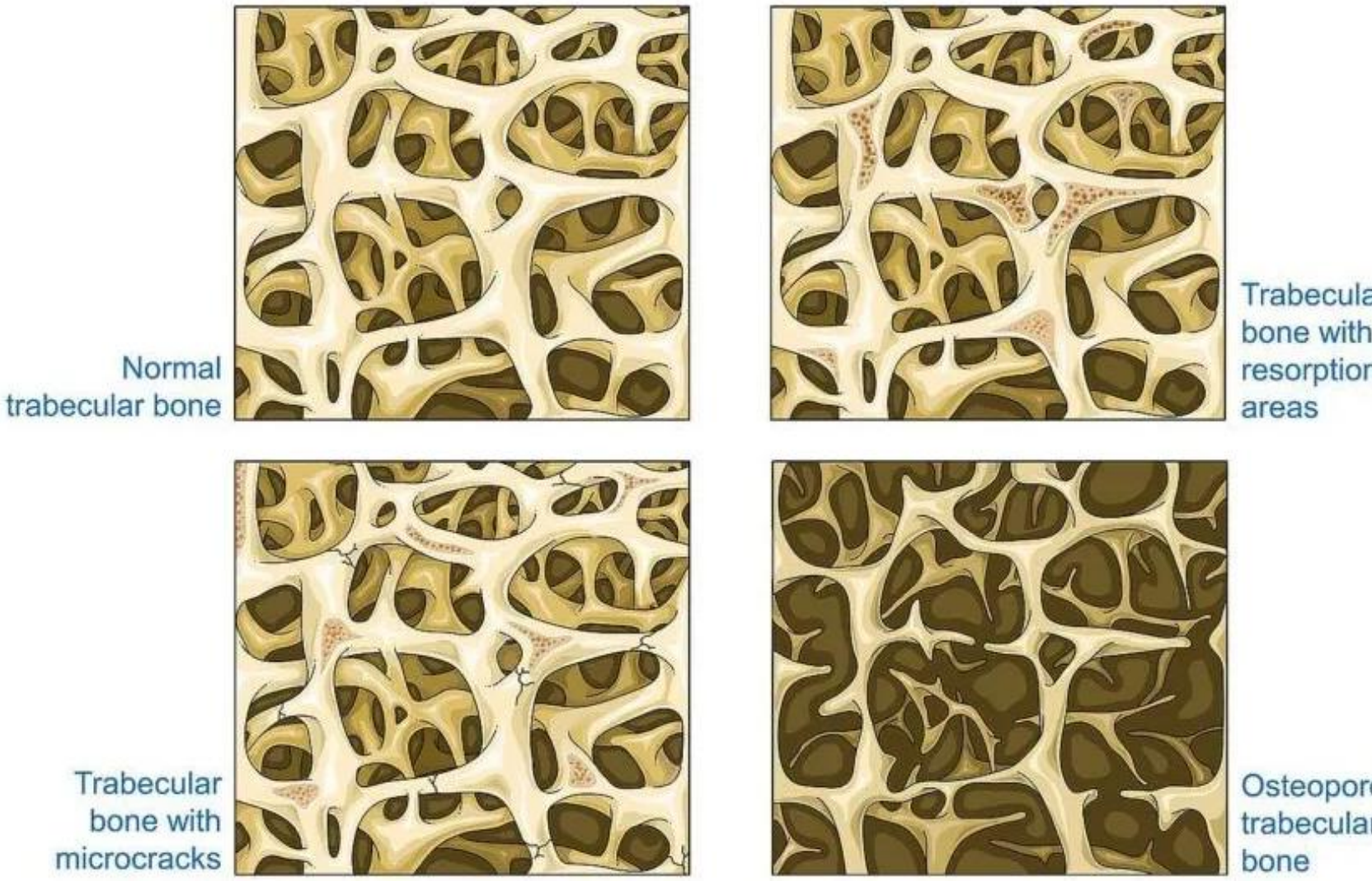
Osteoporosis in CKD

Determinants of bone strength

CKD-OP



The term ***CKD-associated osteoporosis has been proposed to recognize that bone disease in CKD patients is primarily a disorder of bone strength*** *that increases fracture risk*



ORIGINAL ARTICLE

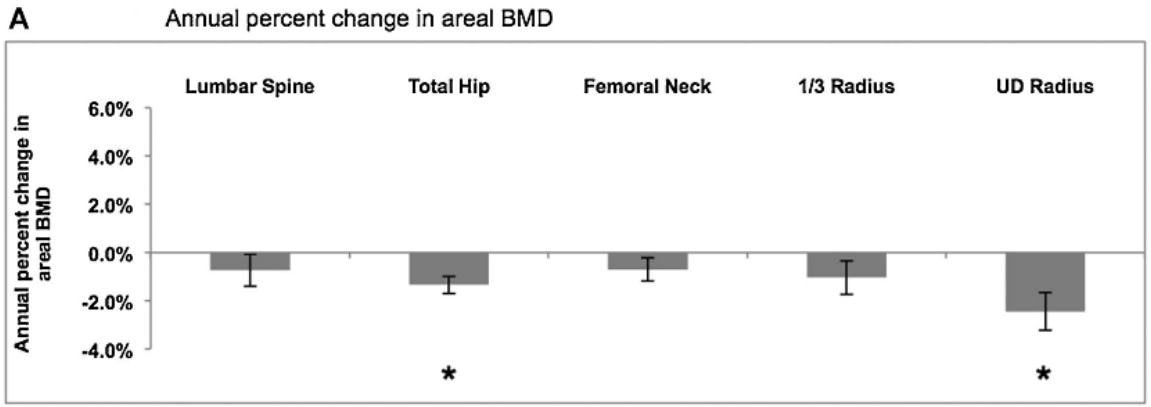
JBMR®

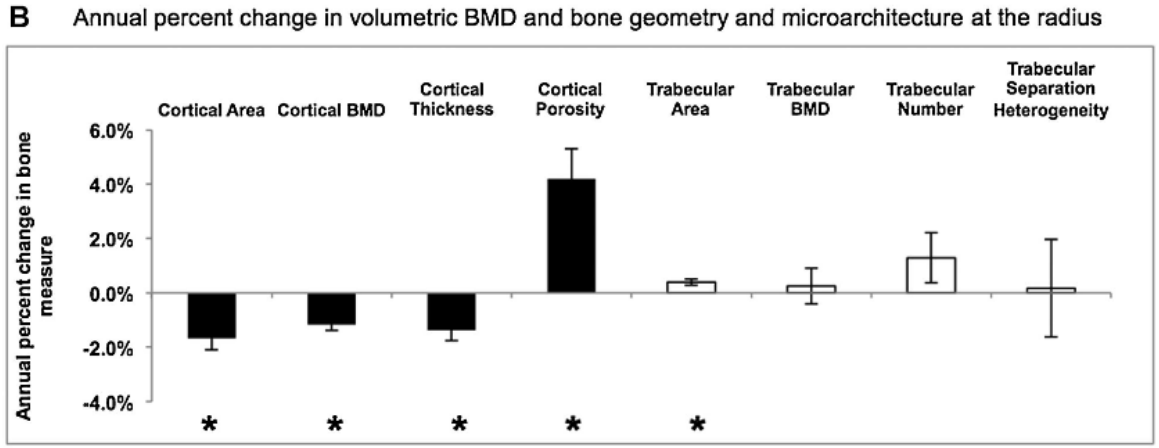
Rapid Cortical Bone Loss in Patients With Chronic Kidney Disease

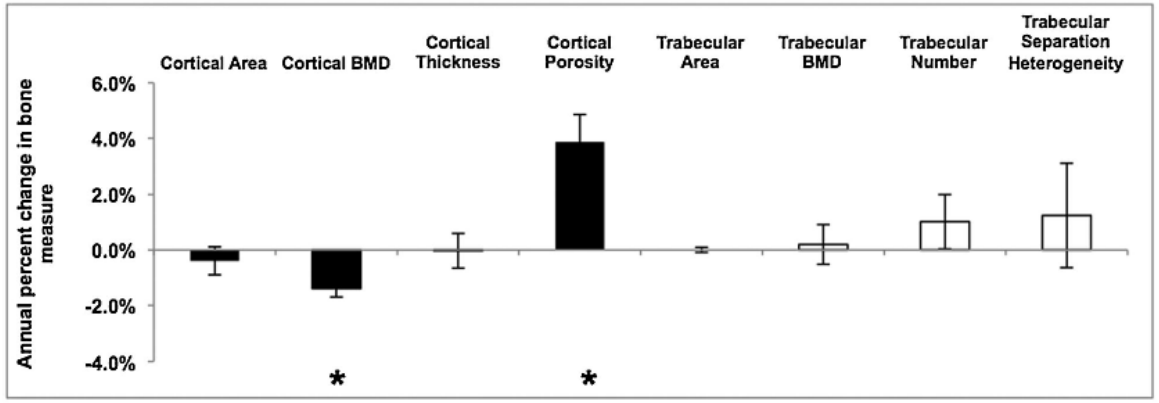
Thomas L Nickolas,[1] Emily M Stein,[2] Elzbieta Dworakowski,[2] Kyle K Nishiyama,[2] Mafo Komandah-Kosseh,[2] Chiyuan A Zhang,[2] Donald J McMahon,[2] Xiaowei S Liu,[3] Stephanie Boutroy,[4] Serge Cremers,[2] and Elizabeth Shane[2]

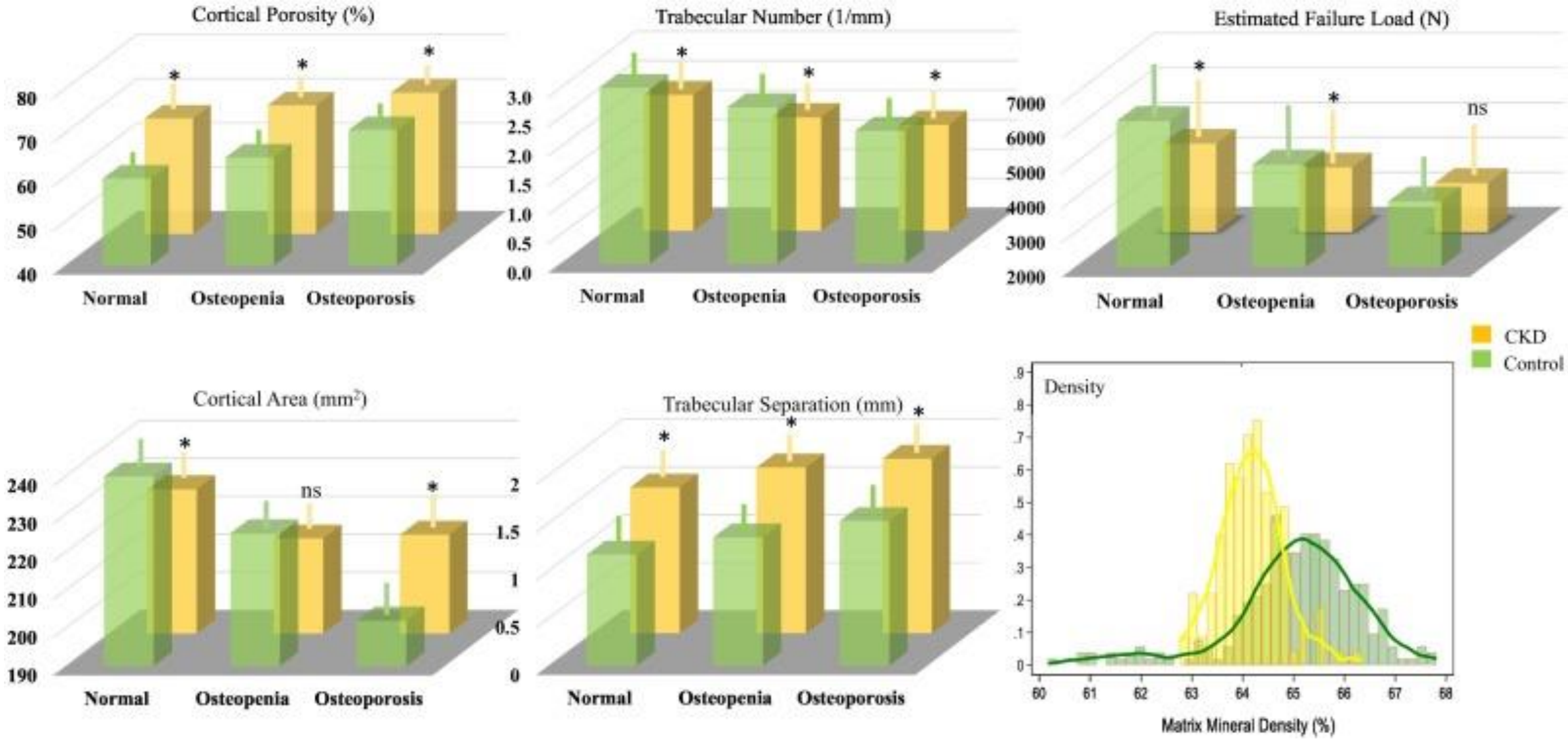
CKD results in Cortical bone loss

In CKD pts the progressive defects are not really on the trabecular compartment BUT the are all in the cortical compartment








Cortical Porosity (%)
80
70
60
50
40
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
*
*
Normal
Osteopenia
Osteoporosis
Trabecular Number (1/mm)
*
*
*
Normal
Osteopenia
Osteoporosis
Estimated Failure Load (N)
7000
6000
5000
4000
3000
2000
*
*
ns
Normal
Osteopenia
Osteoporosis
CKD
Control
Cortical Area (mm²)
240
230
220
210
200
190
*
ns
*
Normal
Osteopenia
Osteoporosis
Trabecular Separation (mm)
2
1.5
1
0.5
0
*
*
*
Normal
Osteopenia
Osteoporosis
Density
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
60
61
62
63
64
65
66
67
68
Matrix Mineral Density (%)

Pts with high-turnover or low-turnover ROD *can show* the same densitometric measurements as a classic "senile" OP profile

