Osteoporosis & Kidney Disease

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SBUMS

Conflict of Interest

Agenda

- The Why:
- *why OP is important ?*

- The What:
- *what is required to make a Dx of OP ?*

- The How:
- *How to screen/monitor ?*

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%

BURDEN OF DISEASE

285,000

NEW FRAGILITY FRACTURES IN 2019

782
FRACTURES **PER DAY**

33
FRACTURES **PER HOUR**

CHANGE IN COST PER INDIVIDUAL

€69.5
2010

€92.3
2019

+33%

€4.3 BILLION

SPENT IN 2019

€2.2 BILLION
LONG-TERM DISABILITY COSTS

€1.8 BILLION
DIRECT COST OF INCIDENT FRACTURES

€303 MILLION
PHARMACOLOGICAL INTERVENTION

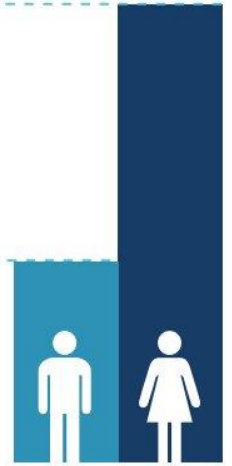
HUGE COST BURDEN FOR OSTEOPOROSIS-RELATED HEALTHCARE

2,945,000

INDIVIDUALS WITH OSTEOPOROSIS IN 2019

79.2%
WOMEN

20.8%
MEN

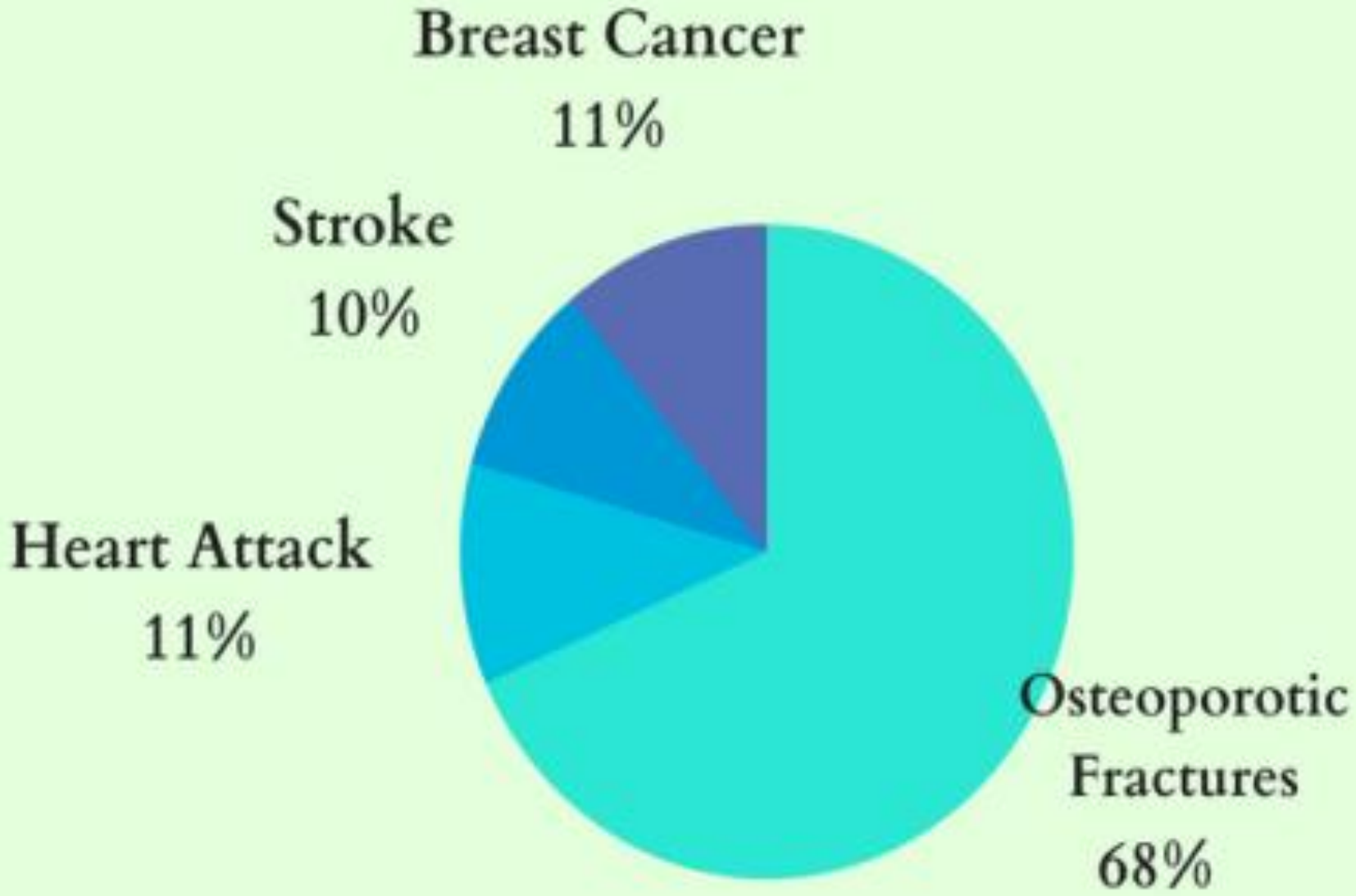


5.4% OF THE TOTAL POPULATION

PROJECTED INCREASE IN THE NUMBER OF
FRAGILITY FRACTURES

+29.6%

Burden of Osteoporosis Worldwide



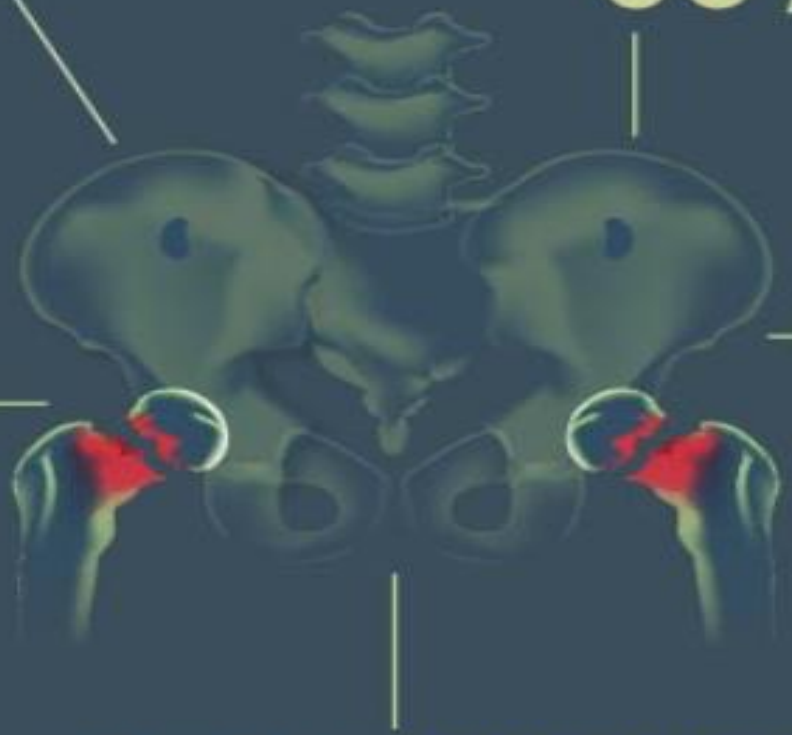
Hip fracture

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

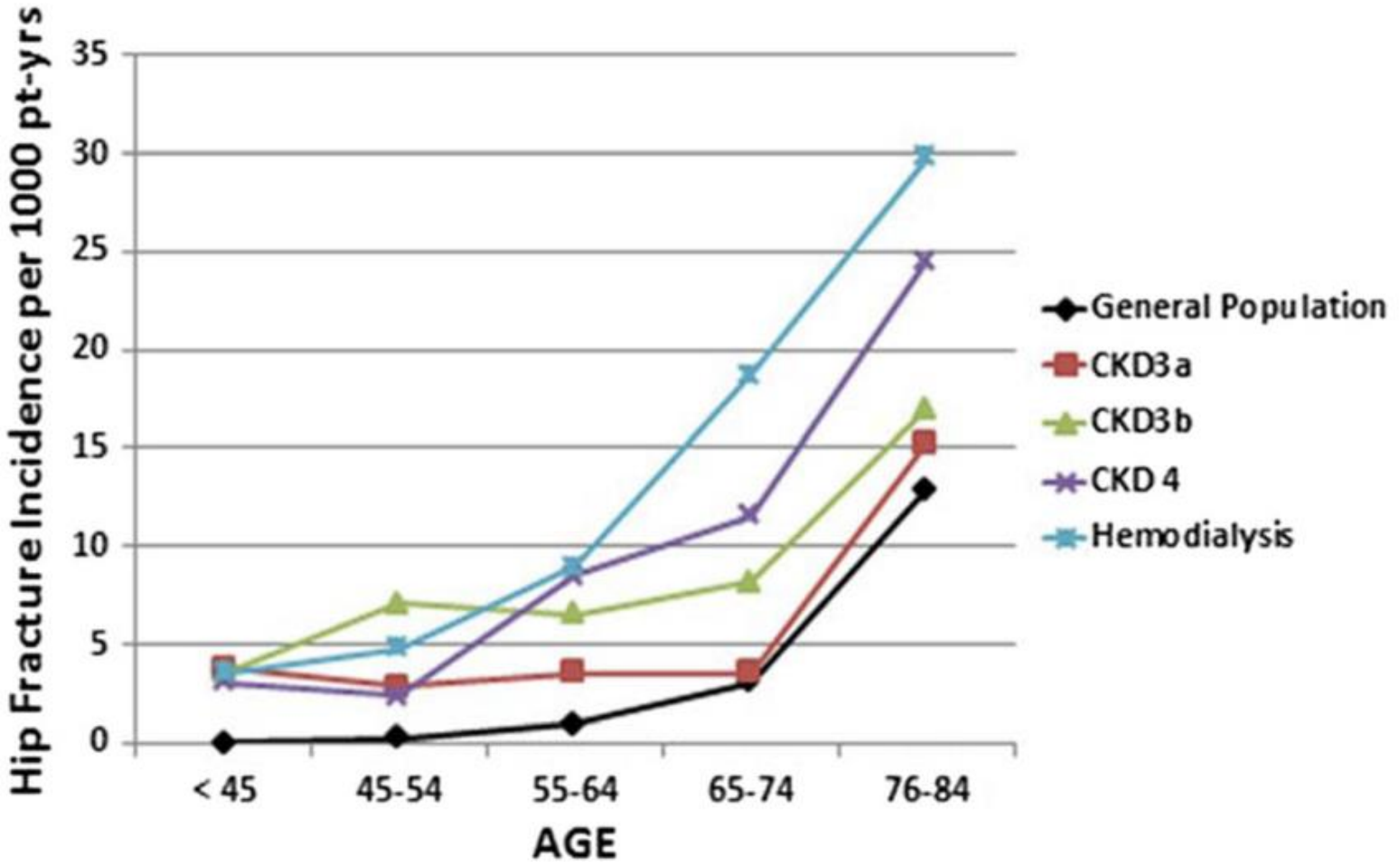
50% OF PEOPLE WITH ONE OSTEOPOROTIC FRACTURE WILL HAVE ANOTHER

Dangerous Duo

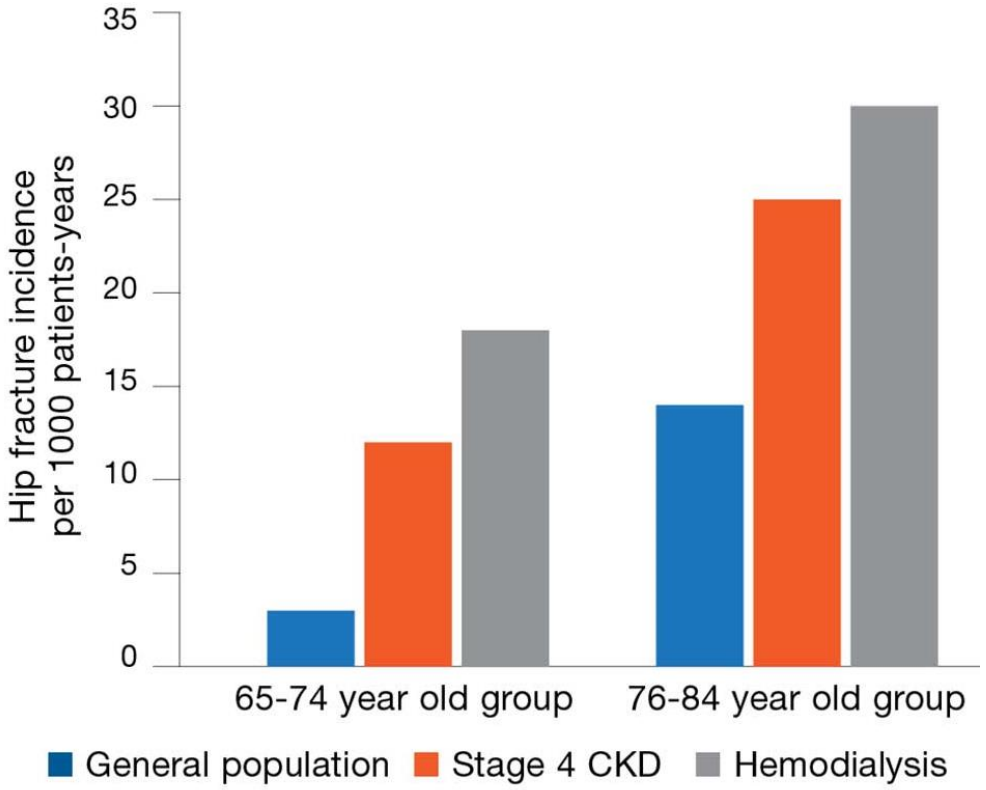
Why do we worry about Bone & CKD pts?