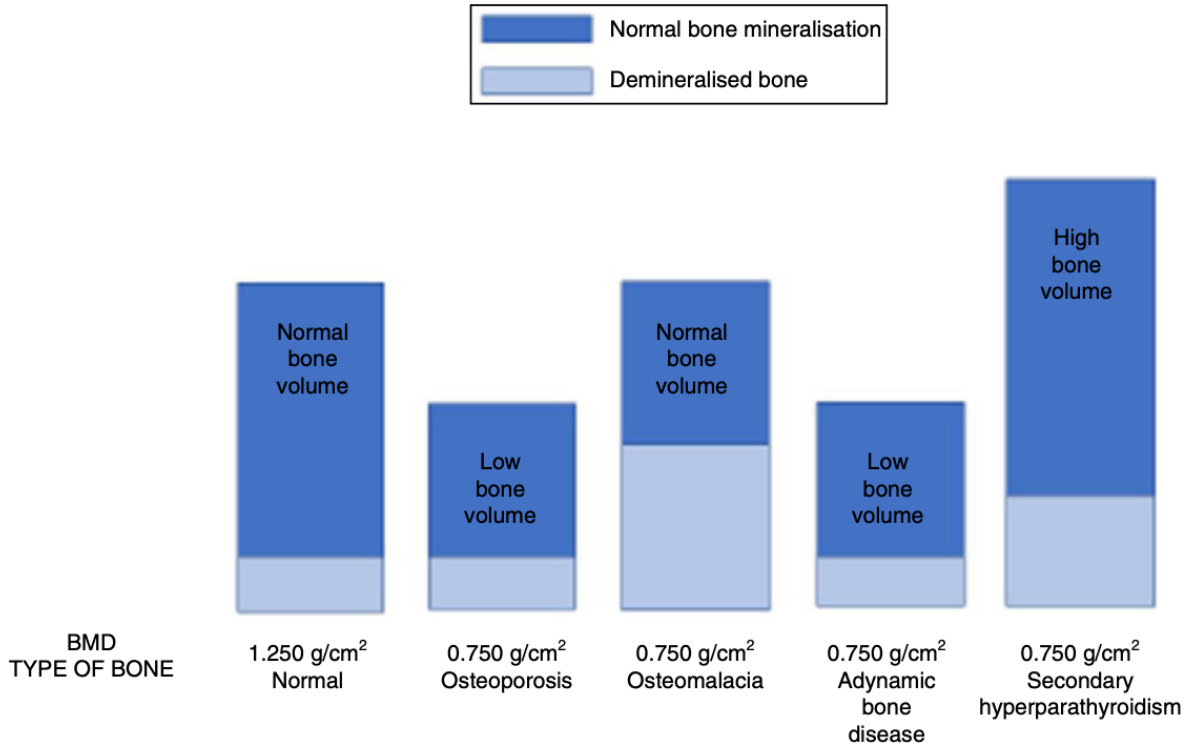
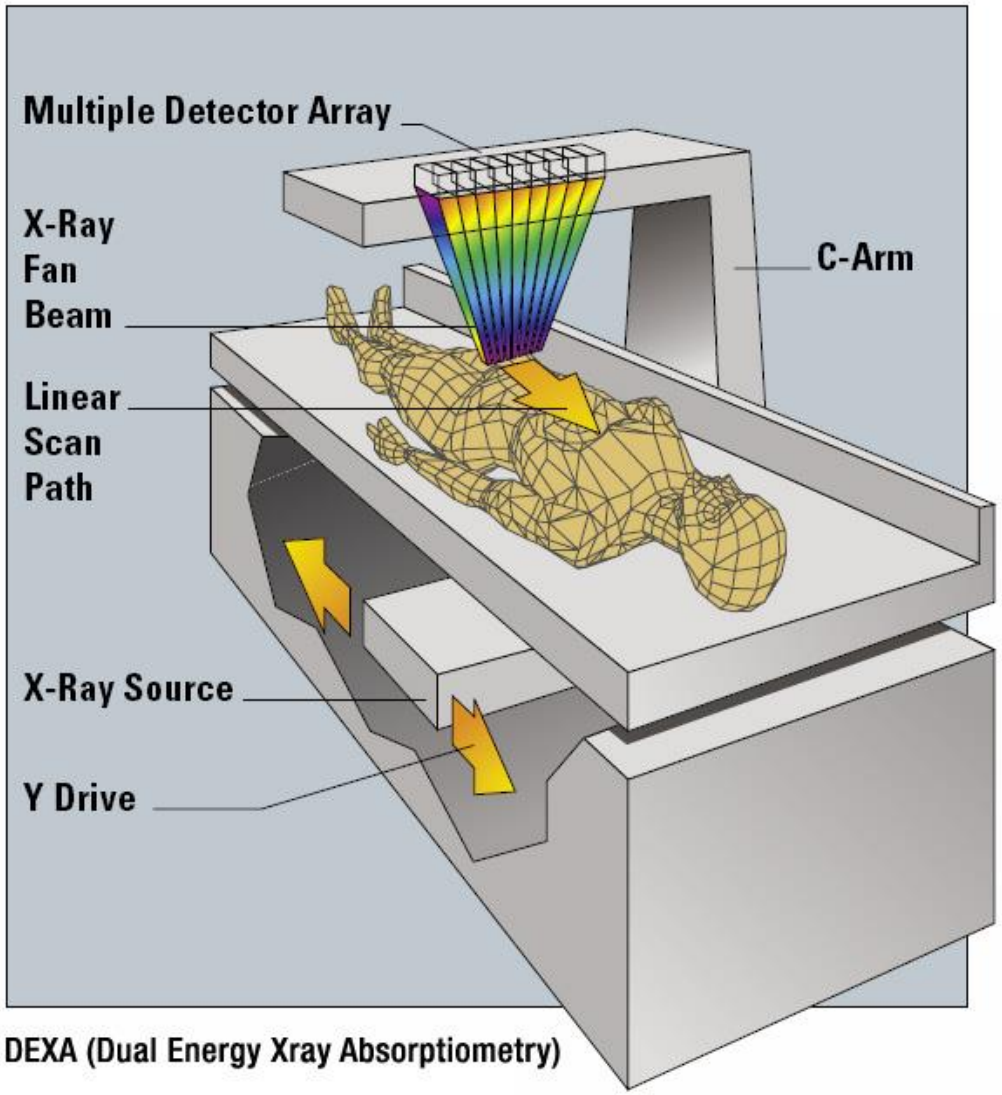
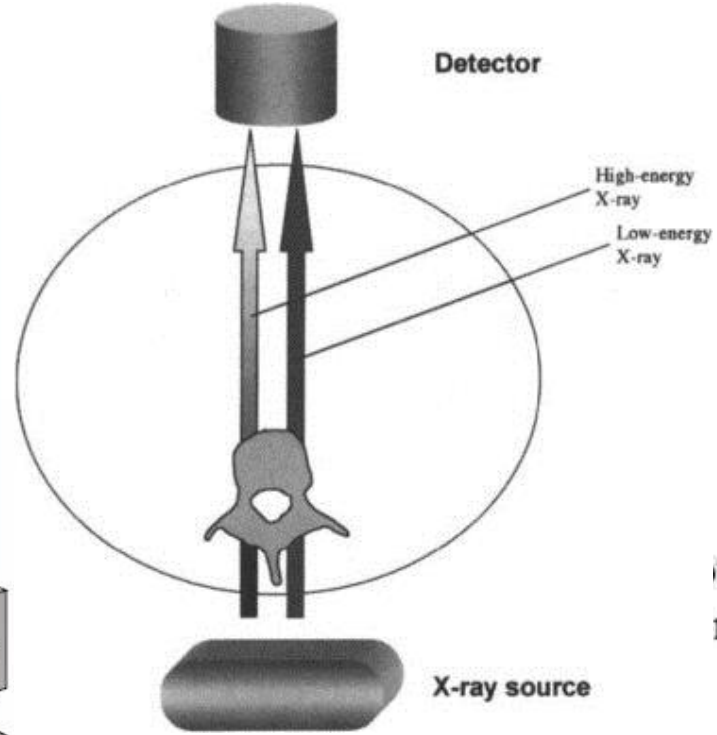


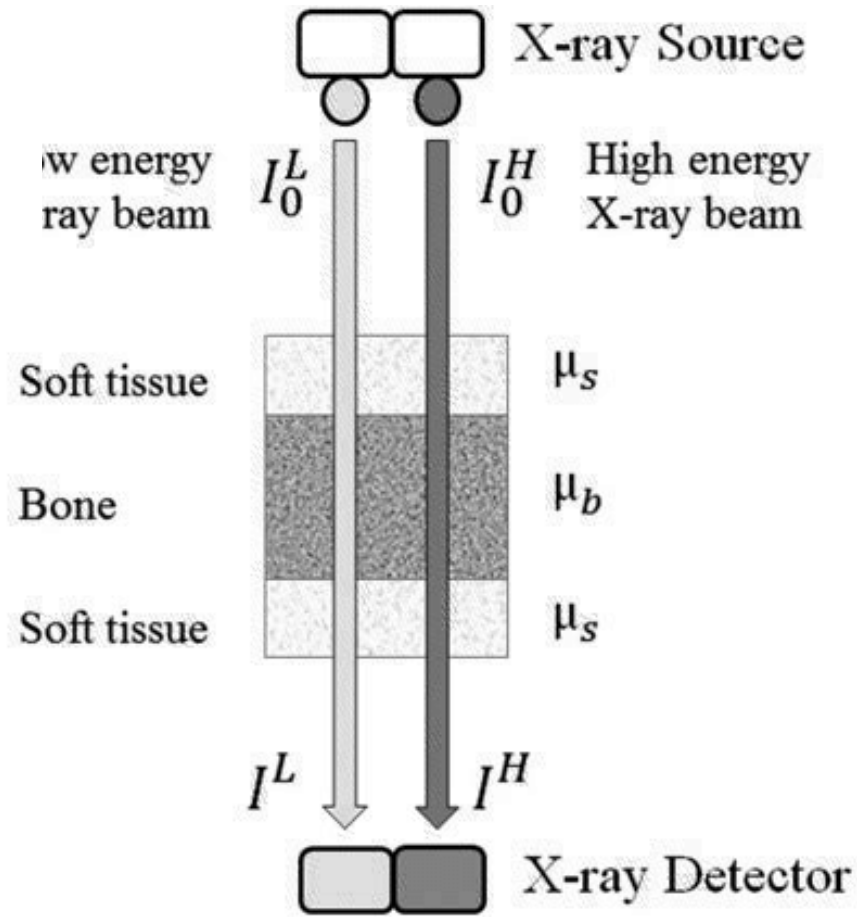
Fig. 6 – The image shows how different pathologies (senile osteoporosis or osteoporosis secondary to hypogonadism, osteomalacia, adynamic bone disease and secondary hyperparathyroidism) can show the same low bone mineral density (in this example, BMD = 0.750 g/cm^2) although they are caused by a completely different bone composition, and require different treatment strategies.[112,133]

Assessment of Bone Quantity and Quality



DEXA (Dual Energy Xray Absorptiometry)



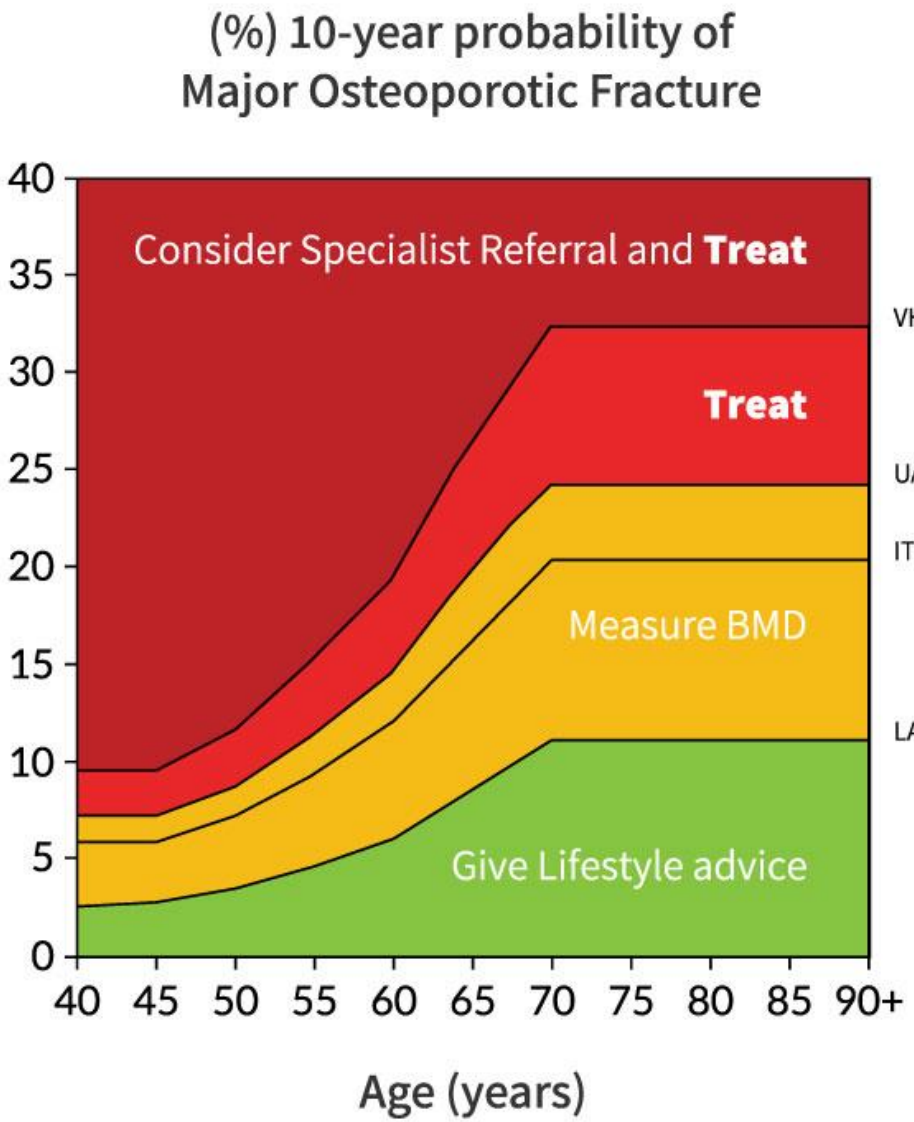


Vertebral Fracture Assessment

- Assessment for vertebral fractures by plain radiography or DEXA can increase recognition of patients with osteoporosis requiring treatment.

- Recommendations suggest that any CKD patient undergoing DEXA imaging and those with clinical suggestions such as loss of vertical height, kyphosis, or long-term glucocorticoid therapy should be assessed for vertebral fractures

FRAX



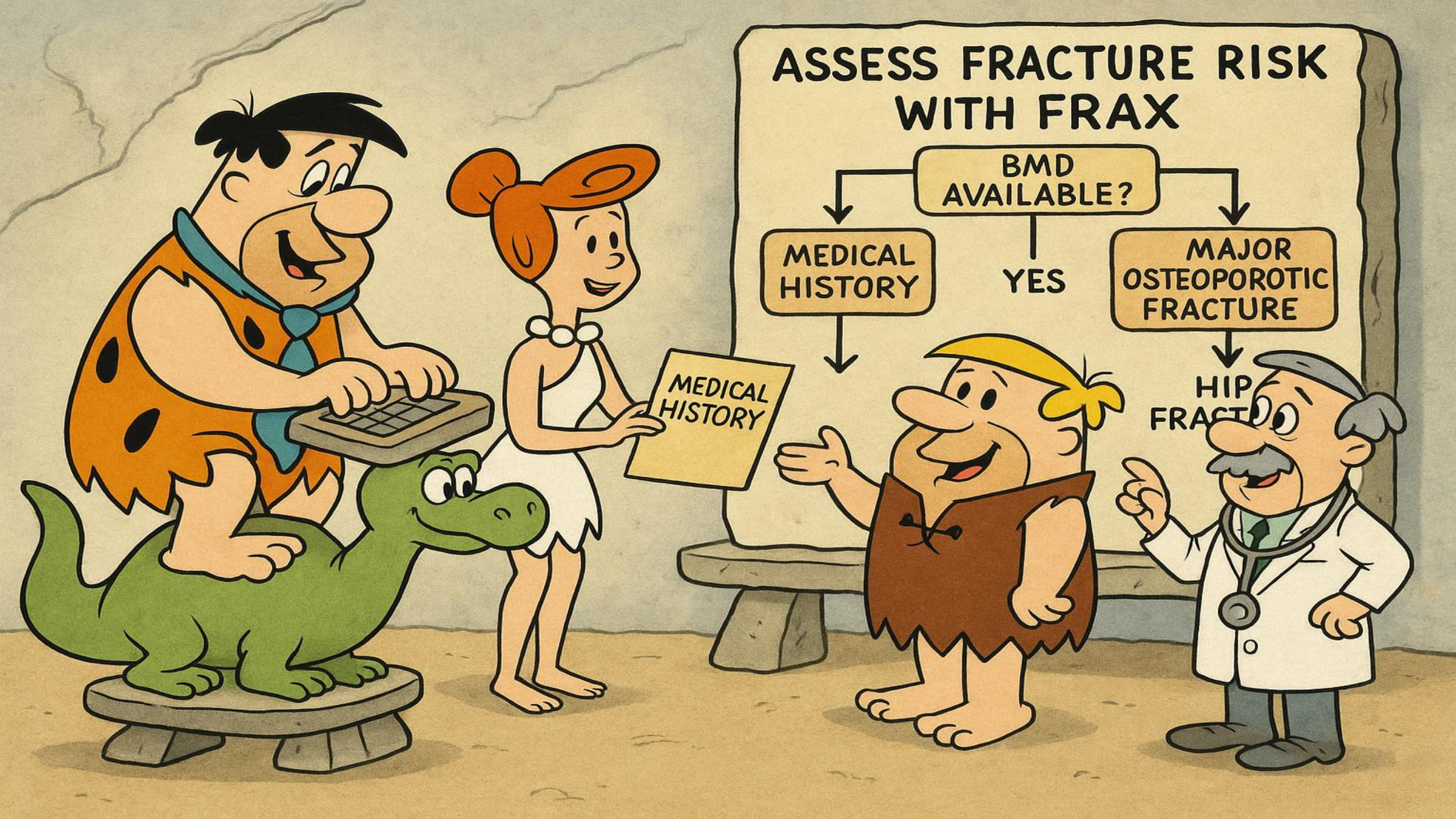
VHRT: Very high risk threshold

UAT: Upper assesment threshold

IT: Intervention threshold

LAT: Lower assesment threshold

Very high risk	Consider Specialist Referral and **Treat**
High risk	**Treat**
Intermediate risk	Measure **B**one **M**ineral **D**ensity (BMD)
Low Risk	Give lifestyle advice


ASSESS FRACTURE RISK WITH FRAX
BMD AVAILABLE?
MEDICAL HISTORY
YES
MAJOR OSTEOPOROTIC FRACTURE
HIP FRACT
MEDICAL HISTORY

Clinical Risk Factors Used in FRAX

- **Age**
- **Sex**
- **Weight**
- **Height**
- **Previous fracture** (after age 50)
- **Parental history of hip fracture**
- **Current smoking**
- **Glucocorticoid use**
- **Rheumatoid arthritis**
- **Secondary causes of osteoporosis** (e.g., type 1 diabetes, osteogenesis imperfecta, untreated hypogonadism, chronic liver disease, etc.)
- **Alcohol intake** ≥3 units/day
- **Femoral neck BMD** (optional but improves accuracy)

The Fracture Risk Assessment Tool (FRAX®) predicts fracture risk in patients with chronic kidney disease

Reid H. Whitlock[1,2], William D. Leslie[1], James Shaw[1], Claudio Rigatto[1,2], Laurel Thorlacius[1], Paul Komenda[1,2], David Collister[1], John A. Kanis[3,4] and Navdeep Tangri[1,2]

[1]Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; [2]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, Canada; [3]Center for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK; and [4]Institute for Health and Aging, Catholic University of Australia, Melbourne, Australia

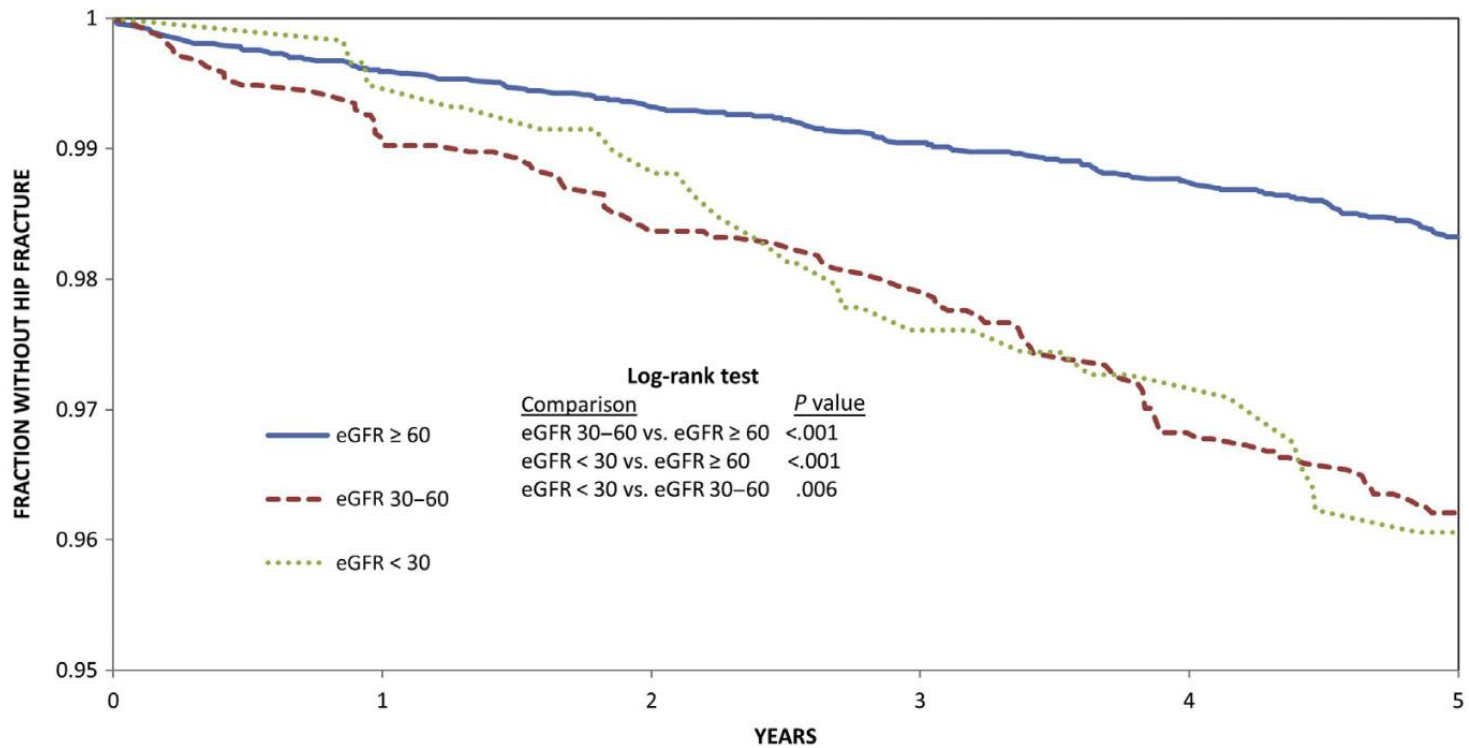


Figure 3 | Kaplan-Meier curve: time to hip fracture. eGFR, estimated glomerular filtration rate.

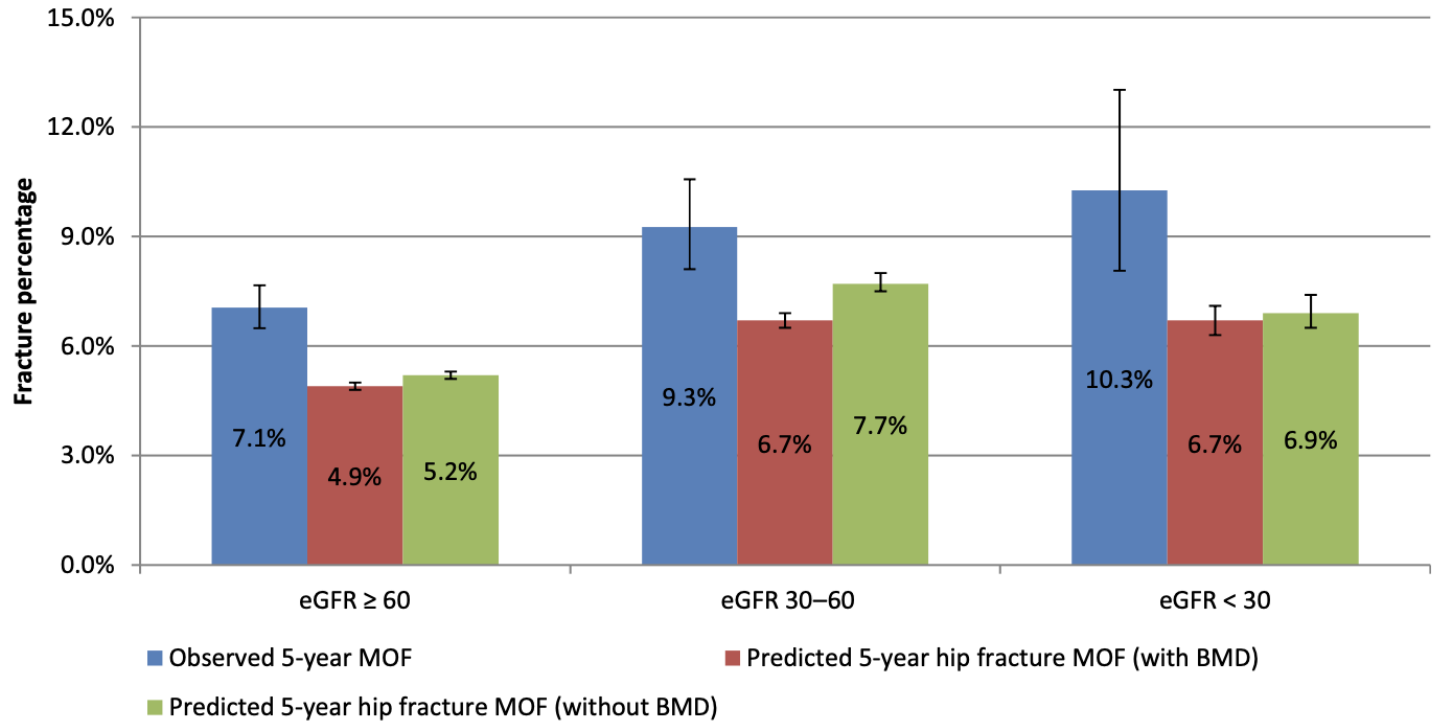


Figure 4| Observed versus predicted 5-year major osteoporotic fracture probability. BMD, bone mineral density; eGFR, estimated glomerular filtration rate; MOF, major osteoporotic fracture. Note: Error bars represent 95% confidence intervals.

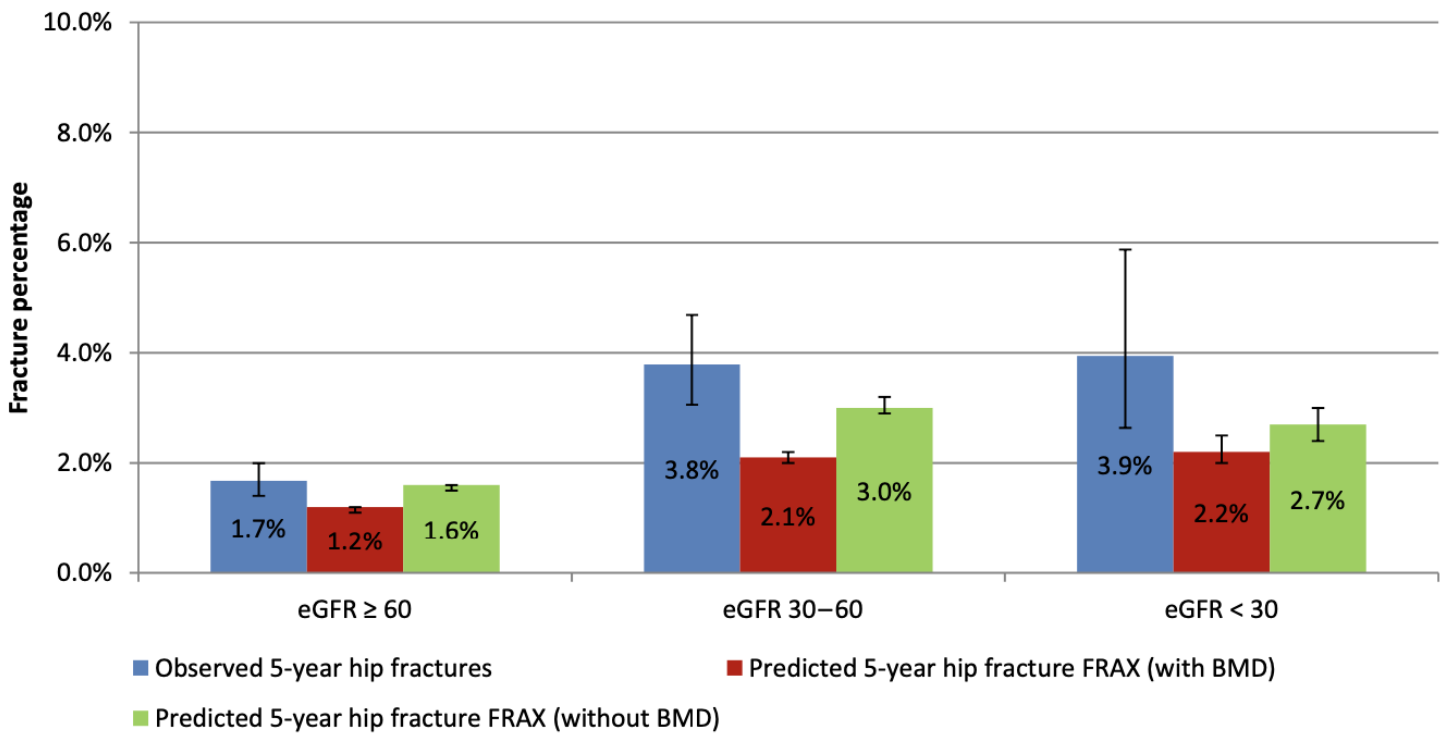


Figure 5 | Observed versus predicted 5-year hip fracture probability. BMD, bone mineral density; eGFR, estimated glomerular filtration rate. Note: Error bars represent 95% confidence intervals.