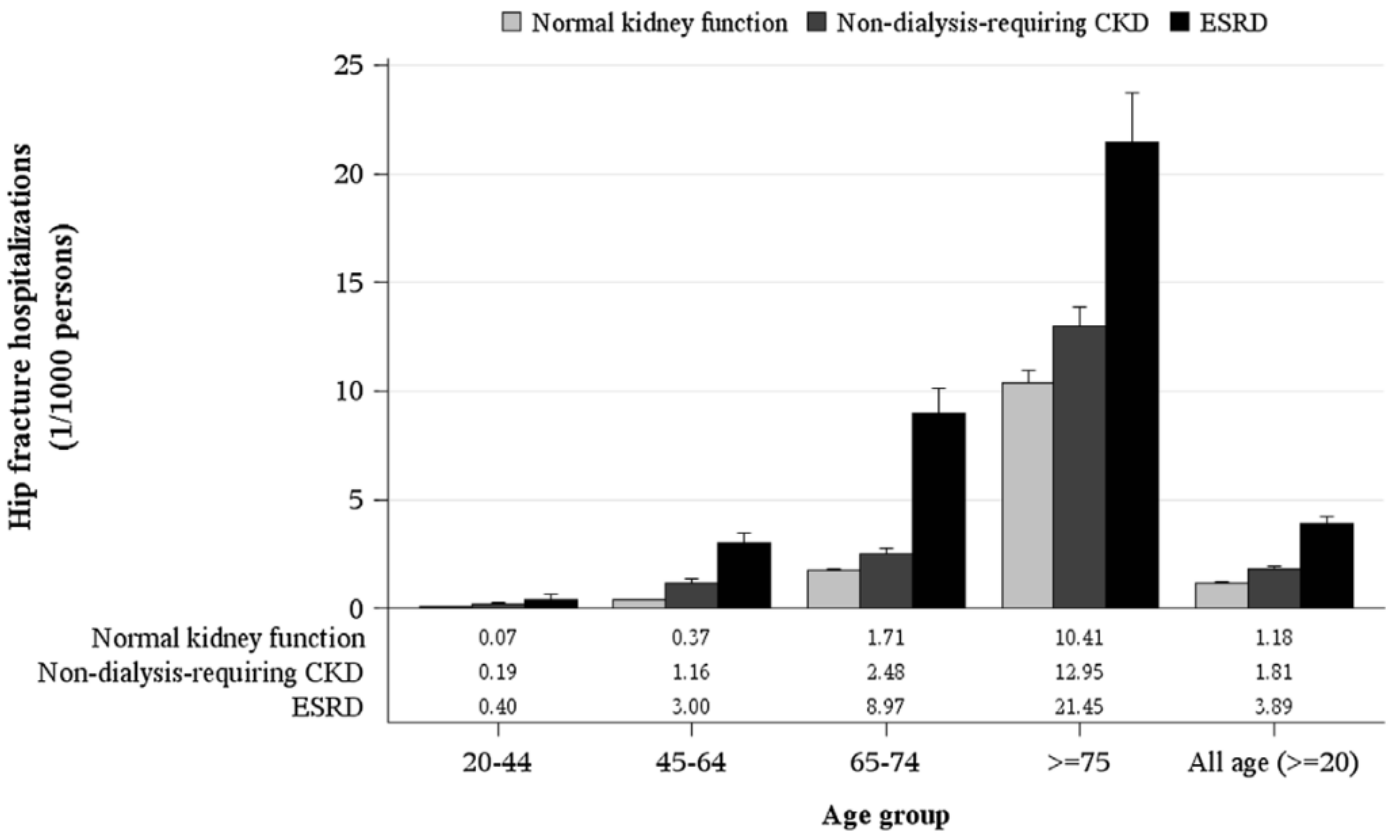
Why OP is important in CKD ?

Hip Fx risk in CKD

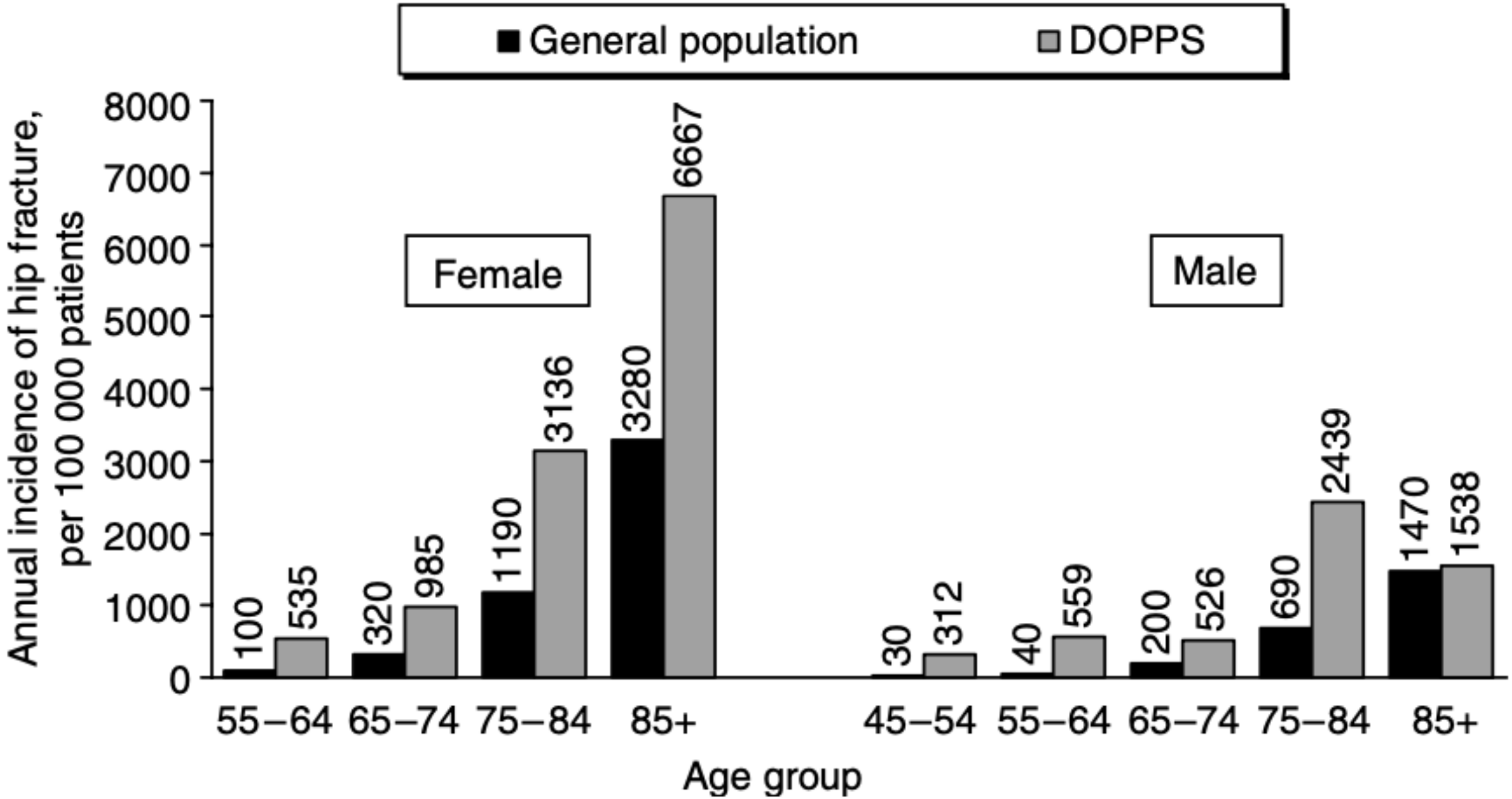


Progressive incidence of Hip fx





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

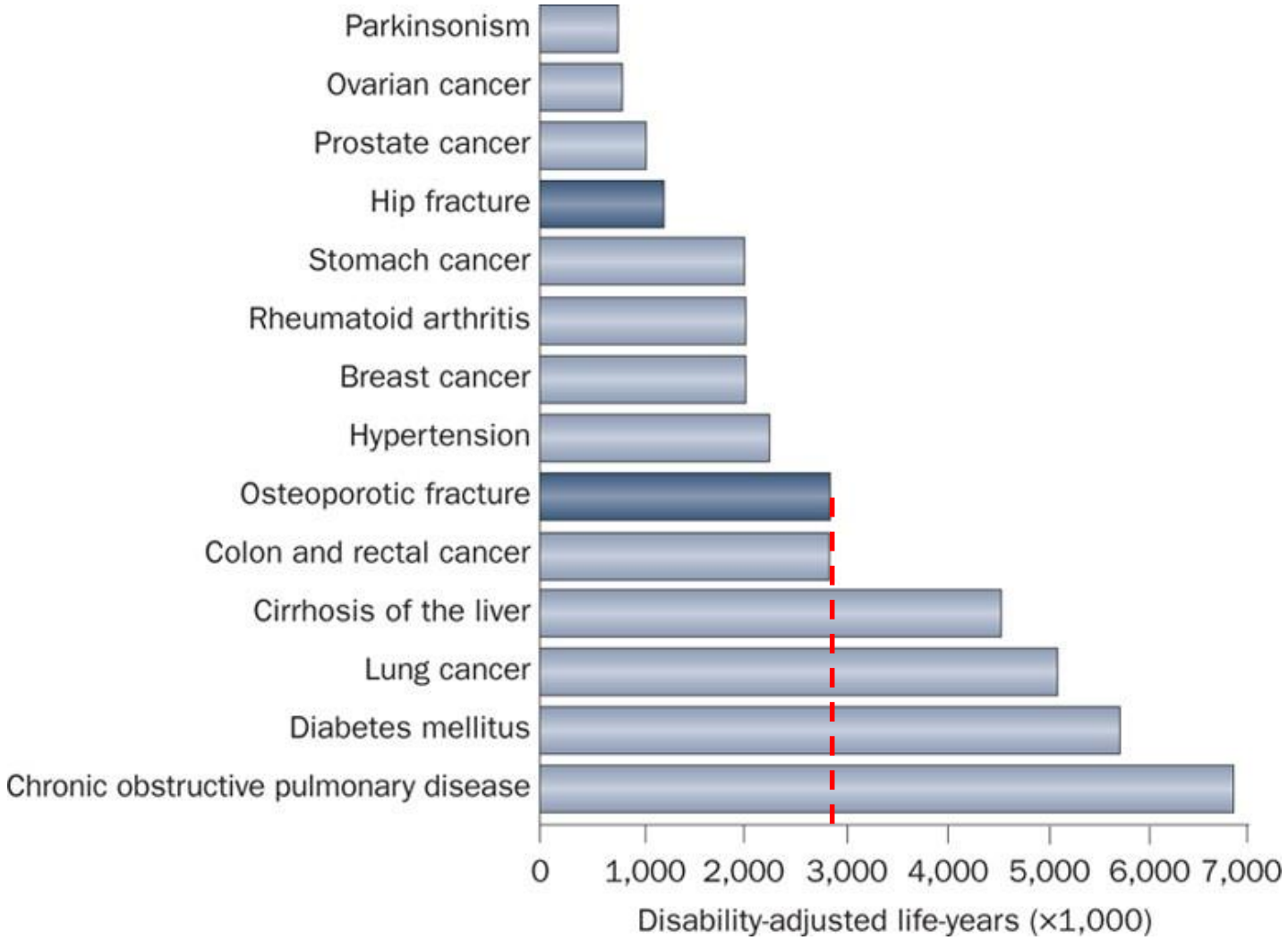

General population
DOPPS
Annual incidence of hip fracture, per 100 000 patients
8000
7000
6000
5000
4000
3000
2000
1000
0
Female
Male
100
535
320
985
1190
3136
3280
6667
30
312
40
559
200
526
690
2439
1470
1538
55–64
65–74
75–84
85+
45–54
55–64
65–74
75–84
85+
Age group

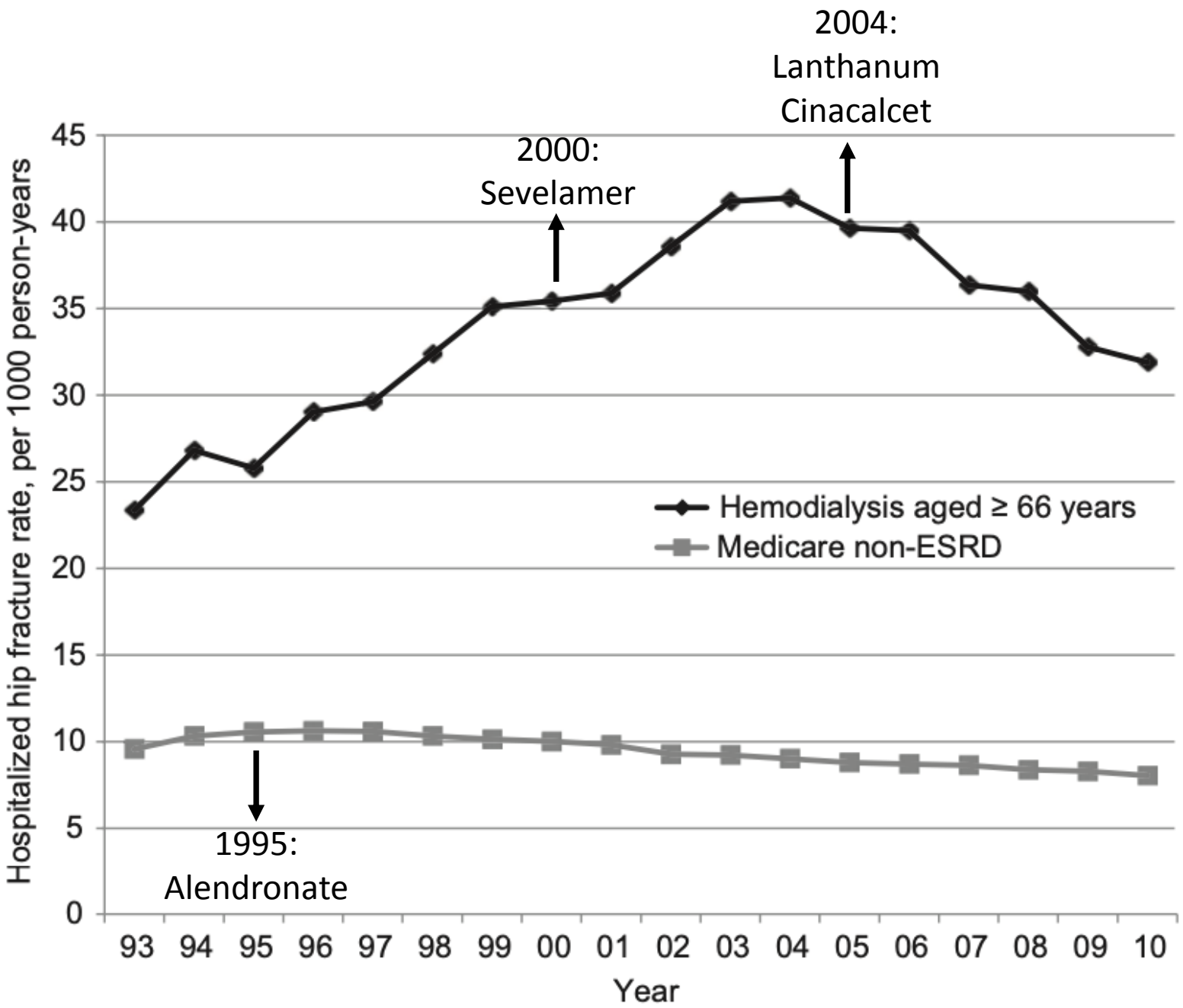
When ESRD pts Fx, they have x 2 risk of **mortality**

Outcome of Hip Fx

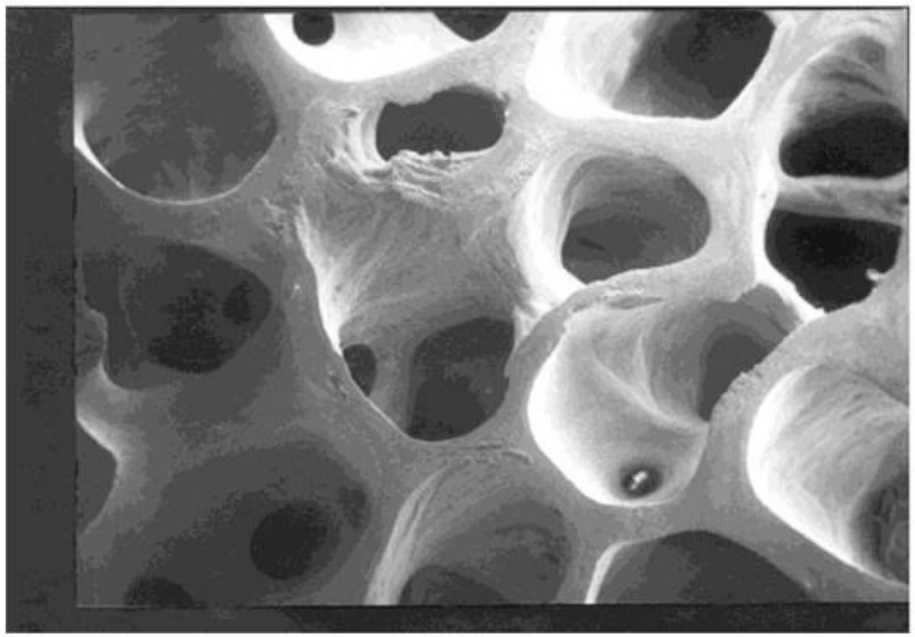
	Normal kidney function	Non-dialysis-requiring CKD	ESRD	*p* Value
Mortality, *n* (%)	3826 (1.6)	1259 (3.7)	285 (5.9)	<0.001
LOS, days, median (10th, 90th percentile)	5 (3, 10)	5 (3, 11)	7 (4, 16)	<0.001[a]
Costs, dollars, median (10th, 90th percentile)	13,314 (8206, 25,483)	14,807 (9194, 28,467)	17,875 (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

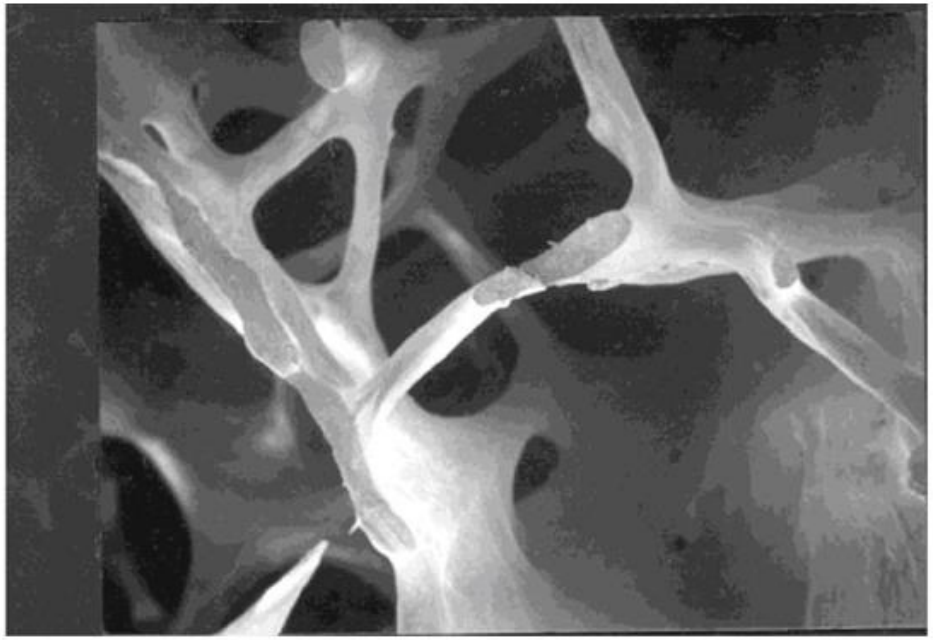



2004:
Lanthanum
Cinacalcet
2000:
Sevelamer
1995:
Alendronate
Hemodialysis aged ≥ 66 years
Medicare non-ESRD
Hospitalized hip fracture rate, per 1000 person-years
0
5
10
15
20
25
30
35
40
45
93
94
95
96
97
98
99
00
01
02
03
04
05
06
07
08
09
10
Year

Definitions



Normal bone



Osteoporotic bone

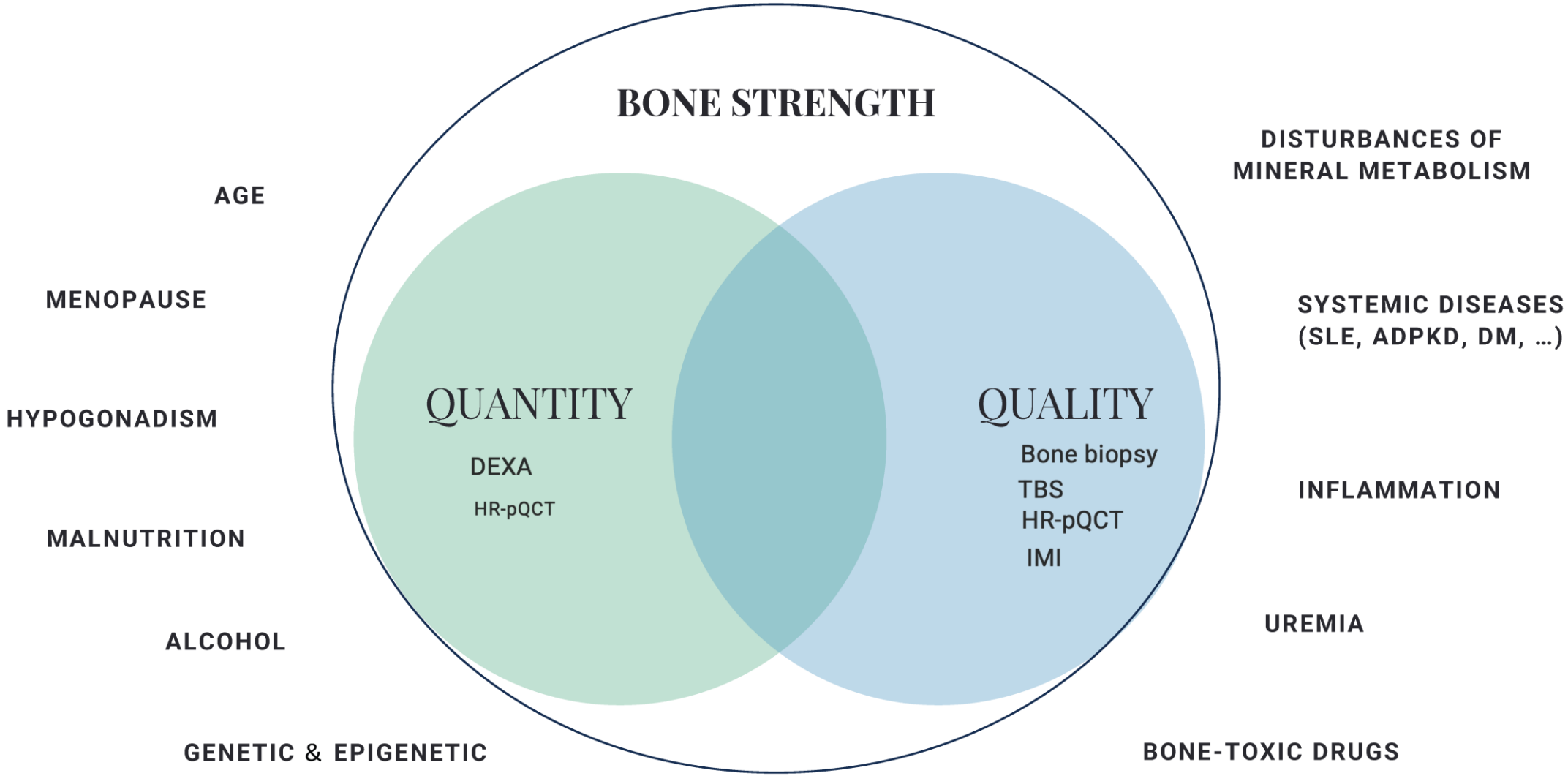
Osteoporosis

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

…by WHO

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


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

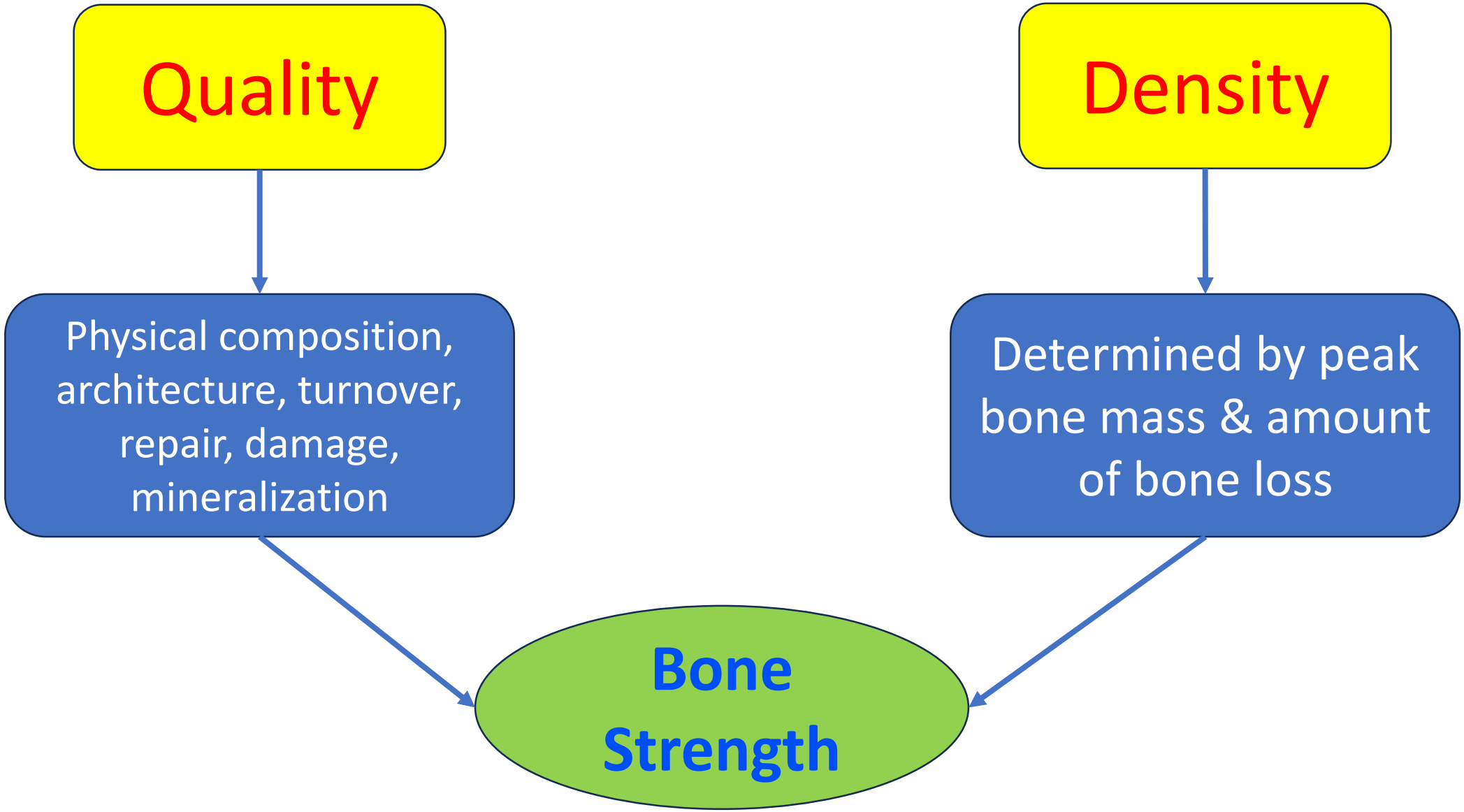
NIH definition (2000)