2 studies for FRAX in ESRD pts

- Poland >>> 2018; 781 pts; data sets were +ve
- >>> FRAX was predictive for both Hip & Major Osteoporotic Fx

- Japan >>> 2012; 485 pts; data sets were –ve,
- >>> FRAX was not predictive

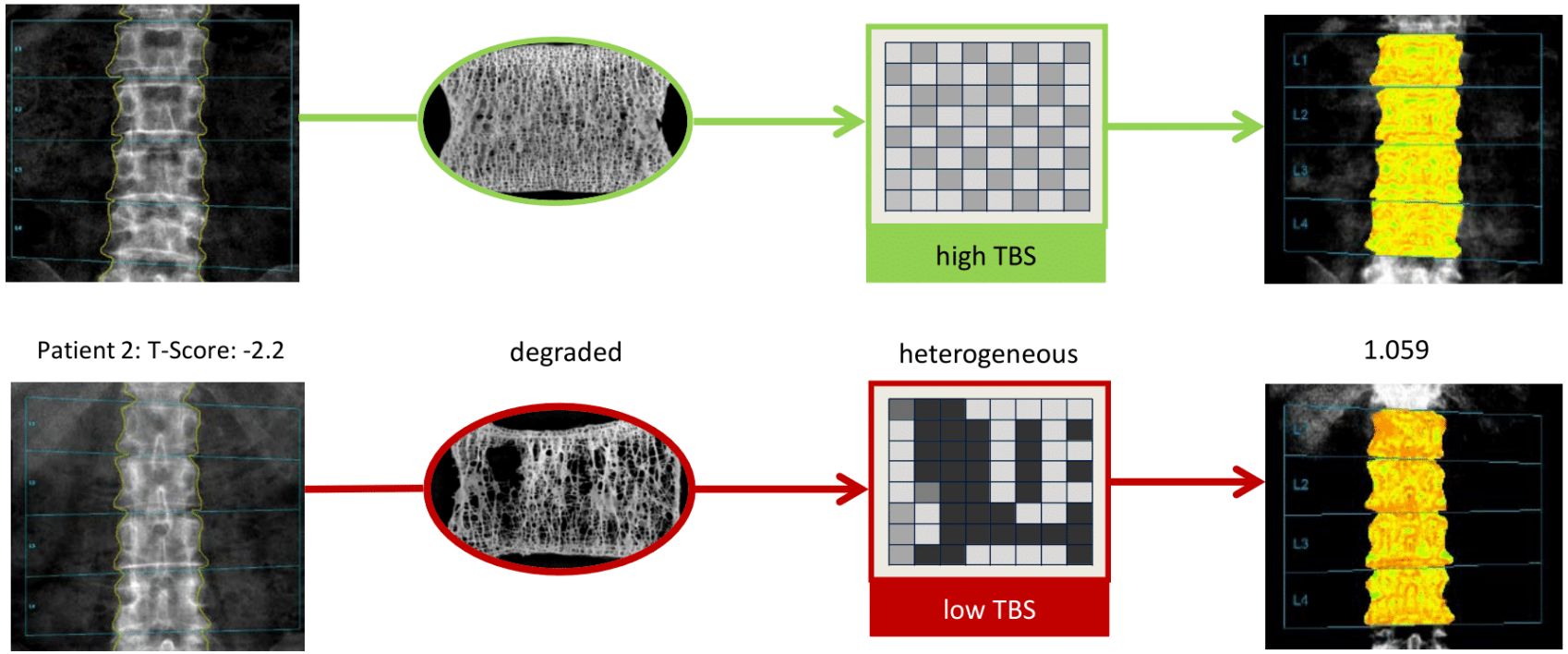
High *vs* low bone turnover

Cortical *vs* trabecular deterioration

CKD fractures are driven by microarchitectural failure, not mineral deficit alone.

Trabecular Bone Score

Same BMD (L1-L4)	Trabecular bone architecture	Gray scale pattern	TBS score (L1-L4) and mapping
Patient 1: T-Score: -2.2	normal	homogeneous	1.406
Patient 2: T-Score: -2.2	degraded	heterogeneous	1.059



In CKD G3–G5D,

low TBS often precedes BMD decline.


GUIDELINES

KDIGO Guidelines

- 2009: published the current definition of CKD-MBD & Suggested that BMD testing not be routinely performed

- BMD *does not* predict fracture risk as it does in the general population, and BMD *does not* predict the *type* of ROD”

- Cross-sectional data showing >>> there are *no association between low BMD and Fx risk in CKD*

Bone Mineral Density and Fracture Risk in Older Individuals with CKD

Robert H. Yenchek, Joachim H. Ix,†‡ Michael G. Shlipak,§‖ Douglas C. Bauer,‖ Nahid J. Rianon,¶ Stephen B. Kritchevsky,** Tamara B. Harris,†† Anne B. Newman,*‡‡ Jane A. Cauley,‡‡ and Linda F. Fried,*‡‡§§ for the Health, Aging, and Body Composition Study*

Summary

Background and objectives Kidney Disease Improving Global Outcomes guidelines recommend against bone mineral density (BMD) screening in CKD patients with mineral bone disease, due to a lack of association of BMD with fractures in cross-sectional studies in CKD. We assessed whether BMD is associated with fractures in participants with and without CKD in the Health, Aging, and Body Composition study, a prospective study of well functioning older individuals.

Design, setting, participants, & measurements Hip BMD was measured by dual-energy x-ray absorptiometry. Osteoporosis was defined as a femoral neck BMD (FNBMD) T score below −2.5 and CKD as an estimated GFR <60 ml/min per 1.73 m^2. The association of BMD with incident nonspine, fragility fractures to study year 11 was analyzed using Cox proportional hazards analyses, adjusting for age, race, sex, body mass index, hyperparathyroidism, low vitamin D level, and CKD. Interaction terms were used to assess whether the association of BMD with fracture differed in those with and without CKD.

Results There were 384 incident fractures in 2754 individuals (mean age 73.6 years). Lower FNBMD was associated with greater fracture, regardless of CKD status. After adjustment, the hazard ratios (95% confidence intervals) were 2.74 (1.99, 3.77) and 2.15 (1.80, 2.57) per lower SD FNBMD for those with and without CKD, respectively (interaction P=0.68), and 2.10 (1.23, 3.59) and 1.63 (1.18, 2.23) among those with osteoporosis in patients with and without CKD, respectively (interaction P=0.75).

Conclusions BMD provides information on risk for fracture in older individuals with or without moderate CKD.

Clin J Am Soc Nephrol 7: 1130–1136, 2012. doi: 10.2215/CJN.12871211

Conclusions. Hemodialyzed patients with low or high PTH or increased b-AP had a high fracture risk. BMD by Dual Energy X-ray Absorptiometry (DEXA), especially at the total hip region, was useful to predict any type of incident of fracture for females with low PTH or to discriminate prevalent spine fracture for every patient.

Nephrol Dial Transplant (2012) 27: 345–351
doi: 10.1093/ndt/gfr317
Advance Access publication 7 June 2011

Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study

Soichiro Iimori[1,2], Yoshihiro Mori[1], Wataru Akita[1], Tamaki Kuyama[1], Shigeru Takada[1], Tomoki Asai[1], Michio Kuwahara[1], Sei Sasaki[2] and Yusuke Tsukamoto[1]

KDIGO reversed their guidelines for DEXA screening

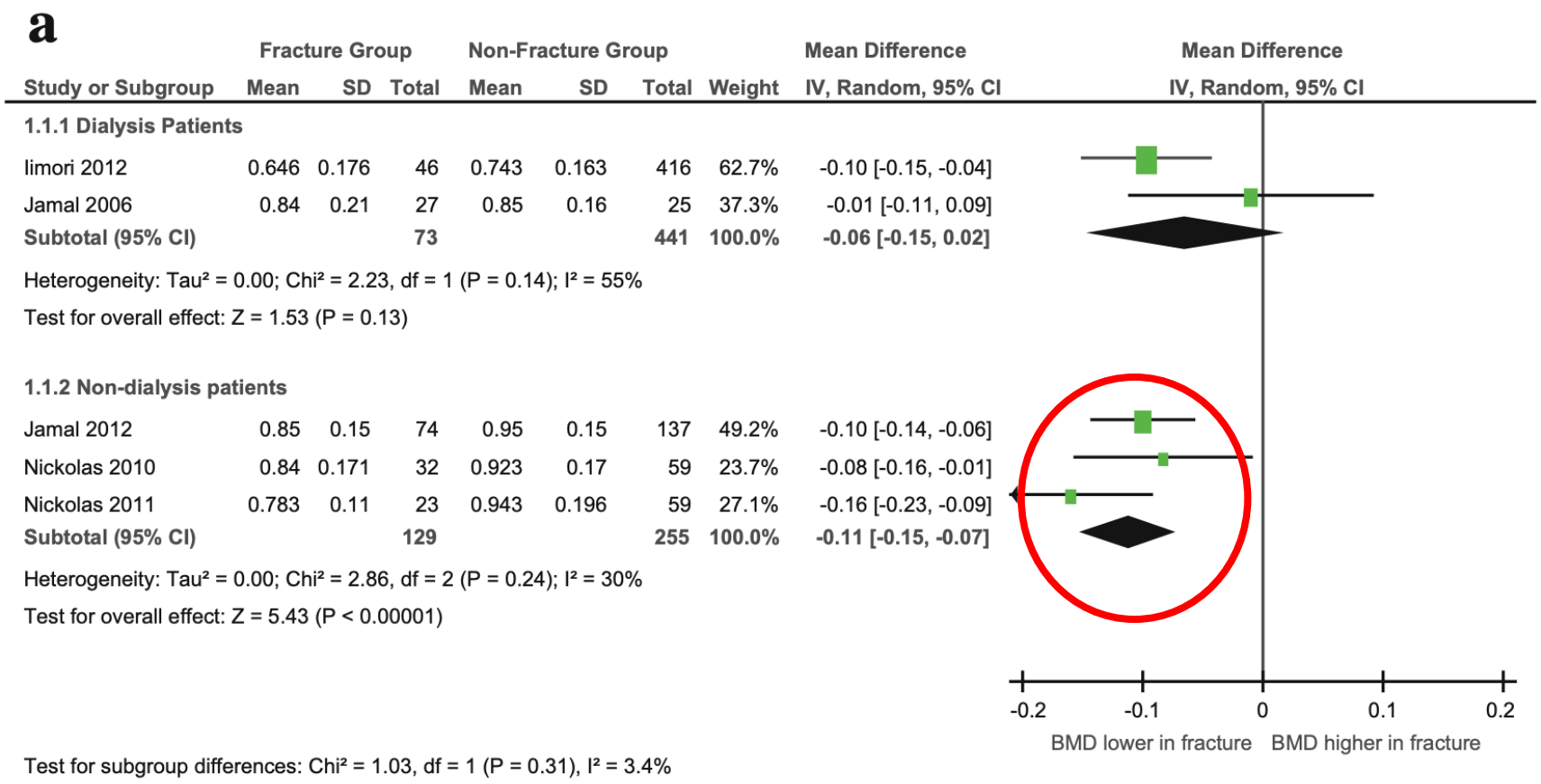
Osteoporos Int (2015) 26:449–458
DOI 10.1007/s00198-014-2813-3

ORIGINAL ARTICLE

Low bone mineral density and fractures in stages 3–5 CKD: an updated systematic review and meta-analysis

R. C. Bucur · D. D. Panjwani · L. Turner · T. Rader · S. L. West · S. A. Jamal

Screen pt with CKD & ESRD with DEXA



KDIGO Guidelines

- 2009: published the current definition of CKD-MBD & Suggested that BMD testing not be routinely performed

- 2017: suggested BMD testing to assess Fx risk ”if results will impact ttt decision”

KDIGO Guidelines

- 2009: formally published the current definition of CKD-MBD & Suggested that BMD testing not be routinely performed

- 2017: suggested BMD testing to assess Fx risk ”if results will impact ttt decision”