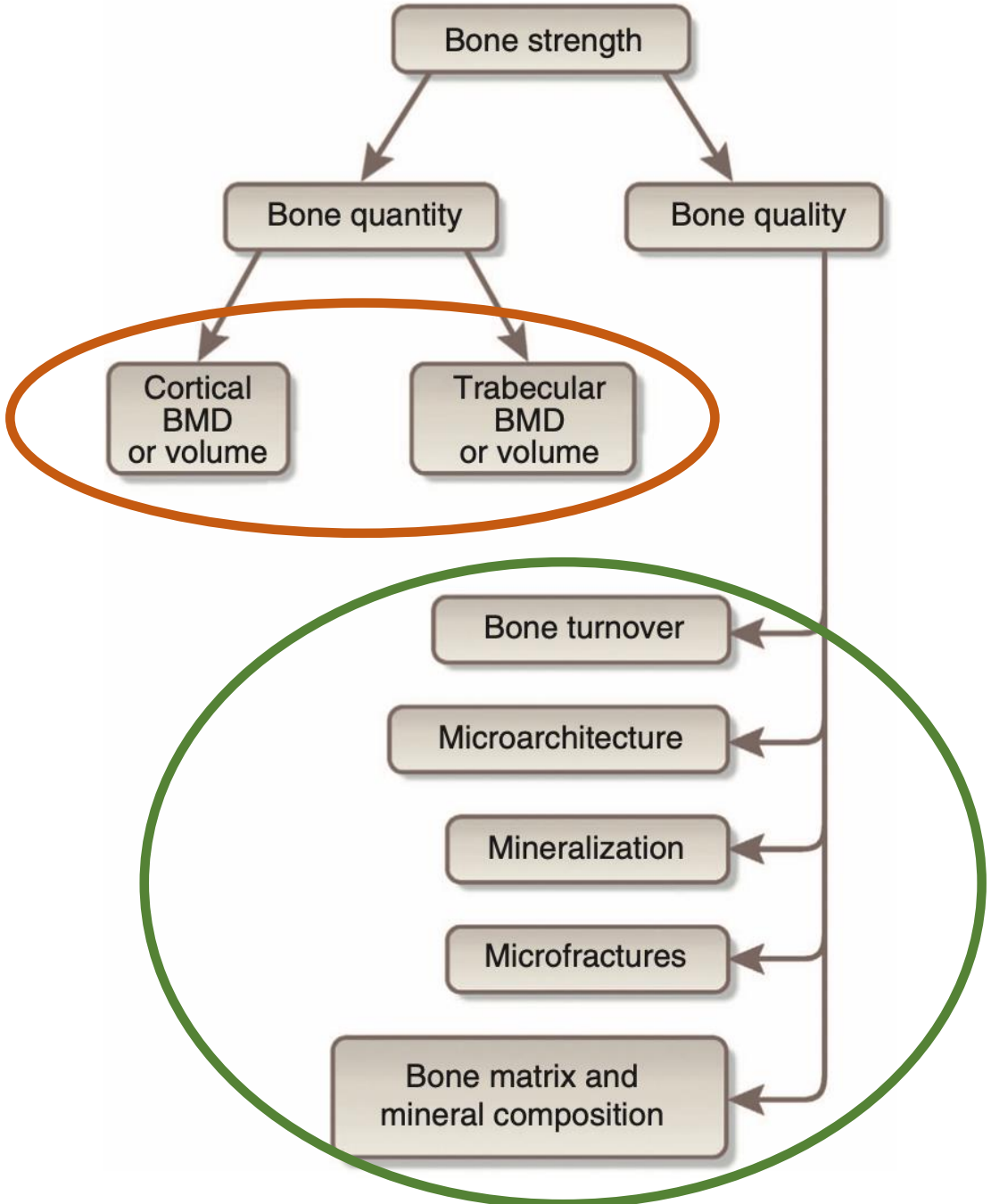
- NJE define OP as =

  skeletal disorder characterized by

  "compromised bone strength (Q&Q)"

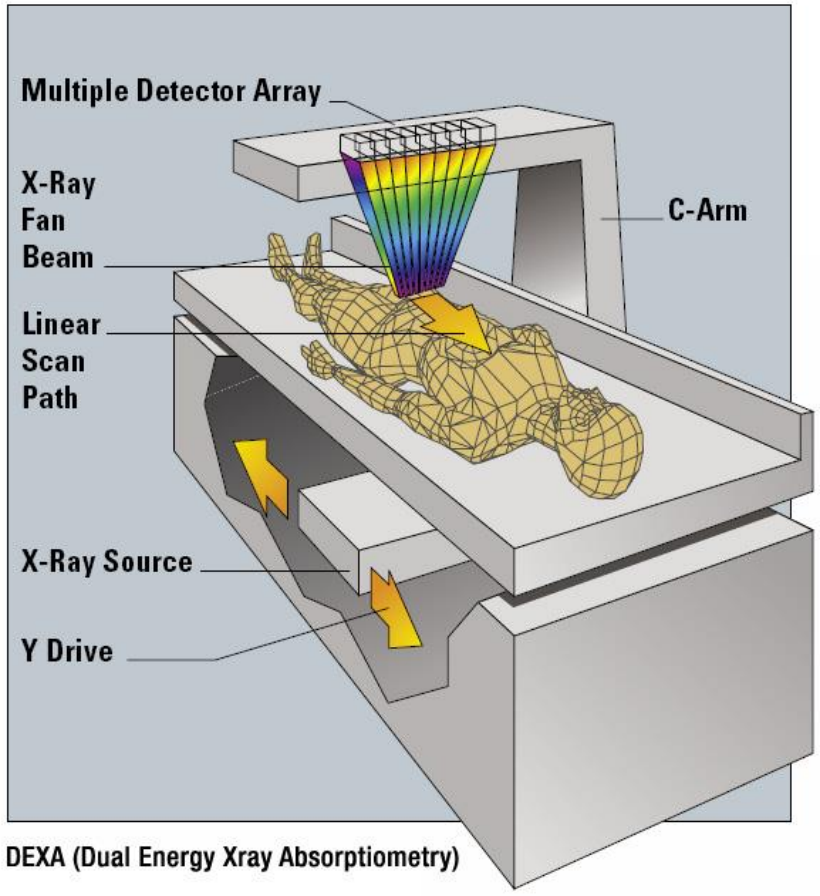
  predisposing to "increased Fx" risk.


Quality
Density
Physical composition, architecture, turnover, repair, damage, mineralization
Determined by peak bone mass & amount of bone loss
Bone Strength

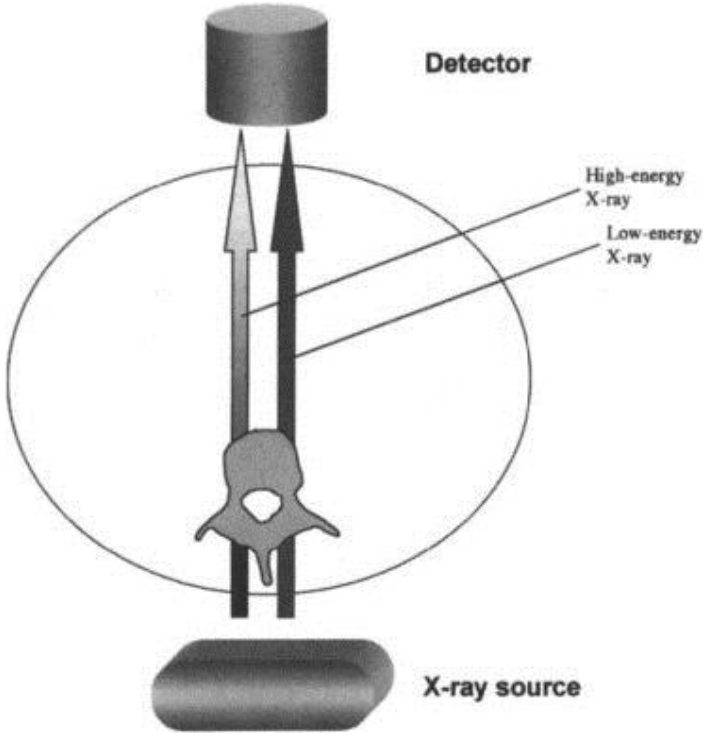

Bone strength
Bone quantity
Bone quality
Cortical BMD or volume
Trabecular BMD or volume
Bone turnover
Microarchitecture
Mineralization
Microfractures
Bone matrix and mineral composition

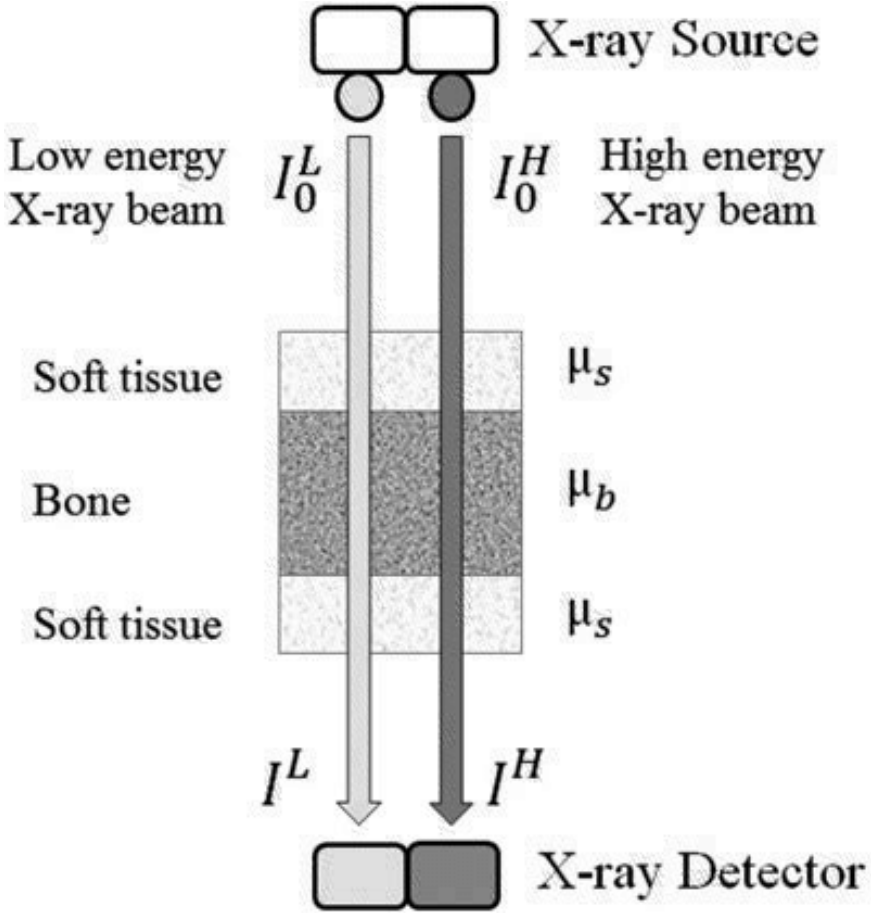
What is required to make a Dx ?

*One beam is absorbed more by **soft tissues** (like fat and muscle),*
*The other by **bone**.*
How much is blocked by bone, tells how dense or strong your bones are.



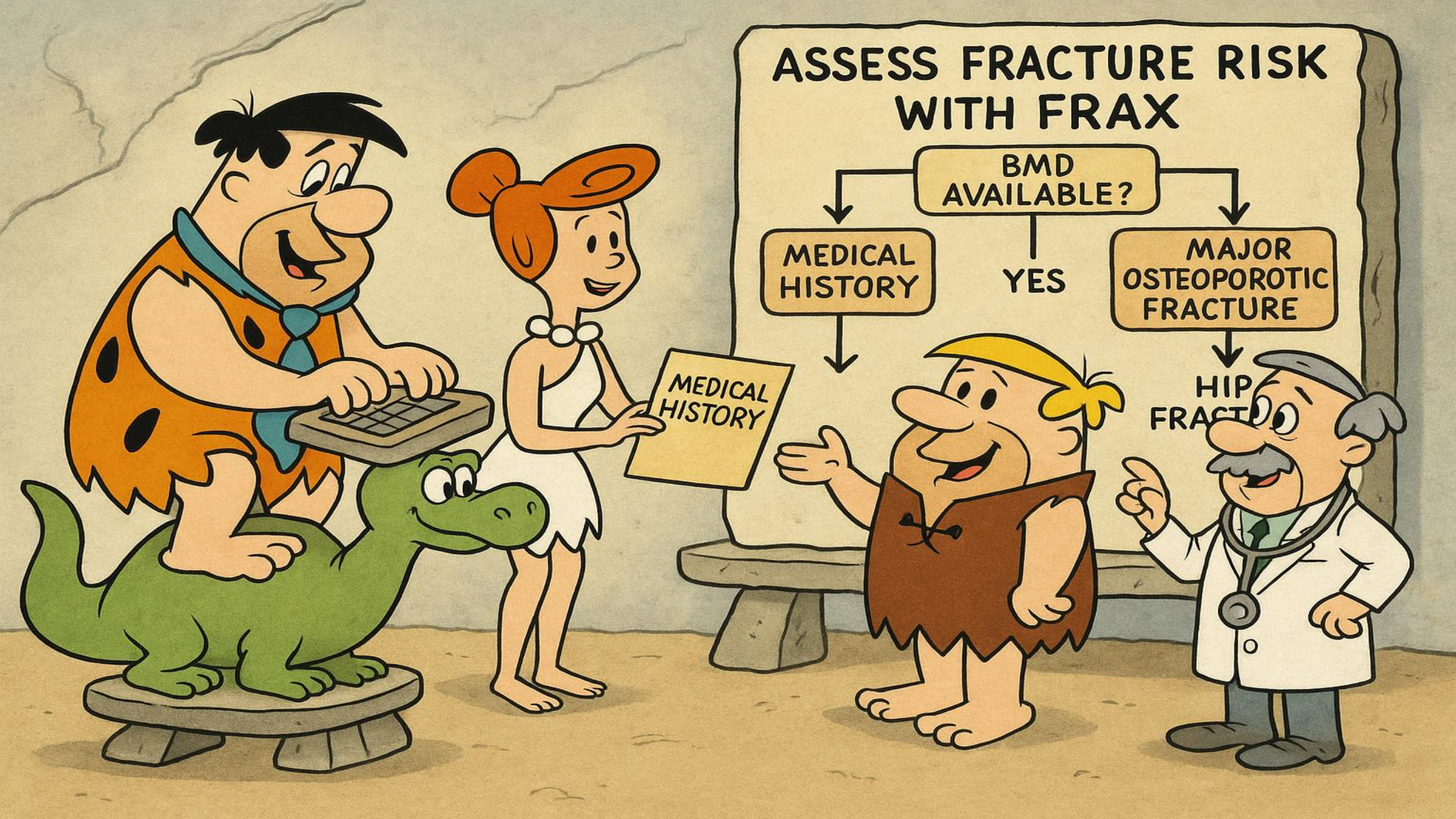
DEXA (Dual Energy Xray Absorptiometry)





Quantitative Ultrasound	Details
Also Known As	**QUS**
Purpose	Measures **bone density** using sound waves
Sample	None
Preparation	No preparation
Procedure	Ultrasound scan of **peripheral sites**
Test Timing	5-10 minutes
Test Price (INR)	1000-3000
Result Value	**T-score & Z-score**
Normal Value	Normal bone density
Accuracy	**Reliable Bone Density Estimation**
Interpretation	**Lower scores indicate an increased risk of osteoporosis**

Computed Tomography Scan	Details
Also Known As	CT Scan, CAT Scan
Purpose	**Detailed cross-sectional images** of bones
Sample	None
Preparation	**Fasting**
Procedure	Scan
Test Timing	10-30 minutes
Test Price (INR)	5000-15000
Result Value	**Detailed images of bones & potential fractures**
Normal Value	Normal bone structure
Accuracy	Advanced DXA
Interpretation	**Helps in diagnosing and evaluating bone conditions based on detailed images obtained**


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

Clinical Dx

•**Fragility fracture** is defined by the **World Health Organisation** as "*a fracture caused by injury that would be insufficient to fracture a normal bone...the result of reduced compressive and/or torsional strength of bone*". Clinically, a fragility fracture may be defined as a fracture "...*that occurs as a result of a minimal trauma, such as a fall from a standing height or less, or no identifiable trauma*"

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

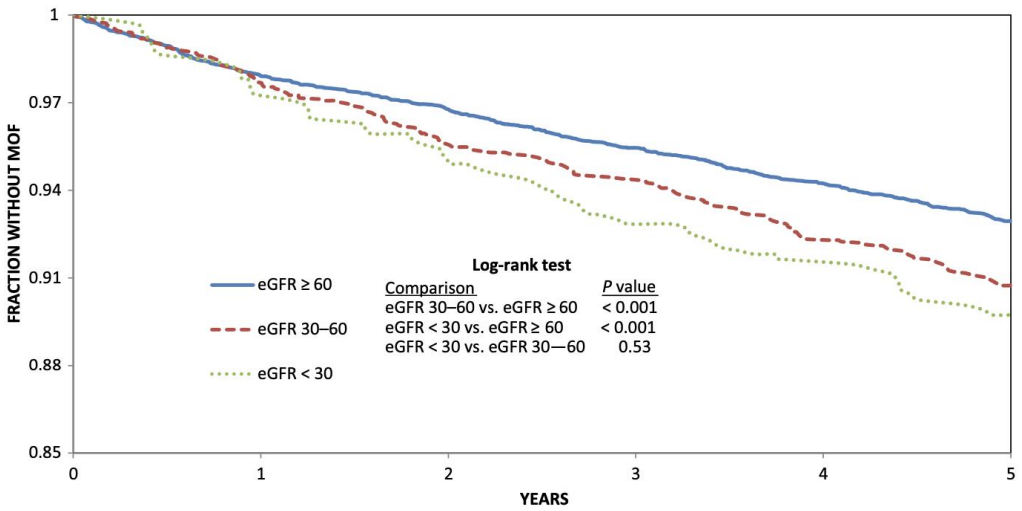


Figure 2| Kaplan-Meier curve: time to major osteoporotic fracture. eGFR, estimated glomerular filtration rate; MOF, majo fracture.

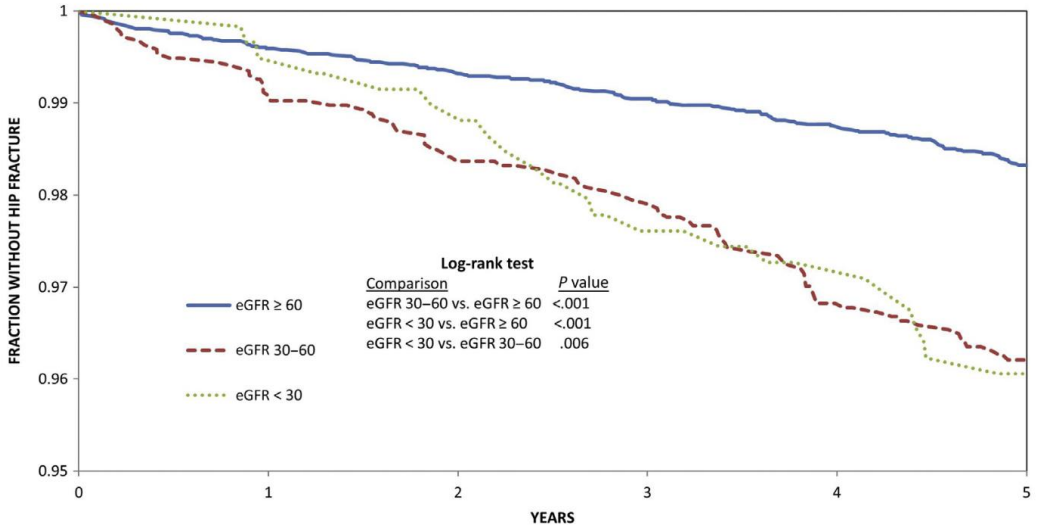


Figure 3| Kaplan-Meier curve: time to hip fracture. eGFR, estimated glomerular filtration rate.

2 studies for FRAX in ESRD pts (not robust)

- 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

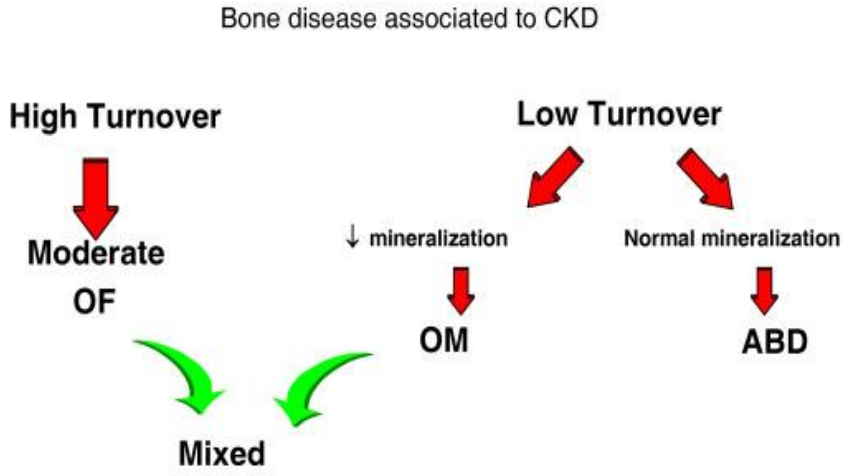
DEFINITIONS

KDIGO CKD-MBD Guidelines, KI Int Suppl 2009

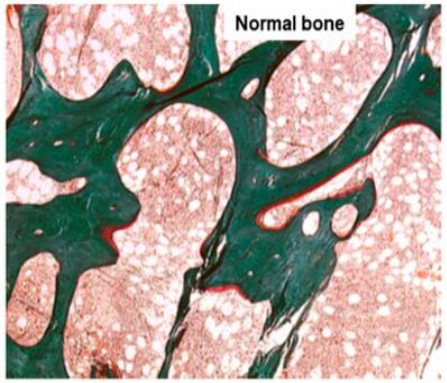
In 2006, (KDIGO) recommended the use of the term chronic kidney disease-mineral and bone disorder (CKD-MBD) in stead of "renal osteodystrophy" to describe a systemic disorder that manifested by either one or a combination of the following:

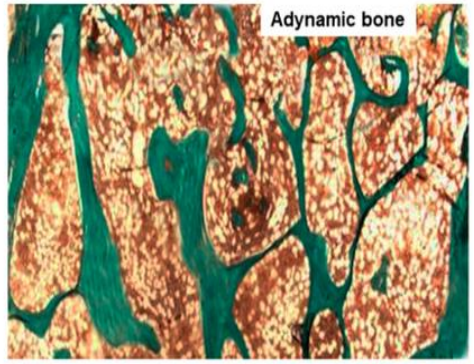
- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Extraskeletal calcification

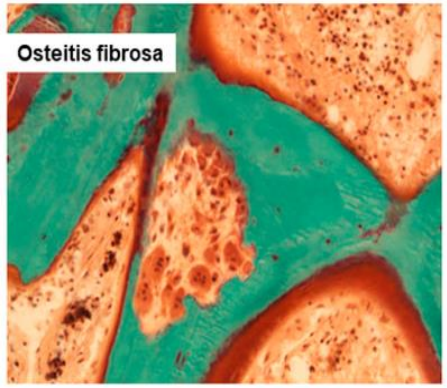
The bone component, we just call that ROD

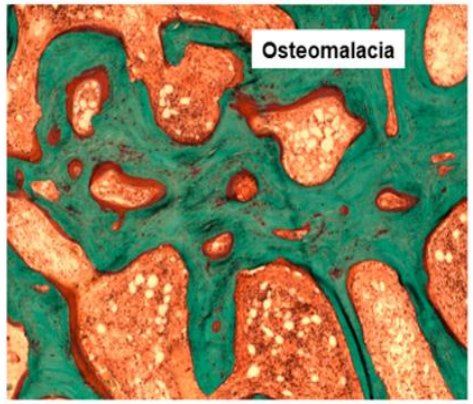


OF osteitis fibrosa OM : osteomalacia ABD : adynamic bone disease
OP osteopetrosis OS osteosclersis CKD : Chronic Kidney Disease