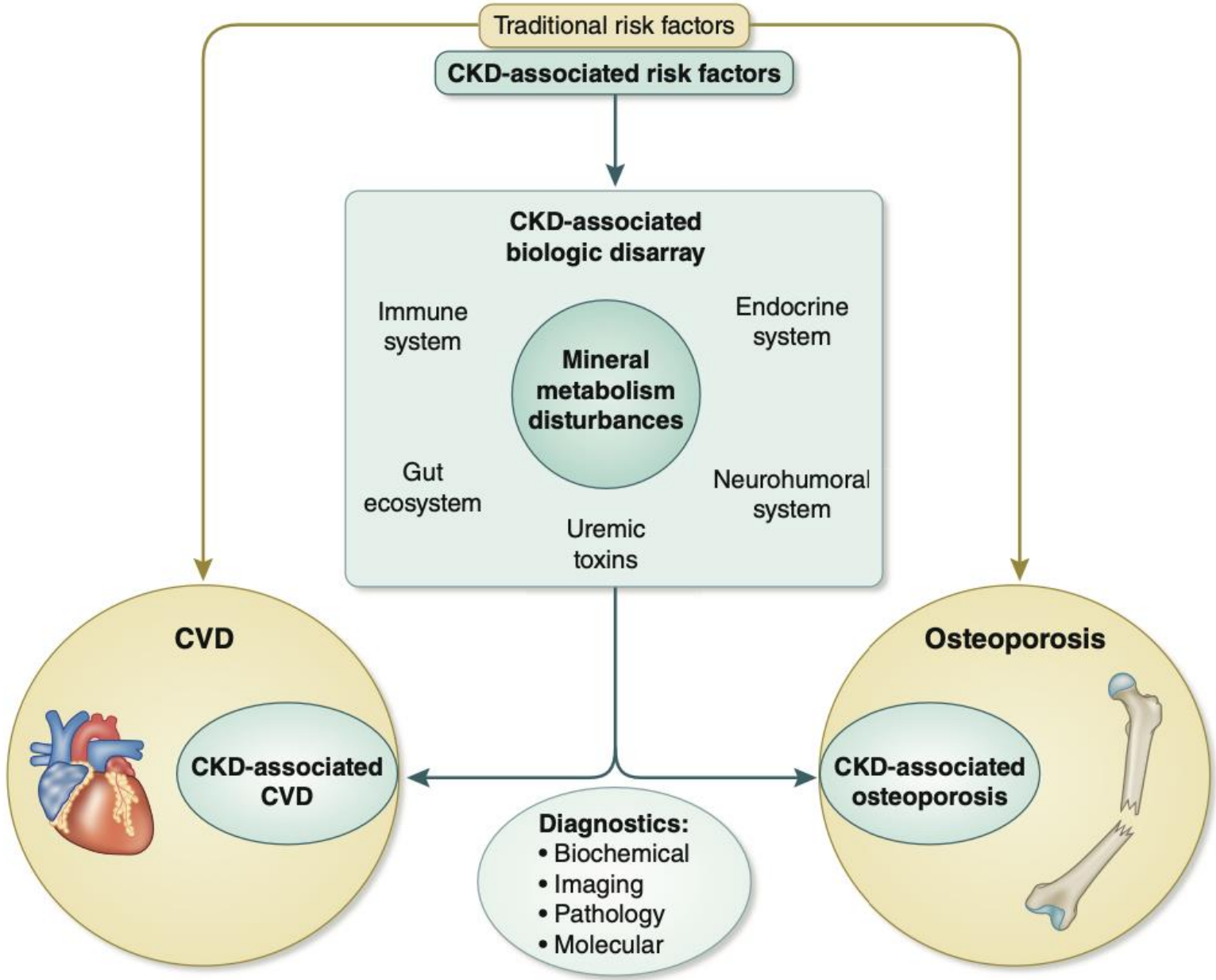
- 2023: consider reframing CKD-MBD in the context of 2 syndromes: CKD-associated OP & CKD-associated CVD

Results form the 2023 Controversies Conferences

- To move to a framework of 2 clinical sdrm in adults:
- 1- CKD-associated OP
- 2- CKD-associated CVD

- Both included within the more general disorders of the CV & skeletal systems.

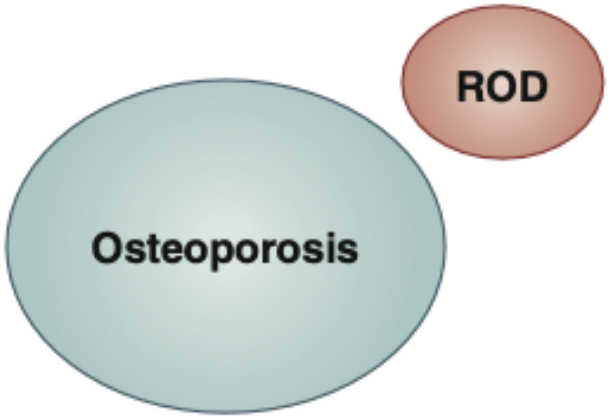
New conceptual framework moving towards personalized care in adults with CKD-MBD



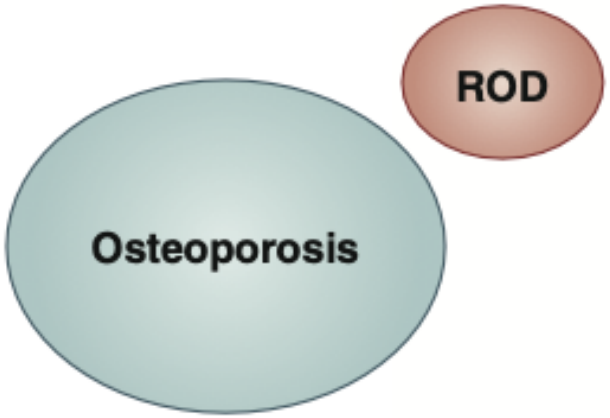
Chronic kidney disease–mineral and bone disorder: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

Markus Ketteler[1], Pieter Evenepoel[2,3], Rachel M. Holden[4], Tamara Isakova[5], Hanne Skou Jørgensen[6,7], Hirotaka Komaba[8], Thomas L. Nickolas[9], Smeeta Sinha[10,11], Marc G. Vervloet[12], Michael Cheung[13], Jennifer M. King[13], Morgan E. Grams[14], Michel Jadoul[15] and Rosa M.A. Moysés[16]; for Conference Participants[17]

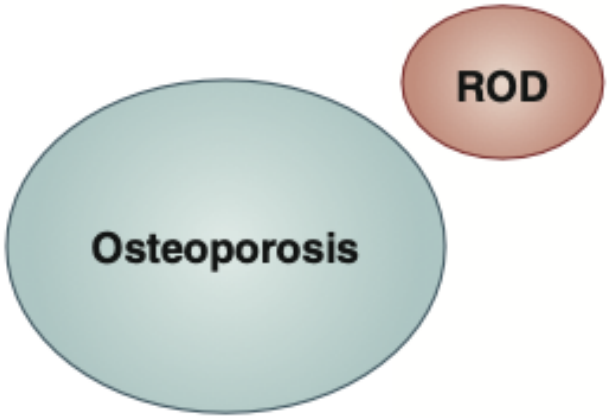


- **Osteoporosis** and **ROD** are separate entities and mutually exclusive diagnoses
- Diagnostic tools and therapeutic interventions are not interchangeable



- **Osteoporosis** and **ROD** are separate entities and mutually exclusive diagnoses
- Diagnostic tools and therapeutic interventions are not interchangeable

- **CKD patients** have a higher risk of fracture than the general population for all age groups
- **Osteoporosis** is defined as a disorder of bone that decreases bone strength, defined by bone mass and quality
- **ROD** is due to global disorders in bone strength
- **Therapies** for protecting against fractures must be personalized and based on bone turnover and mineralization



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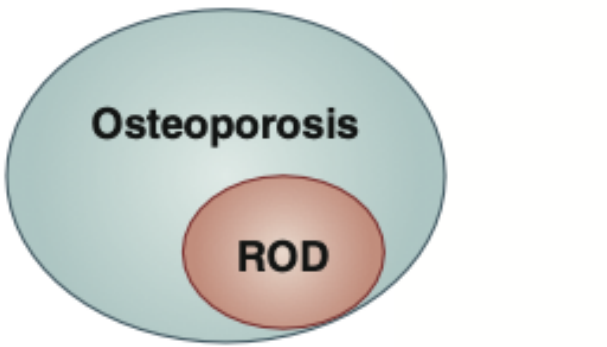

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- **Osteoporosis** is defined as a disorder of bone that decreases bone strength, defined by bone mass and quality
- **ROD** is due to global disorders in bone strength
- **Therapies** for protecting against fractures must be personalized and based on bone turnover and mineralization

All CKD patients with a significantly reduced BMD are diagnosed with OP, +/- ROD

Can we enhance the sensitivity of screening?

Table 2 | Bone turnover markers and fracture prediction in CKD

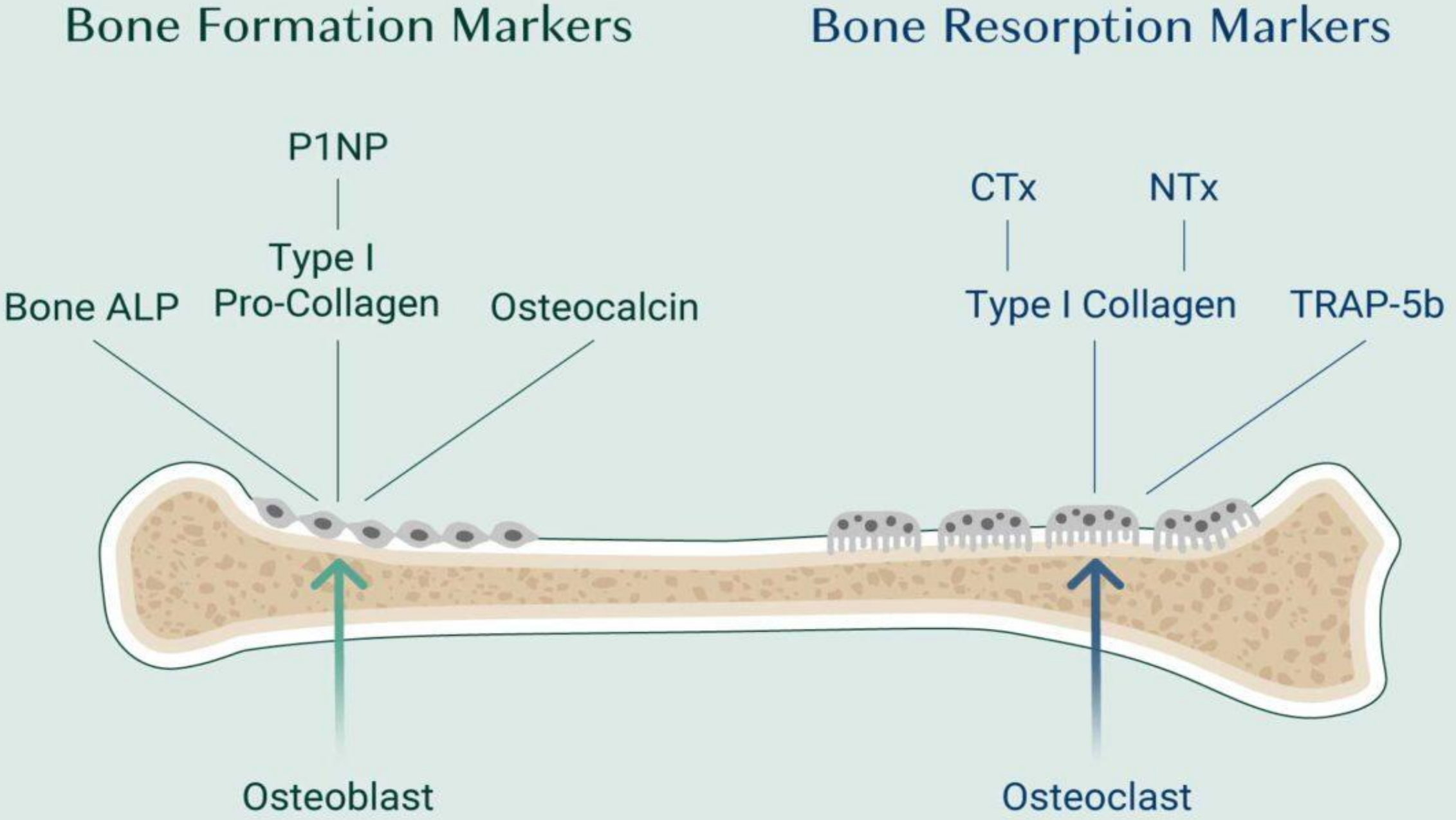
Study reference	Target group	Patients	Fracture incidence	Marker	HR or OR (95% CI)	AUC
Barrera-Baena *et al.*,[8] 2023, COSMOS study	CKD G5D, prevalent HD	6274	28.5/1000 pat. yr	PTH	HR 1.04 (1.01–1.08)	
Kashgary *et al.*,[9] 2023	CKD G5D, prevalent HD	328	20/1000 pat. yr	BALP	OR 1.004 (1.001–1.007)	0.665
				Osteoporosis	OR 1.003 (0.998–1.007)	NA
Matias *et al.*,[10] 2020	CKD G5D, prevalent HD	341	31/1000 pat. yr	Mean BALP	HR 1.21 (1.16–1.33)	
				Mean PTH <300/ >800 ng/l [>32 nmol/l/<85 nmol/l]	HR 1.24 (1.18–1.29)	
Iimori *et al.*,[11] 2012	CKD G5D, prevalent HD	485	19/1000 pat. yr	BALP	HR 1.04 (1.03–1.04)	0.766
				PTH	HR 1.00 (1.00–1.00)	NA
				DXA femoral neck	HR 0.96 (0.94–0.99)	0.610
				DXA total hip	HR 0.97 (0.94–0.99)	0.659
Chen *et al.*,[12] 2016	CKD G5D, prevalent dialysis	685 (629 HD, 56 PD)	33/1000 pat. yr	Fetuin A high vs. low	HR 0.34 (0.20–0.57)	
				PTH	HR 1.04 (1.008–1.12)	
Geng *et al.*, 2019[13]	CKD G3–G4	5108	Incidence 18%	PTH >101 ng/l [11 nmol/l] as continuous variable	HR 1.16 (0.93–1.45)	
Maruyama *et al.*,[14] 2014	CKD G5D, prevalent HD	185,277	16/1000 pat. yr	ALP	HR 1.011 (1.006–1.014)	

ALP, alkaline phosphatase; AUC, area under the curve; BALP, bone-specific alkaline phosphatase; CI, confidence interval; CKD, chronic kidney disease; COSMOS, Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study; DXA, dual-energy X-ray absorptiometry; HD, hemodialysis; HR, hazard ratio; NA, not available; pat. yr, patient year; OR, odds ratio; PD, peritoneal dialysis; PTH, parathyroid hormone.