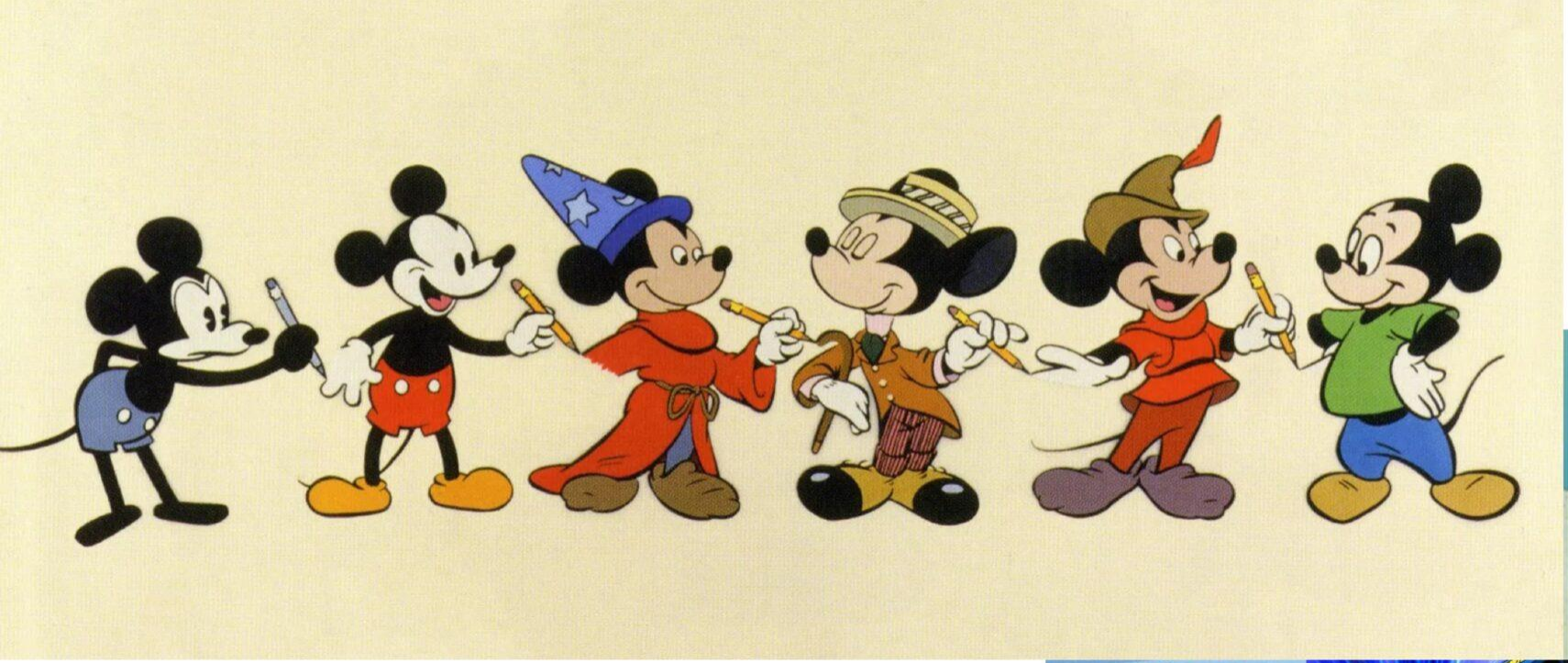


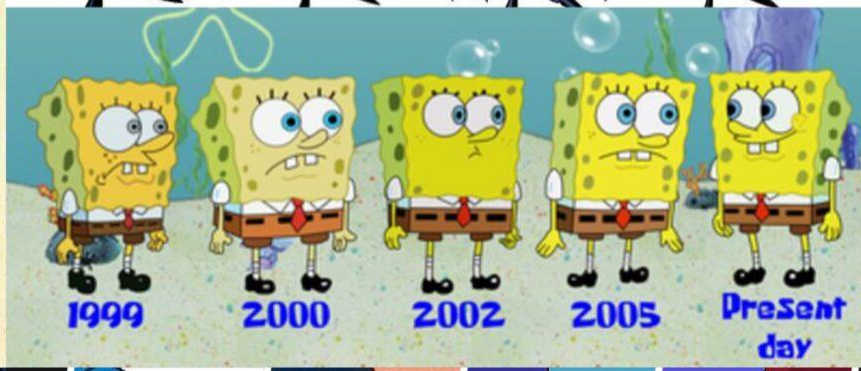


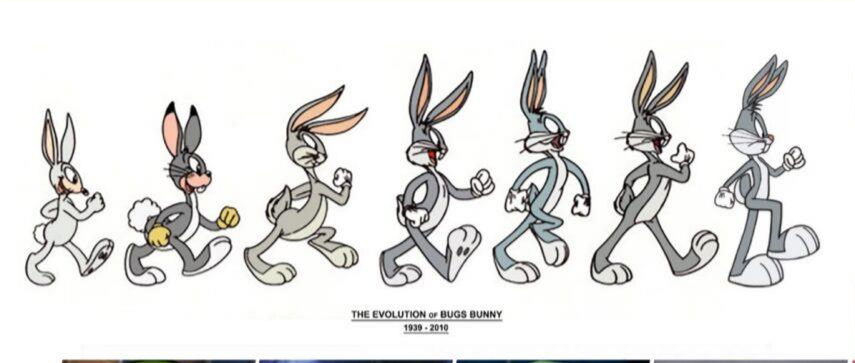




Type of Renal Osteodystrophy	Turnover	Mineralization	Volume
Osteomalacia	Low	Abnormal	Low to Medium
Osteitis Fibrosa	High	Normal	Normal to High
Adinamic Bone Disease	Low	Normal	Low to Normal
Mixed Osteopathy	Normal to High	Abnormal	Low to Normal
Osteoporosis	Normal	Normal	Low




1999
2000
2002
2005
Present day

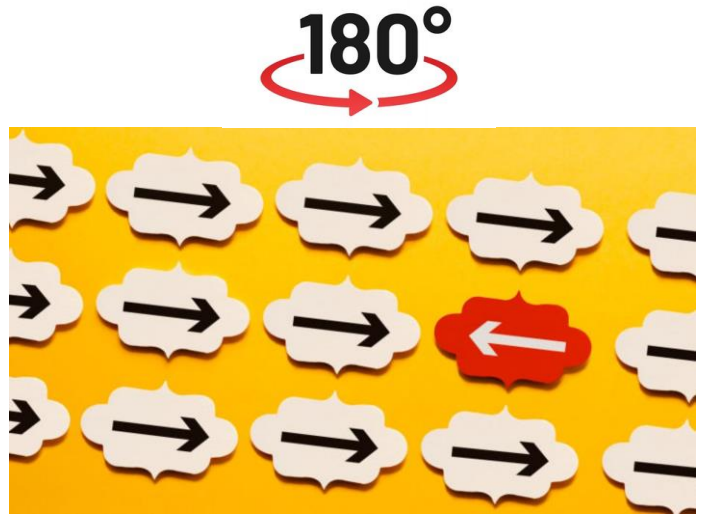

THE EVOLUTION OF BUGS BUNNY
1939 - 2010


1988-1991
1998-2005

GUIDELINES

2009

- CKD-MBD definition
- BMD testing not be routinely performed
- cross-sectional data showing, there are no association between low BMD and Fx risk in CKD



GUIDELINES

2009

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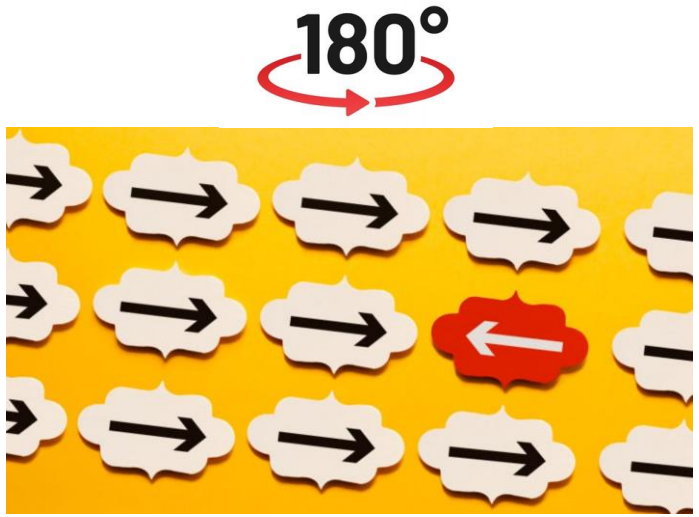


2017

☞ reversal of decision

☞Longitudinal studies : "low BMD & Fx risk"

☞ ***we should get BMD testing to assess Fx risk if your result will impact ttt decisions***

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]

A meta why KDIGO reversed their guidelines for DEXA screening !

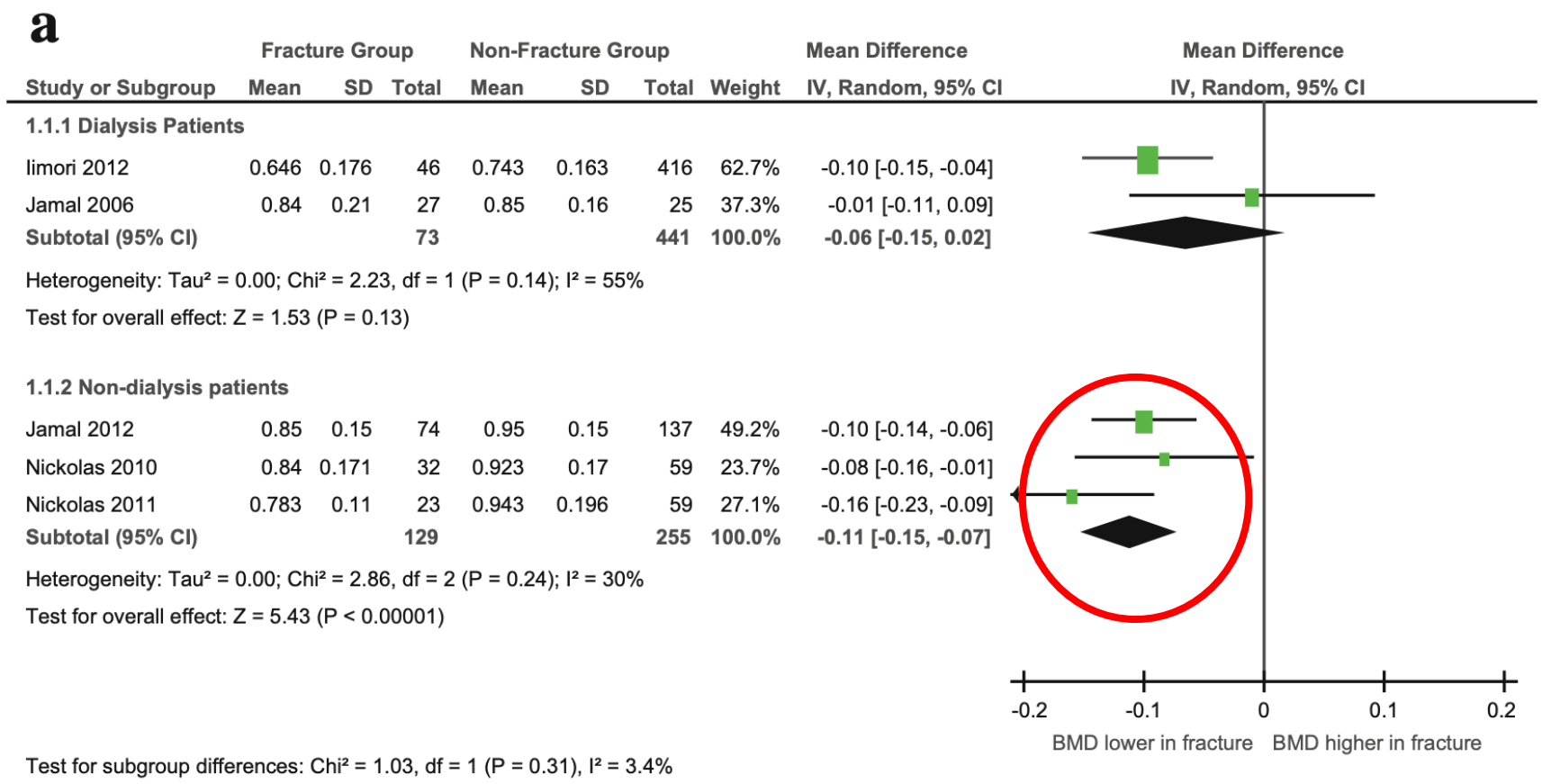
Osteoporos Int (2015) 26:449–458
DOI 10.1007/s00198-014-2813-3

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

So, to screen pt with CKD & ESRD with DEXA



a

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Dialysis Patients								
Iimori 2012	0.646	0.176	46	0.743	0.163	416	62.7%	-0.10 [-0.15, -0.04]
Jamal 2006	0.84	0.21	27	0.85	0.16	25	37.3%	-0.01 [-0.11, 0.09]
Subtotal (95% CI)			**73**			**441**	**100.0%**	**-0.06 [-0.15, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 1 (P = 0.14); I² = 55%								
Test for overall effect: Z = 1.53 (P = 0.13)								
1.1.2 Non-dialysis patients								
Jamal 2012	0.85	0.15	74	0.95	0.15	137	49.2%	-0.10 [-0.14, -0.06]
Nickolas 2010	0.84	0.171	32	0.923	0.17	59	23.7%	-0.08 [-0.16, -0.01]
Nickolas 2011	0.783	0.11	23	0.943	0.196	59	27.1%	-0.16 [-0.23, -0.09]
Subtotal (95% CI)			**129**			**255**	**100.0%**	**-0.11 [-0.15, -0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%								
Test for overall effect: Z = 5.43 (P < 0.00001)								

Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 3.4%

TMV classification =

…better characterization of bone disorders in CKD

Condition	**Bone turnover**	**Mineralization**	**Bone volume**
Osteomalacia	Low	Abnormal	Low to medium
Adynamic bone disease	Low	Normal	Low to normal
Mild hyperparathyroidism	Medium	Normal	Variable
Advanced hyperparathyroidism (Osteitis fibrosa)	High	Normal	Variable
Mixed uremic osteodystrophy	High	Abnormal	Normal

Table 1. Glossary of terms

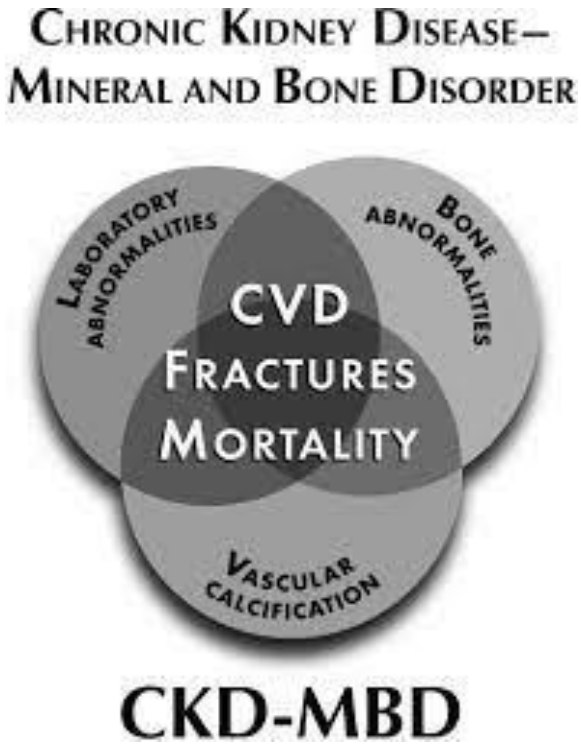
Term	Definition
Primary osteoporosis	Chronic, progressive disease characterized by low bone mass, microarchitecture deterioration of bone tissue, bone fragility, and a consequent increase in fracture risk (51)
Postmenopausal	Caused by estrogen deficiency in postmenopausal women
Age related	Associated with aging in both men and women
Secondary osteoporosis	Osteoporosis secondary to medical conditions, nutritional deficiencies, and medication side effects (52)
CKD-MBD	A systemic disorder of mineral and bone metabolism due to CKD manifested by abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities of bone turnover, mineralization, volume, linear growth, or strength; and vascular or other soft tissue calcification
Renal osteodystrophy	A disorder of bone quality and strength secondary to CKD; the bone component of CKD-MBD
Adynamic bone disease	Low or absent bone formation and turnover (53)