KDIGO tell us that we can use bone biomarkers

PTH & bsAlp can work, can be used to evaluate bone disease in the clinic

No need always to go for BBx


Bone Formation Markers
Bone Resorption Markers
P1NP
Type I
Pro-Collagen
Bone ALP
Osteocalcin
CTx
NTx
Type I Collagen
TRAP-5b
Osteoblast
Osteoclast

U-shaped PTH & Survival in ESRD

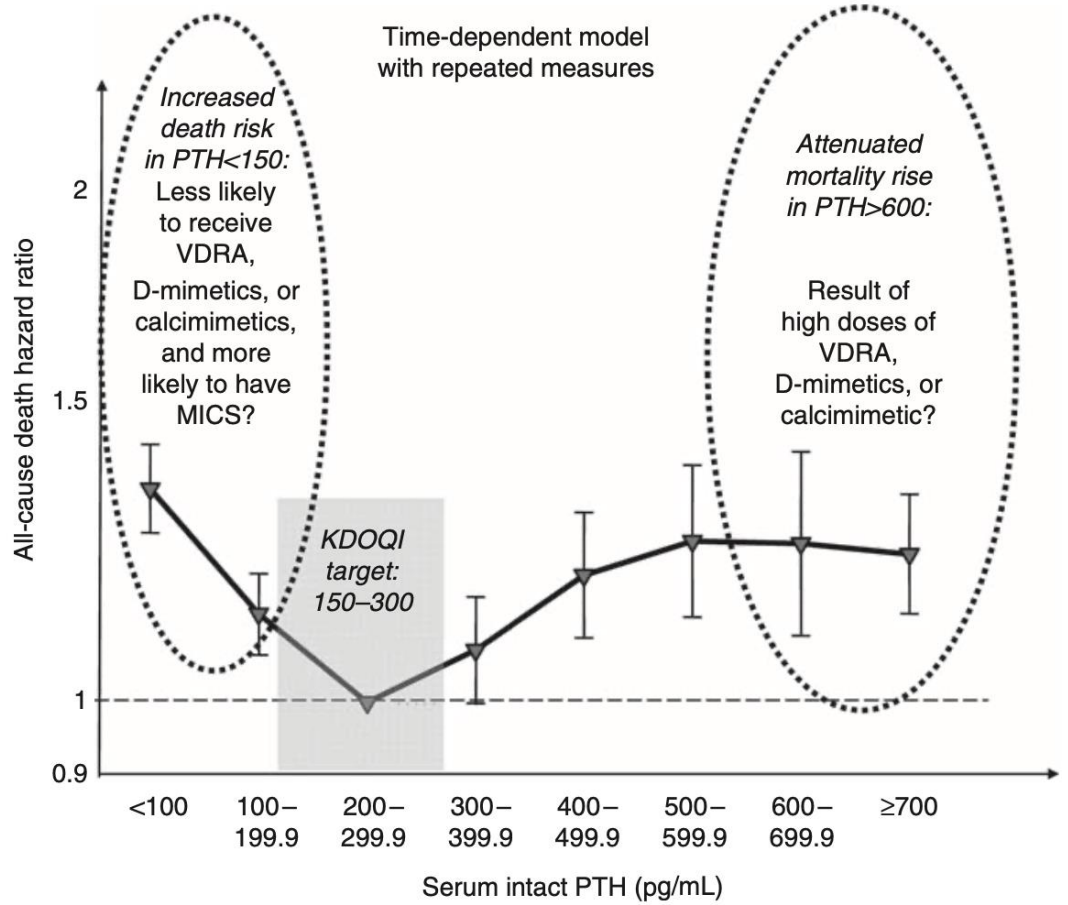


Figure 2 | The U-shaped association between serum intact parathyroid hormone (PTH) and survival in 58,058 maintenance hemodialysis patients over 2 years (adapted from Kalantar-Zadeh *et al.*[15]). KDOQI, Kidney Disease Outcome Quality Initiative; MICS, malnutrition–inflammation complex; VDRA, vitamin D receptor activator.

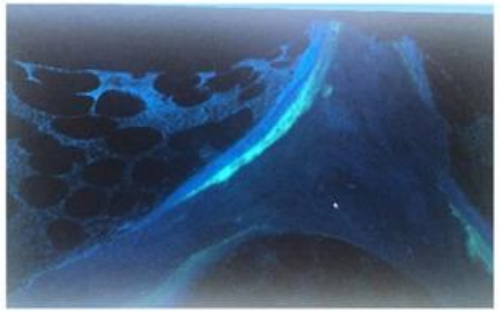
Diagnostic Accuracy of Noninvasive Bone Turnover Markers in Renal Osteodystrophy

Methods

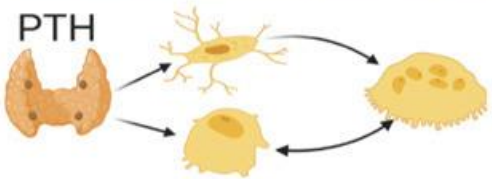
Participants

N = 199 kidney transplant candidates and recipients

Bone biopsy



Bone biomarkers

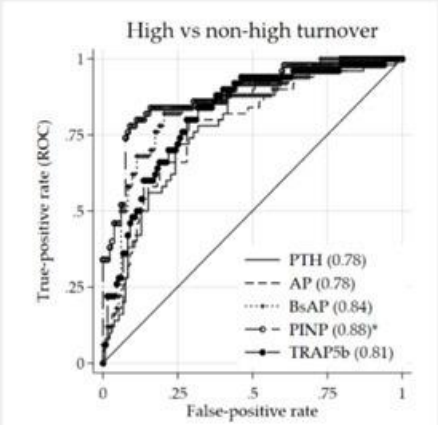


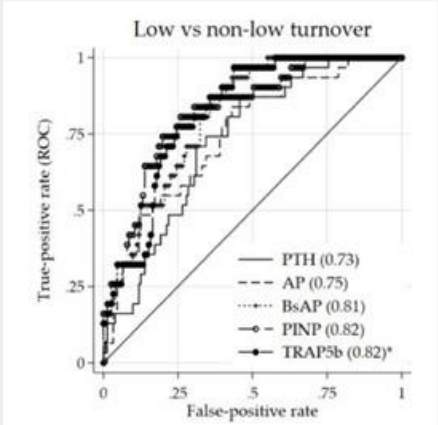
BsAP
P1NP

TRAP5b

Exploration Set (N = 100)

Optimal Diagnostic Cutoffs



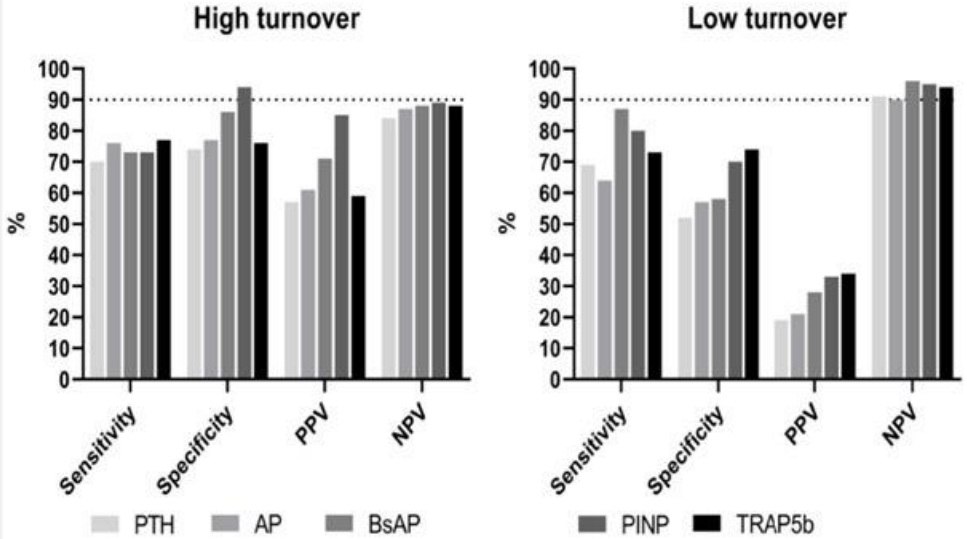


Two-step approach

i) Estimation of optimal diagnostic cutoffs
ii) Validation of cutoffs in a separate cohort

Validation Set (N = 99)

Diagnostic Performance



Results

High negative predictive values were found for both high and low bone turnover

CONCLUSION: Circulating bone turnover markers show acceptable diagnostic performance for bone turnover and may be used to rule out high and low bone turnover.

Hanne Skou Jørgensen, Geert Behets, Liesbeth Viaene, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2021.07.027

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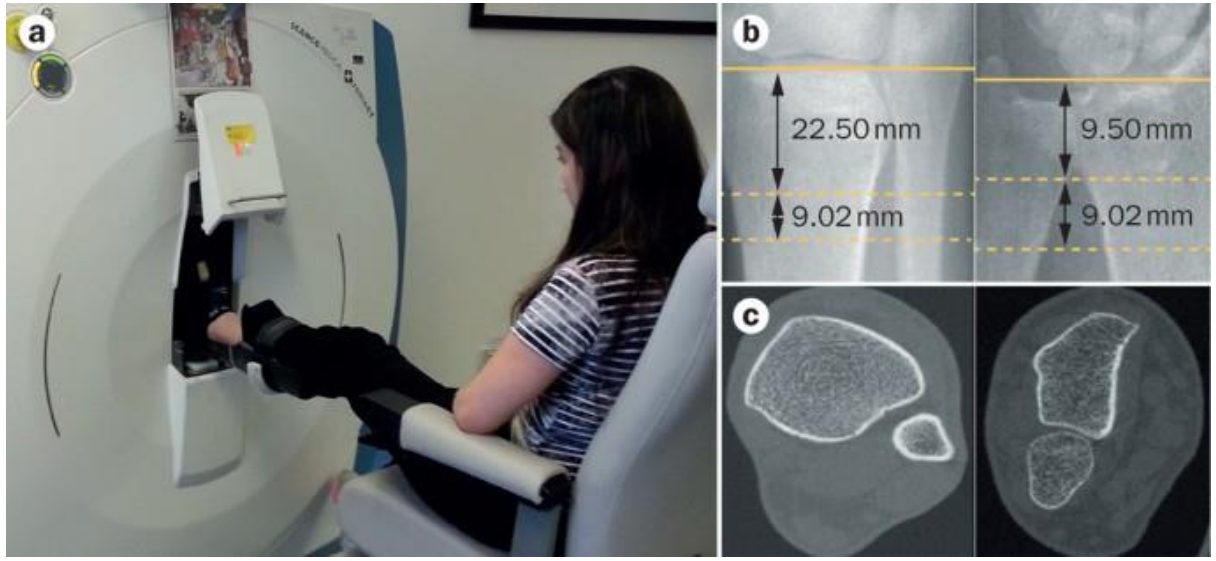
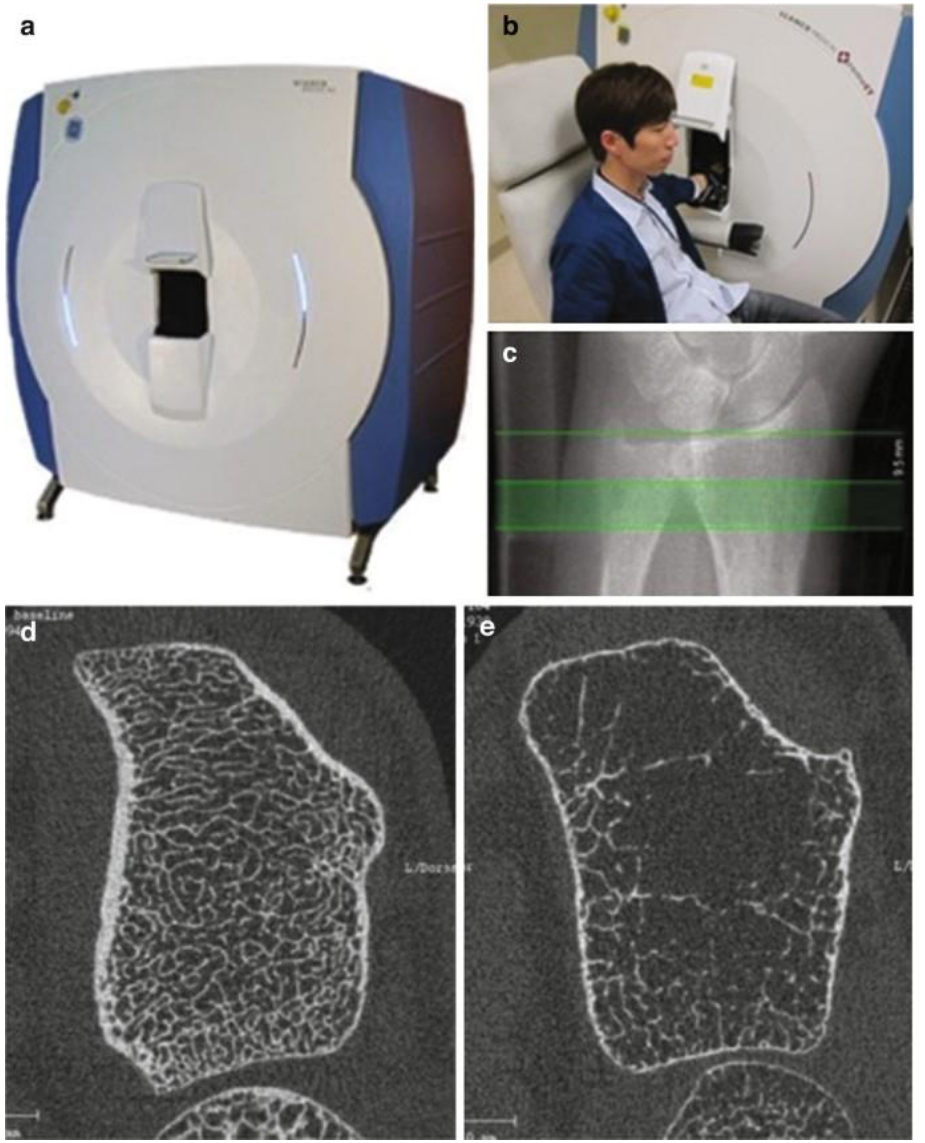
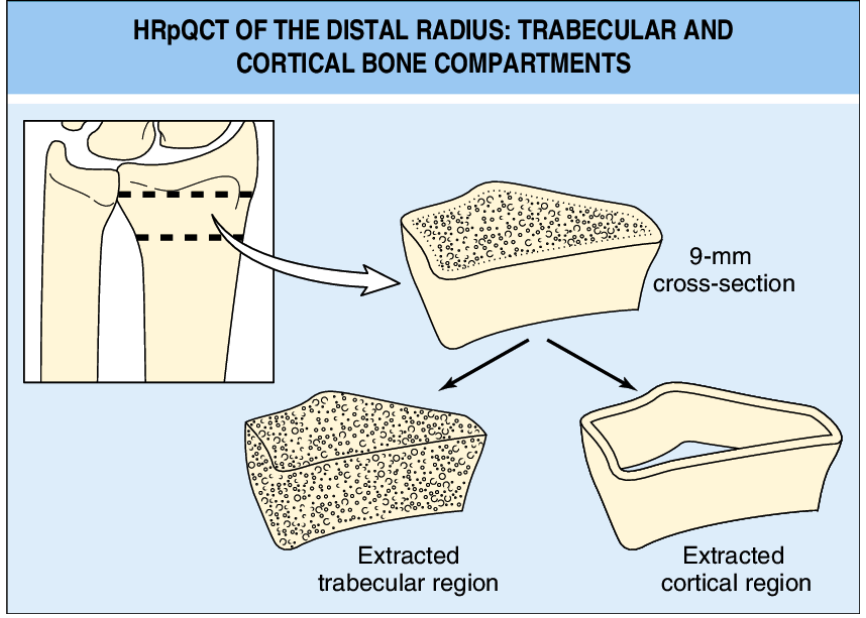
AMERICAN JOURNAL OF KIDNEY DISEASES