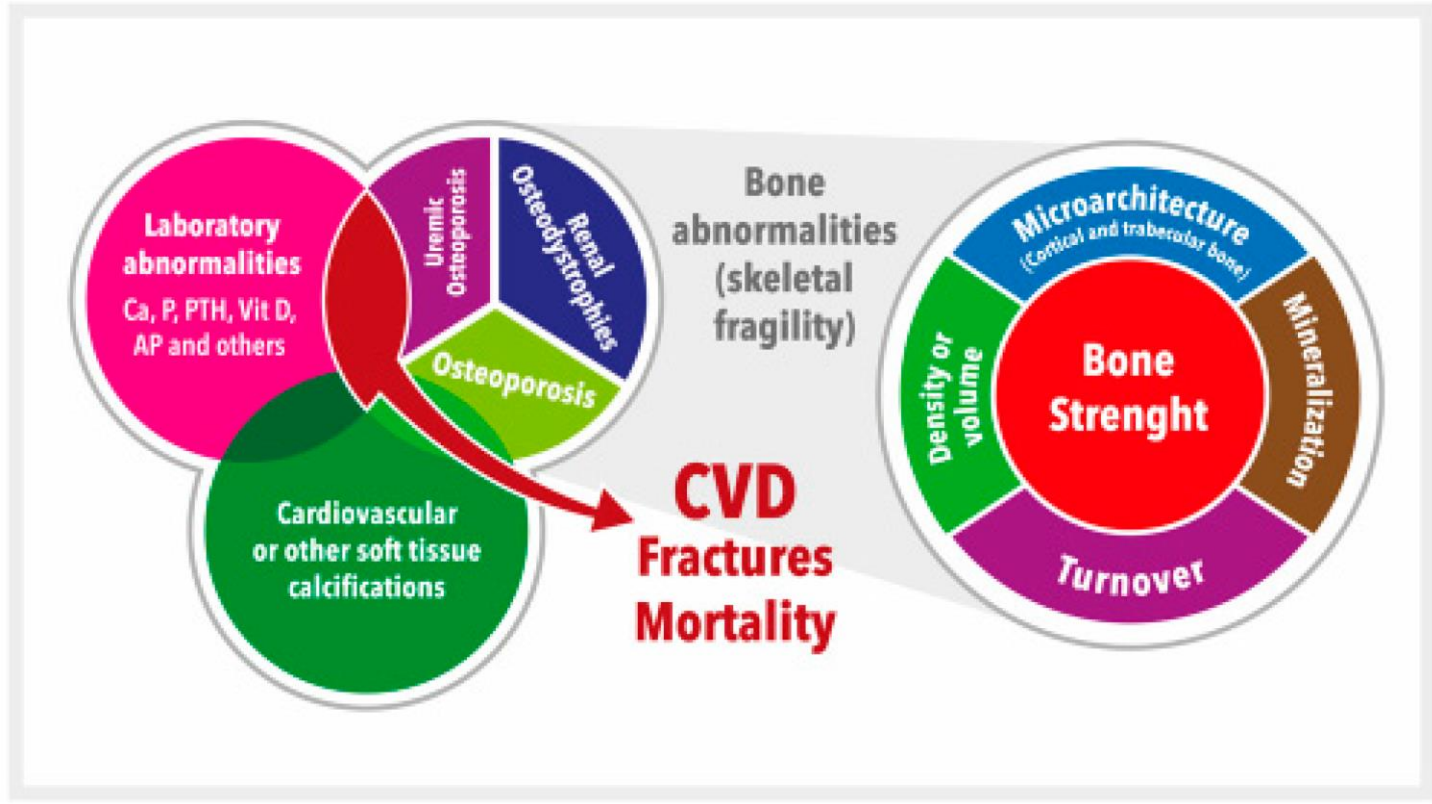
CKD-MBD, CKD mineral and bone disease; PTH, parathyroid hormone.

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

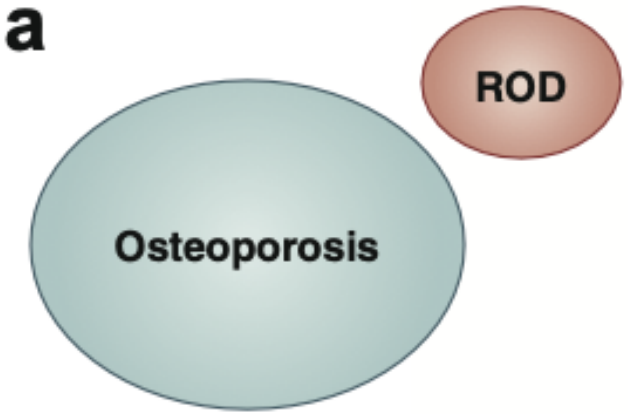
OPEN

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]



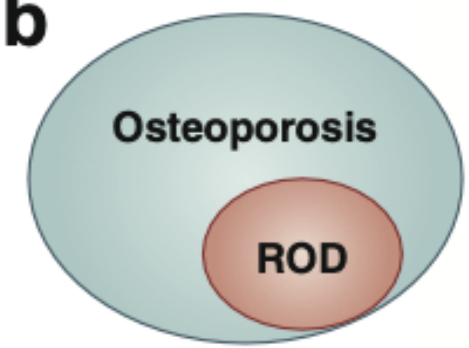


a



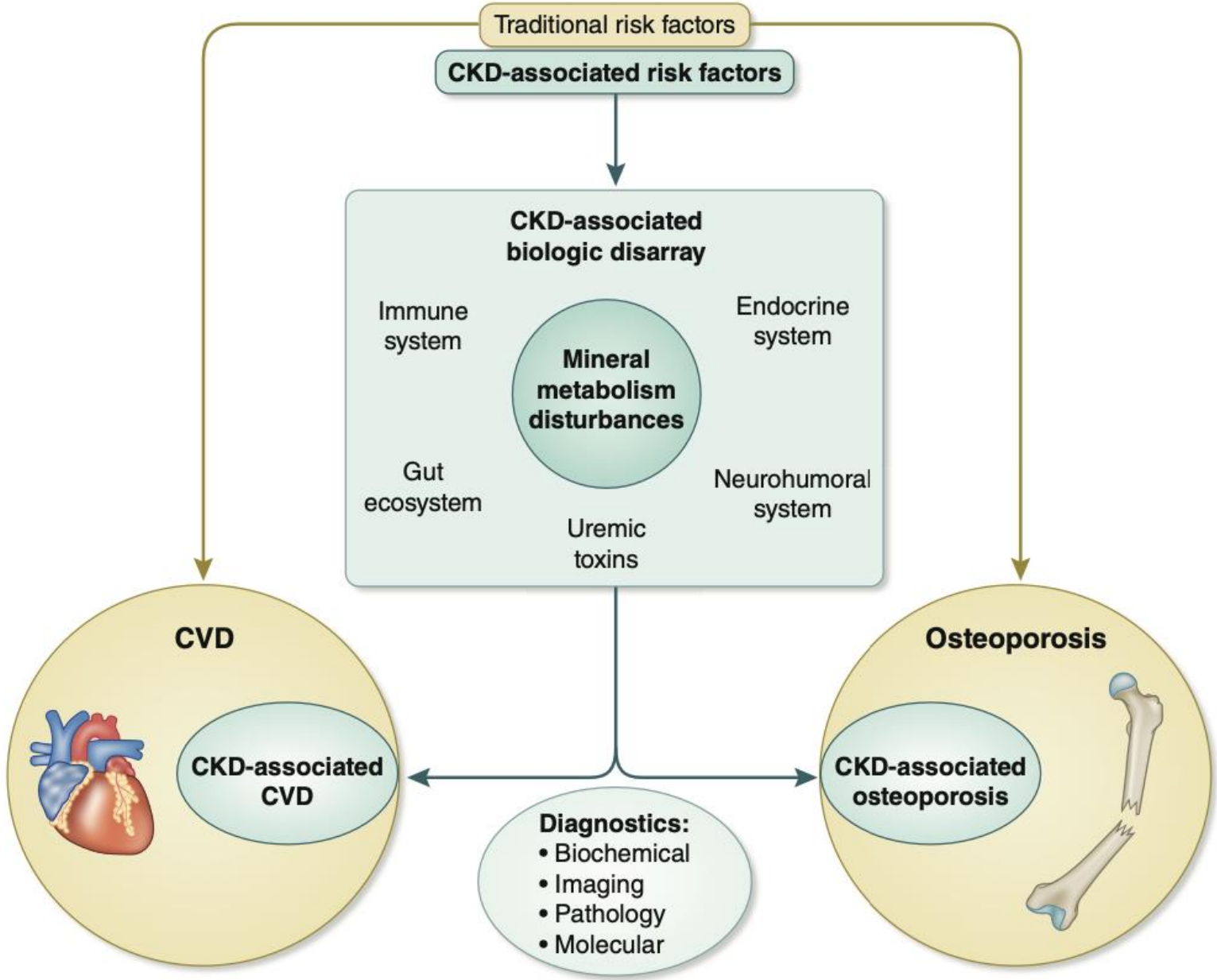
- **Osteoporosis** and **ROD** are separate entities and mutually exclusive diagnoses
- Diagnostic tools and therapeutic interventions are not interchangeable

b



- **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

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



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]