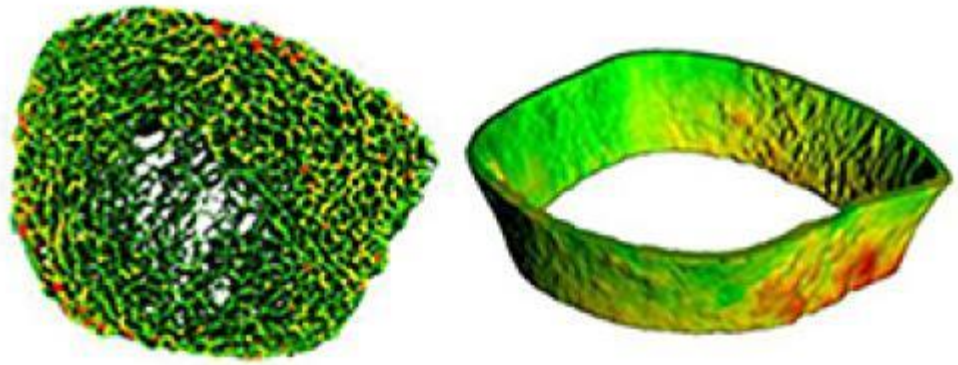
HR-pQCT

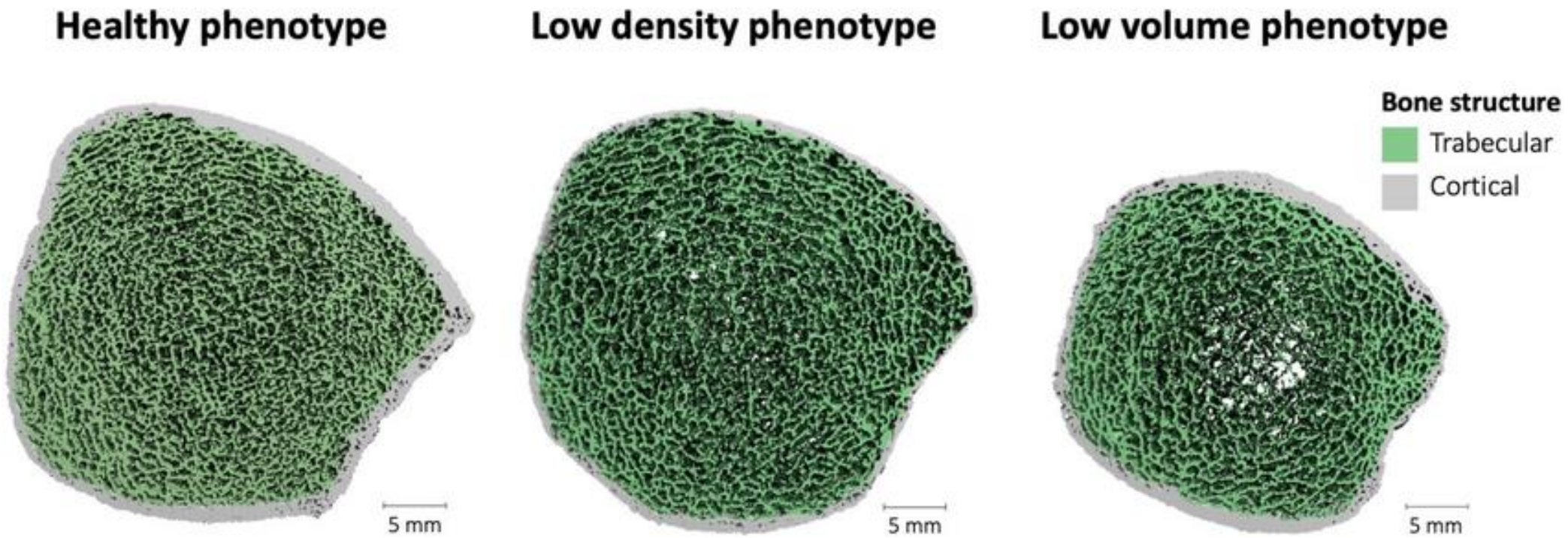


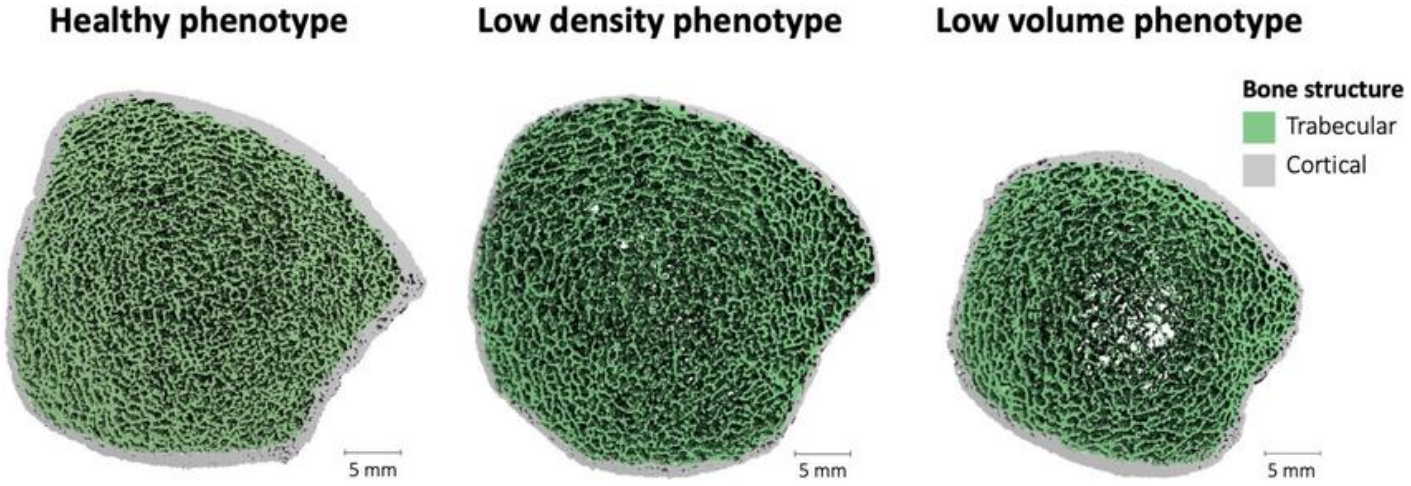
Quantifies both bone density & bone quality (micro-architecture)
Detects early changes in bone quality seen in **CKD**
Poor micro-architecture contributes to Fx risk
independently of BMD




HRpQCT OF THE DISTAL RADIUS: TRABECULAR AND CORTICAL BONE COMPARTMENTS
9-mm cross-section
Extracted trabecular region
Extracted cortical region




Healthy phenotype
Low density phenotype
Low volume phenotype
Bone structure
Trabecular
Cortical
5 mm
5 mm
5 mm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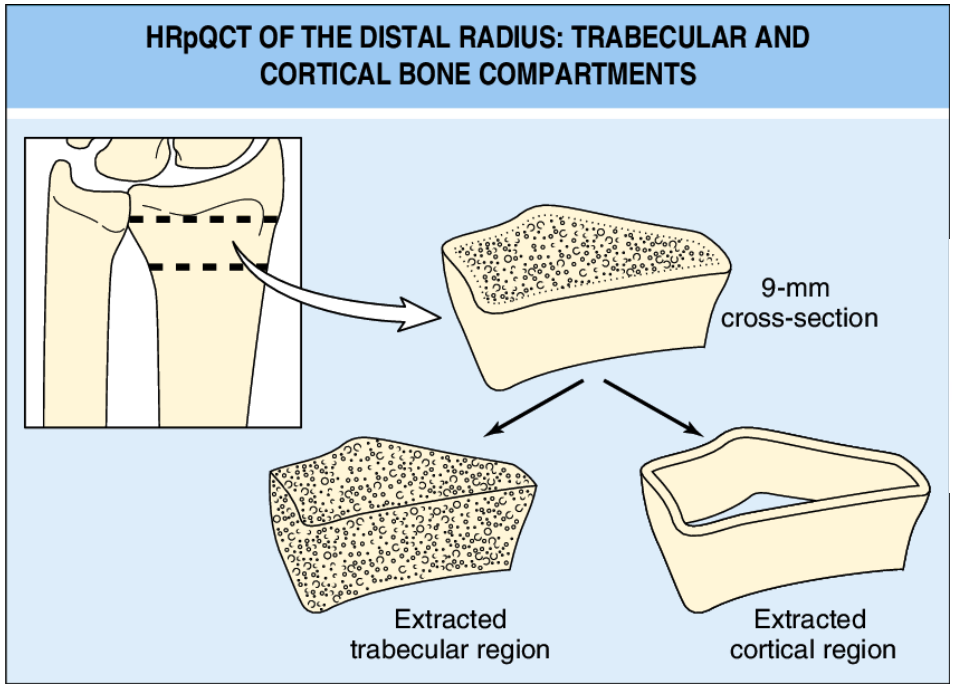
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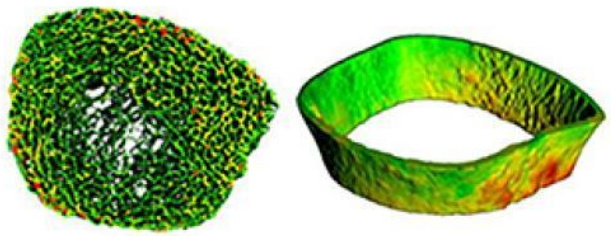
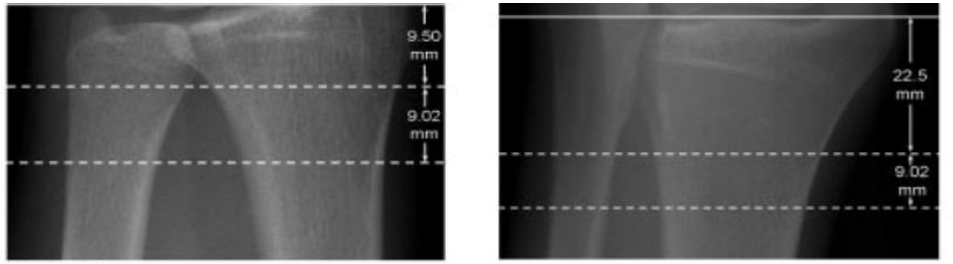
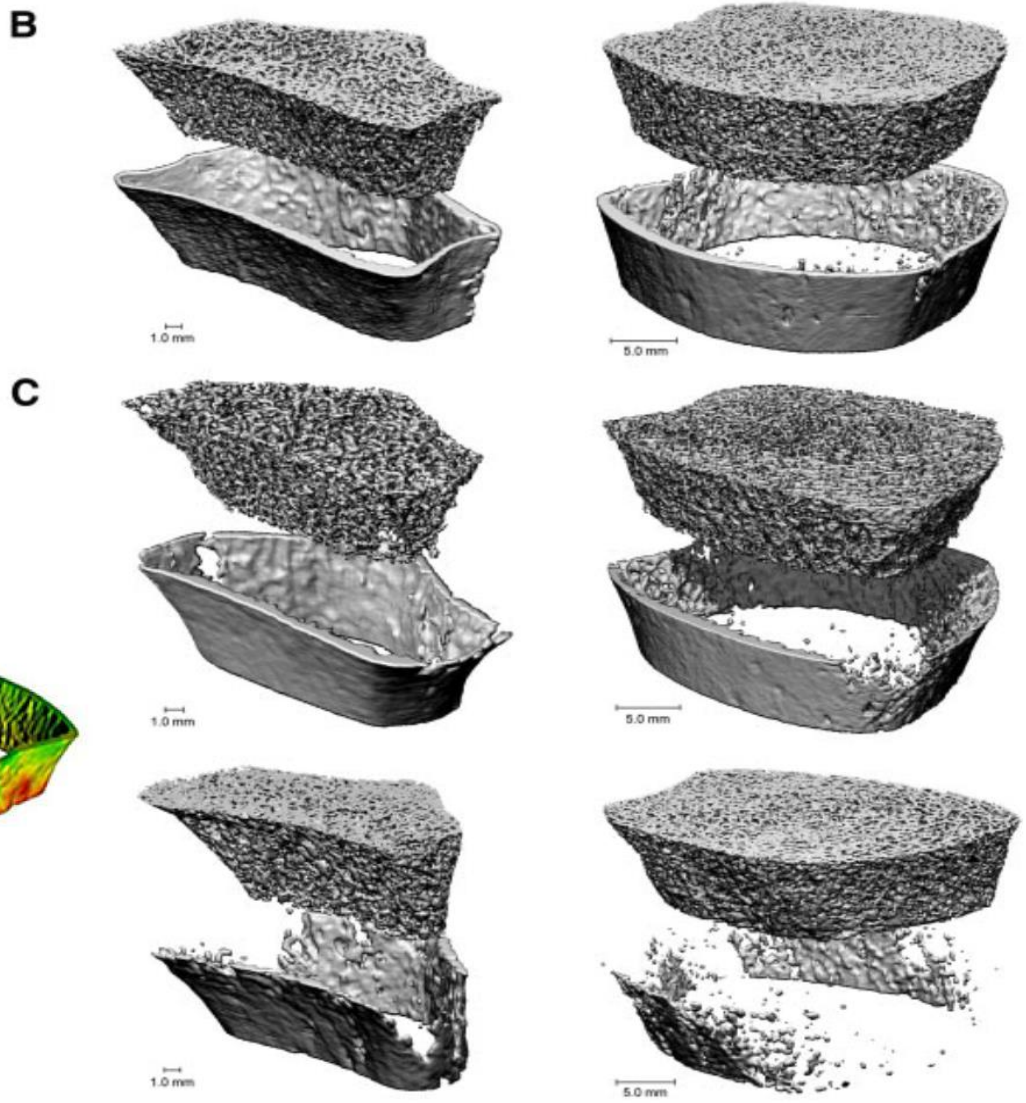


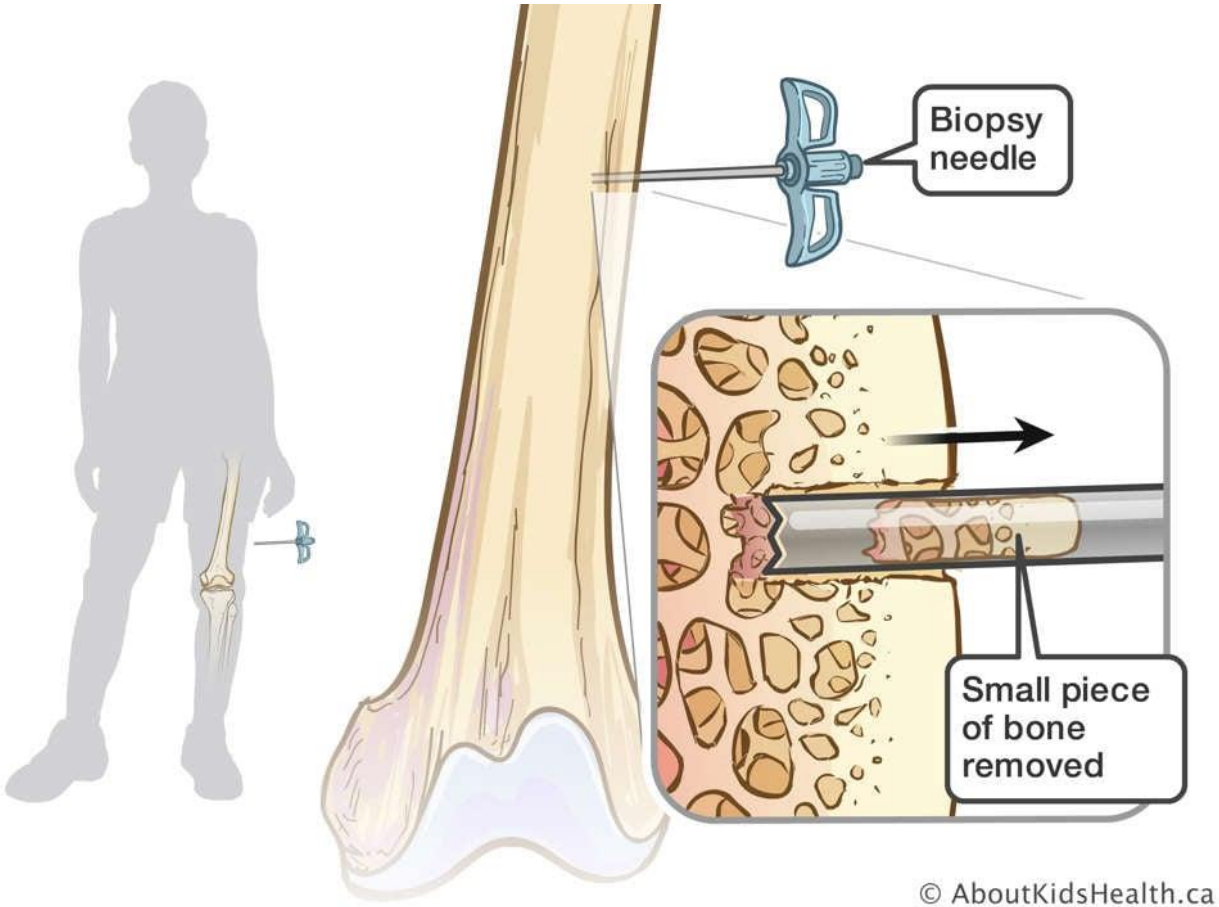

9.50 mm
9.02 mm
22.5 mm
9.02 mm

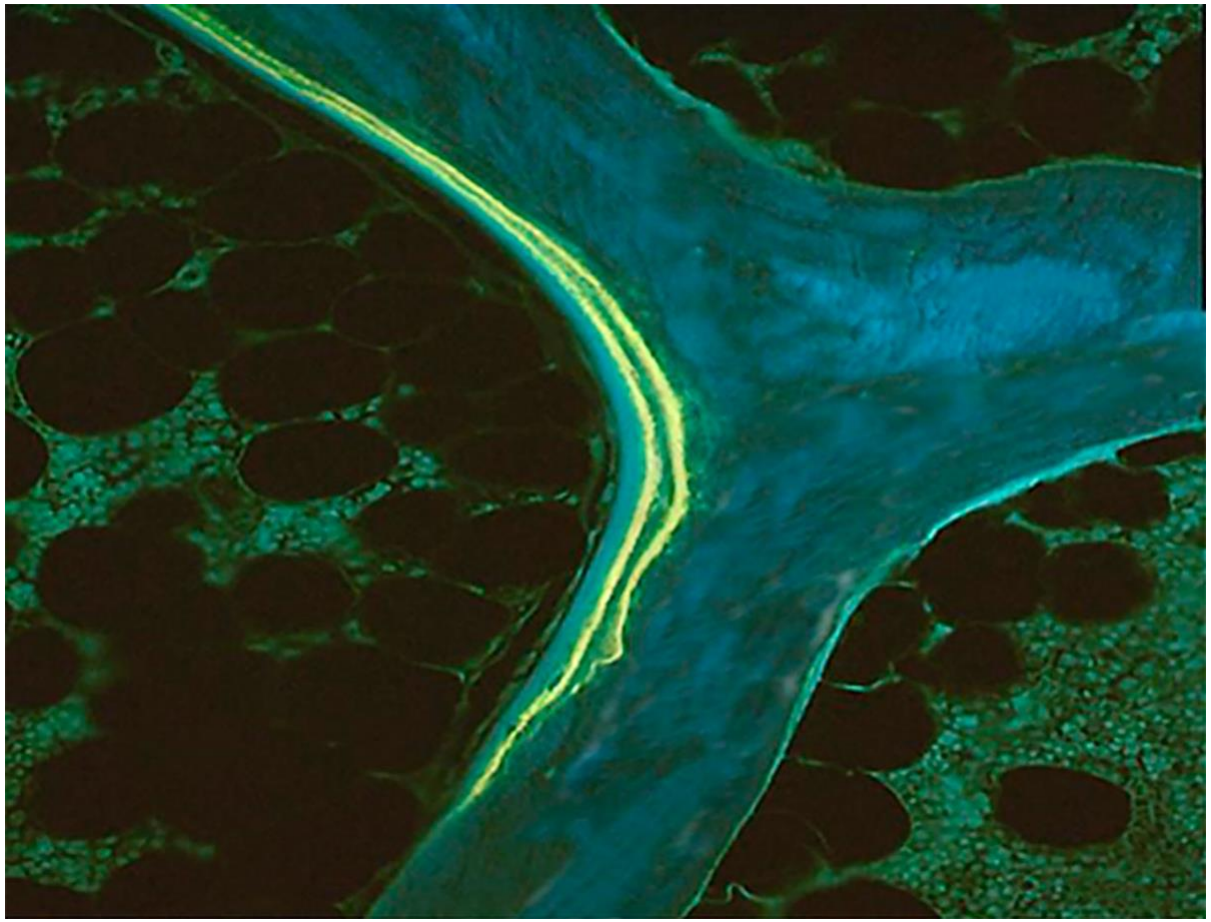

B
C
1.0 mm
5.0 mm
1.0 mm
5.0 mm
1.0 mm
5.0 mm

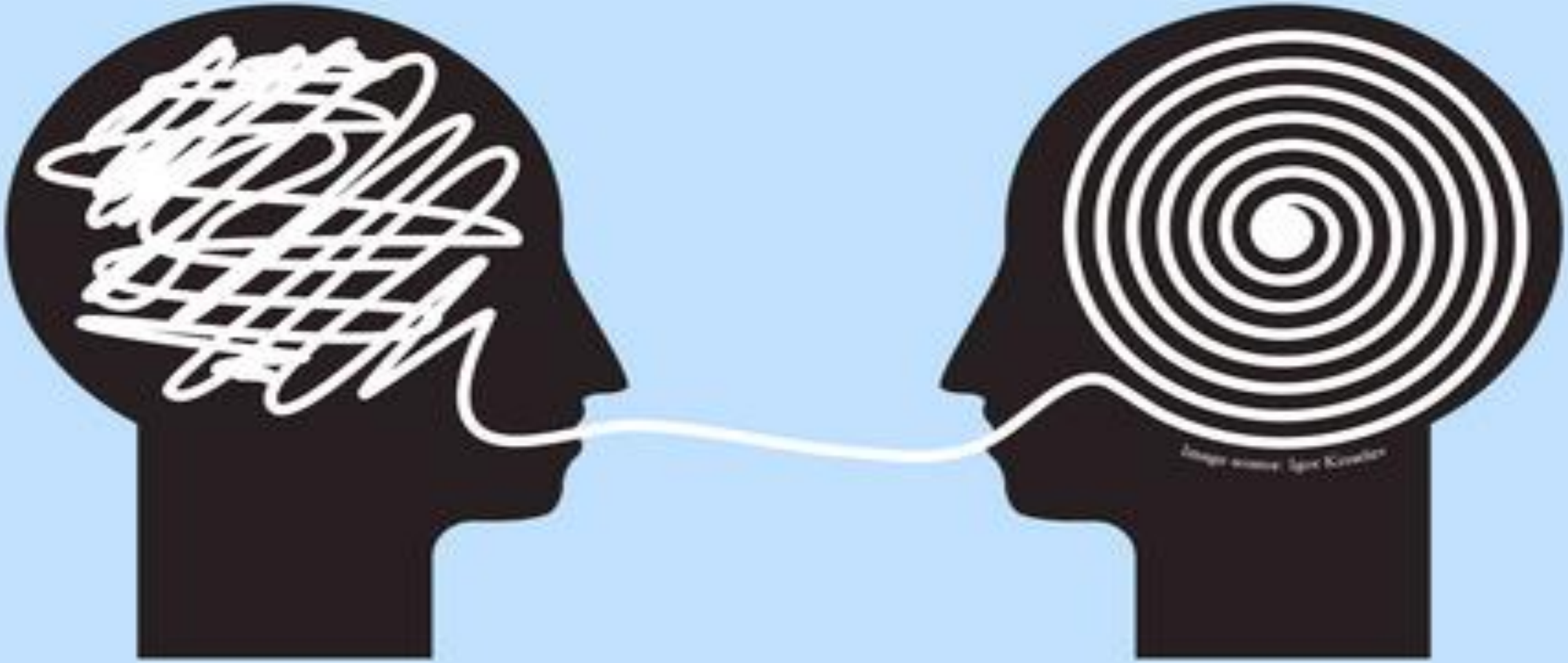
Bone histomorphometry

If everything fails >>> BBx

Bone Biopsy is the Gold Standard @ the iliac crest







Why management is really unclear and challenging in CKD ?

- 1- Kidney pts are complex and the pathophysiology is complex

  traditional and kidney related risk factors for Fx

  High and Low bone turnover lead to low bone strength but they have really different ttt !

- 2- Inadequate Dx tools

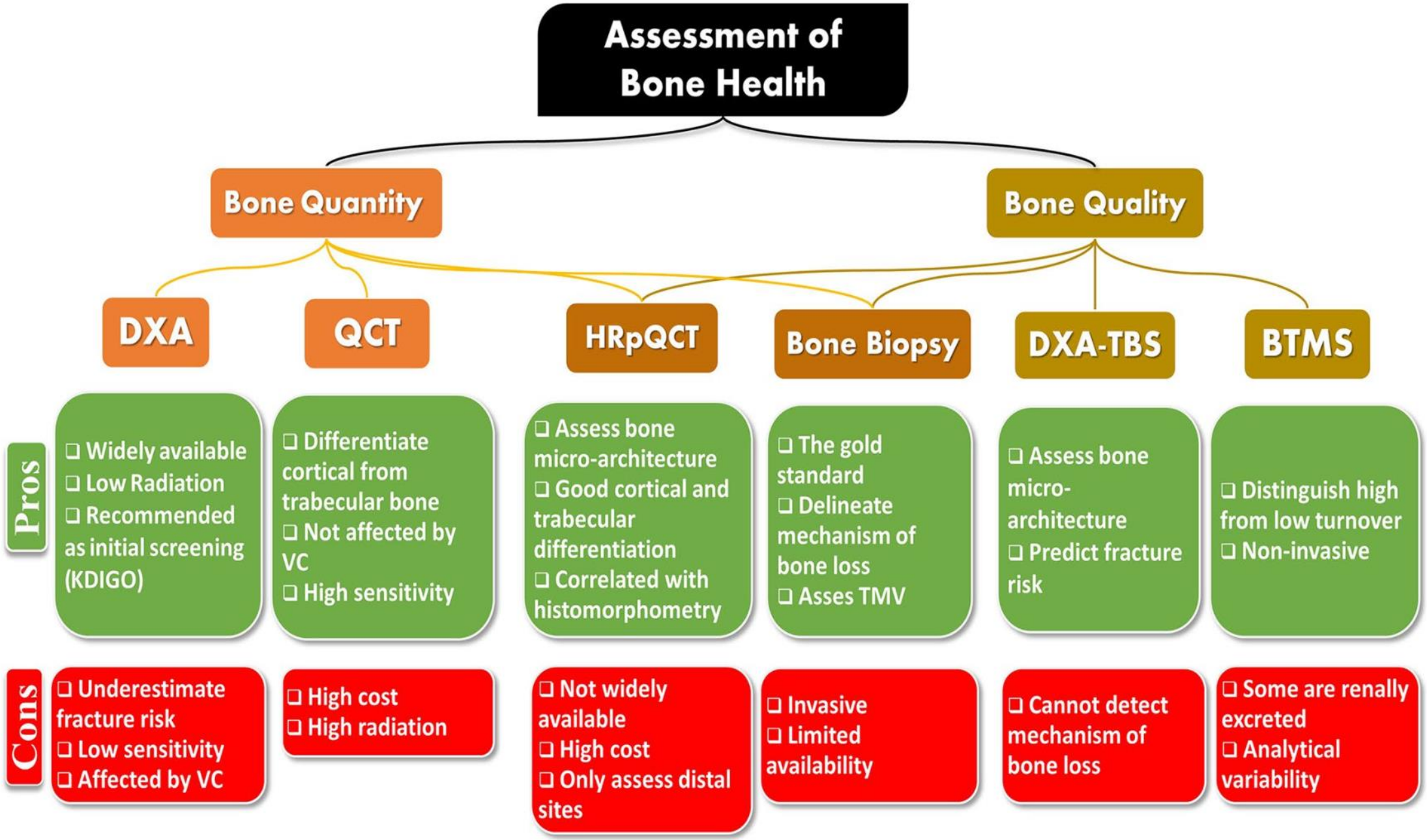
  DEXA gives information about the quantity or the density of bones, but tells nothing about the quality of bones, like turnover and mineralization, that are important for pts with CKD

  Knowing about the quality of bone, is very important and we have very limited tools to figure out that.

- 3- Unclear risk benefit profiles of ttt

  NO, Primary RCT with **Fx outcomes** in CKD 3-5 including Dx pts, they are just BMD outcomes !

Conclusion


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

Final thoughts

- Patients with CKD have a **higher risk of bone fractures** than the general population
- CKD-OP is due to global impairments in bone quality & strength
- Fx rates & clinical outcomes are worse for CKD pts than the general population
- CKD pts should be risk classified for Fx (we have tools) & treated
- Consider DEXA for pts with CKD/ESRD who are post-menopausal or have risk factors for OP
- Biomarkers like PTH, PO4, bsAlp, they are useful but are complicated by the thresholds that would very vary with lab, and also by stage of CKD
- If PTH is elevated, it would have a good NPV of 90% for R/O ABD
- The mean barriers is expertise and reading the pathology and not the techniques

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