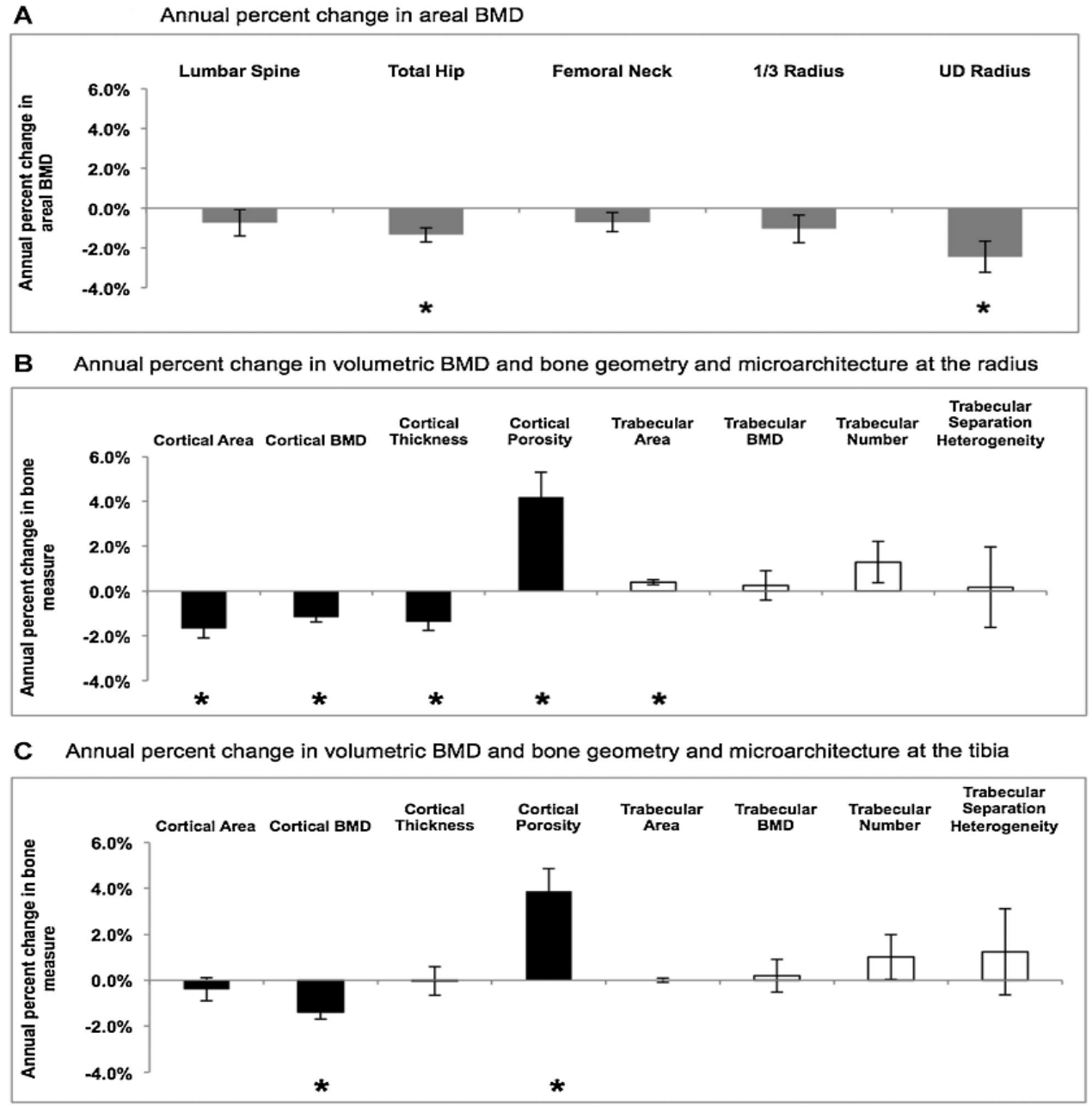


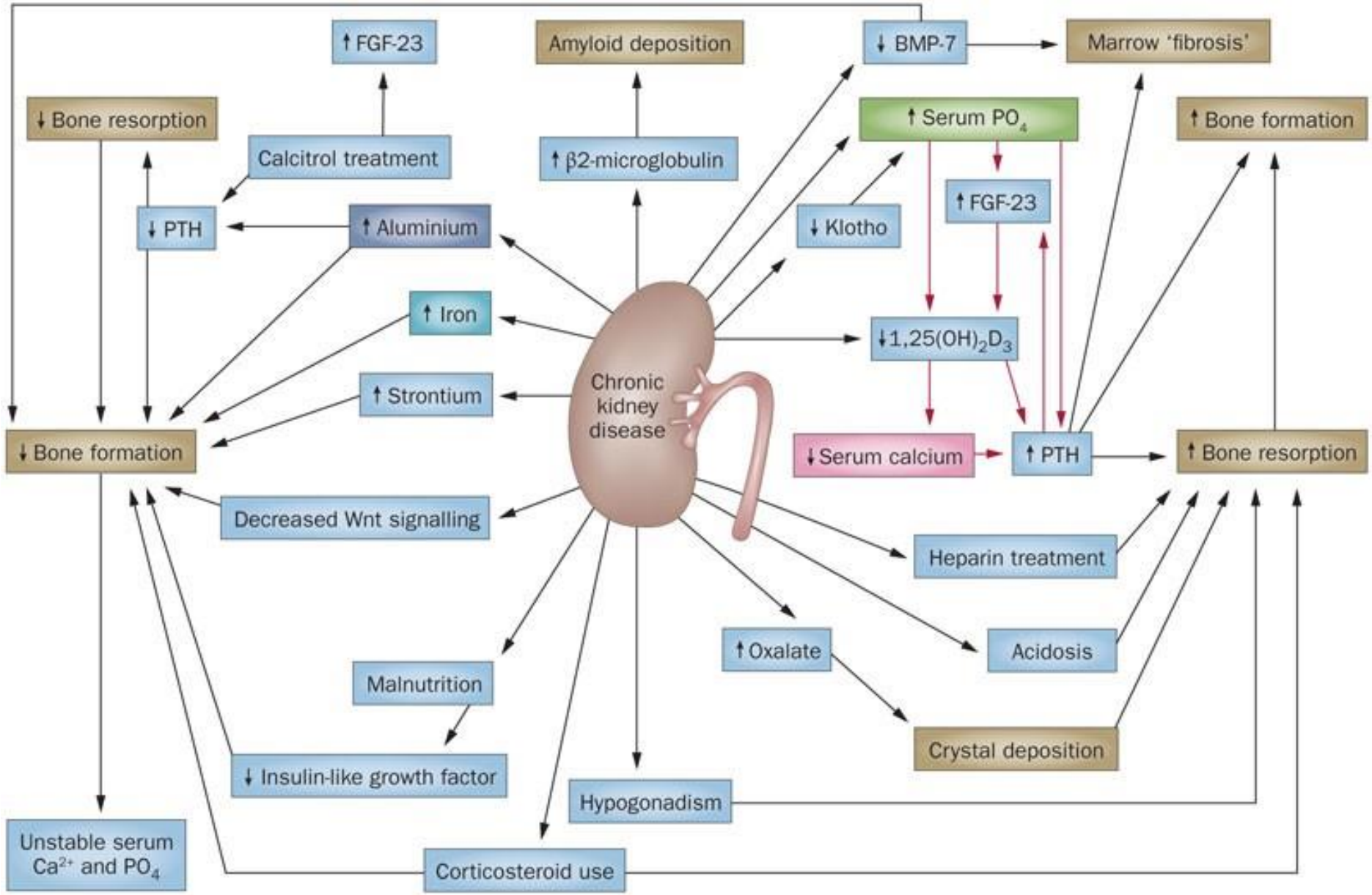
Fig. 1. Annual percent change from baseline in areal BMD by DXA (*A*) and volumetric BMD and bone geometry and microarchitecture by HRpQCT at the distal radius (*B*) and tibia (*C*) (mean ± SEM).

Why Management is really unclear & challenging in CKD ?

3 buckets…

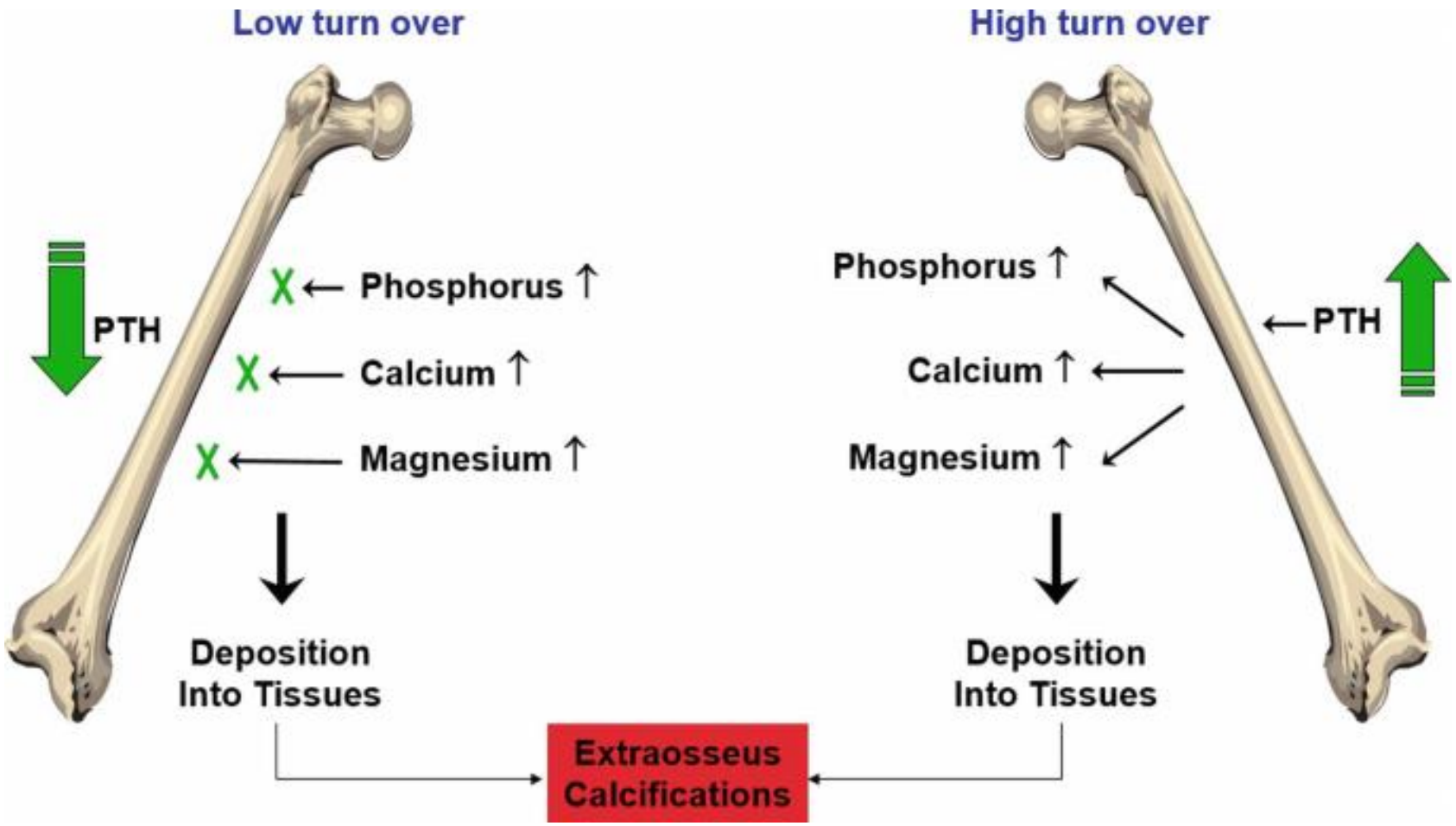
- 1- Kidney pts are complex and the pathophysiology is complex
- Pts have both traditional and kidney related risk factors for Fx (many of them interact with each other)
- Ex: High and Low bone turnover lead to low bone strength but they have really different ttt !

- 2- the second is, we have really 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
- Even in the general population, it is estimated that about 70% of Fx occurs in those pts whose T-score is >2.5 = T-score that don't meet the definition of OP
- <<<knowing about the quality of bone, is very important and we have very limited tools to figure out that.

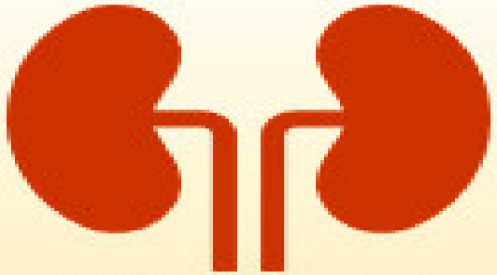

↑ FGF-23
Amyloid deposition
↓ BMP-7
Marrow 'fibrosis'
↓ Bone resorption
Calcitrol treatment
↑ β2-microglobulin
↑ Serum PO_4
↑ Bone formation
↓ PTH
↑ Aluminium
↓ Klotho
↑ FGF-23
↑ Iron
↓1,25$(OH)_2D_3$
Chronic kidney disease
↑ Strontium
↓ Bone formation
↓ Serum calcium
↑ PTH
↑ Bone resorption
Decreased Wnt signalling
Heparin treatment
↑ Oxalate
Acidosis
Malnutrition
Crystal deposition
↓ Insulin-like growth factor
Hypogonadism
Unstable serum Ca^{2+} and PO_4
Corticosteroid use

The higher the PTH, more likely to have a higher bone turn over & vice versa

PTH < 150 pg/mL
High Ca,
low/high PO4,
Low Vit D,
high FGF23,
low Klotho



PTH > 600 pg/mL
Low Ca,
high PO4,
low Vit D, high FGF23,
low Klotho



GFR > 90 ml/min

Cascade of disturbances in FGF23 in CKD-MBD

↓ Renal extraction of FGF23 => ↑ plasma intact FGF23

↓ Klotho expression

↓ Plasma calcium

↓ Calcitriol synthesis

↑ PTH secretion

↑ Plasma phosphate

CKD related factors & toxins

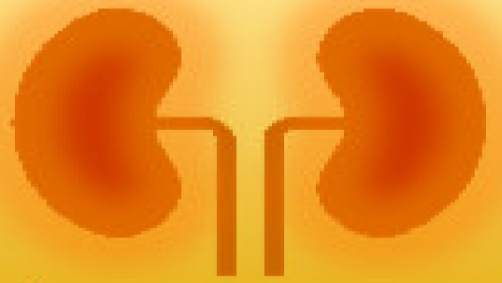
↑ FGF23

Secretion of factors from injured kidneys

Disturbance in the circadian clock

Disturbed calcium & phosphate sensing

GFR < 15 ml/min



Off-target effects of FGF23 ↑↑

Renal osteodystrophy

Uremic vasculopathy

Parathyroid disease

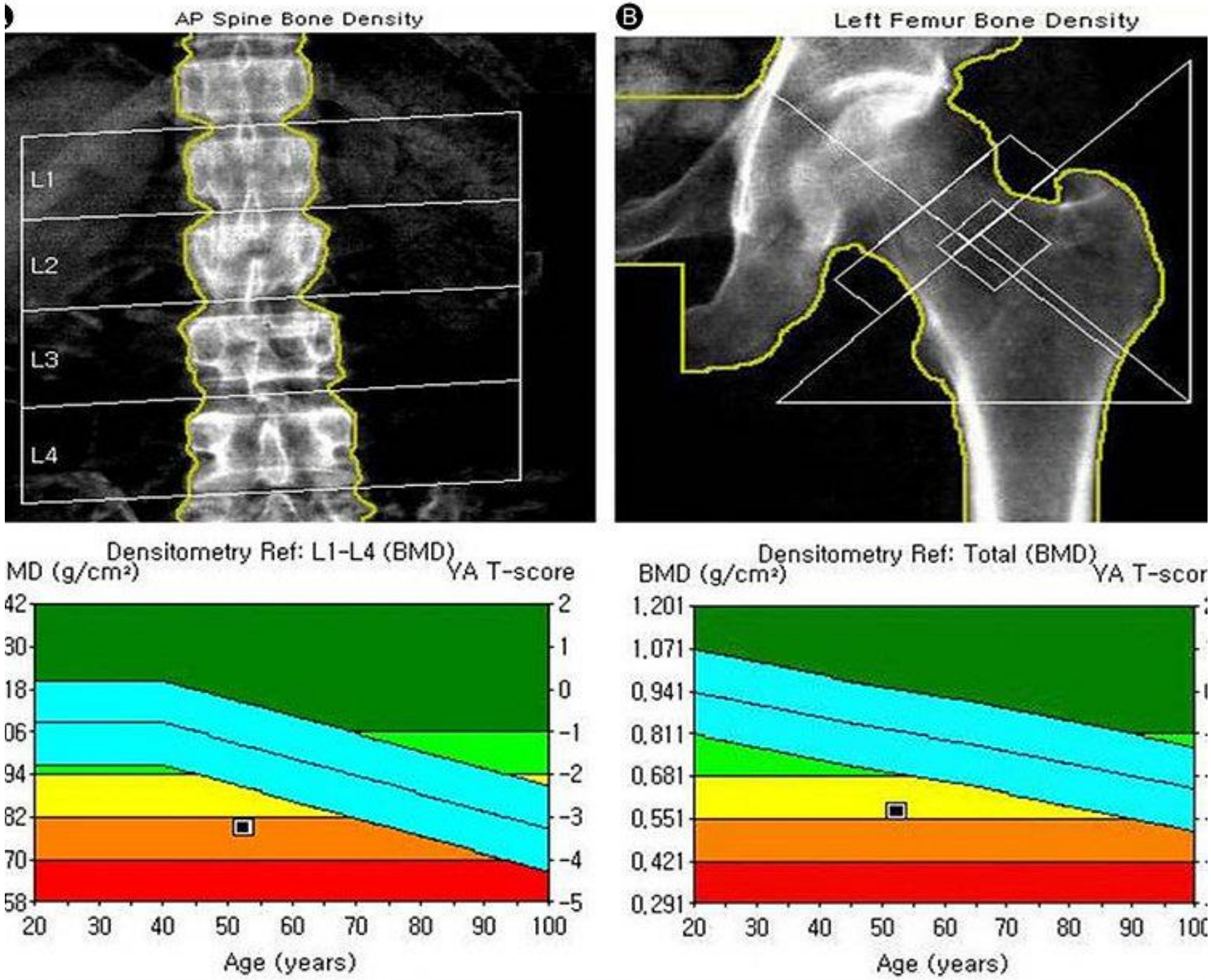
Heart

Liver

Erythropoiesis

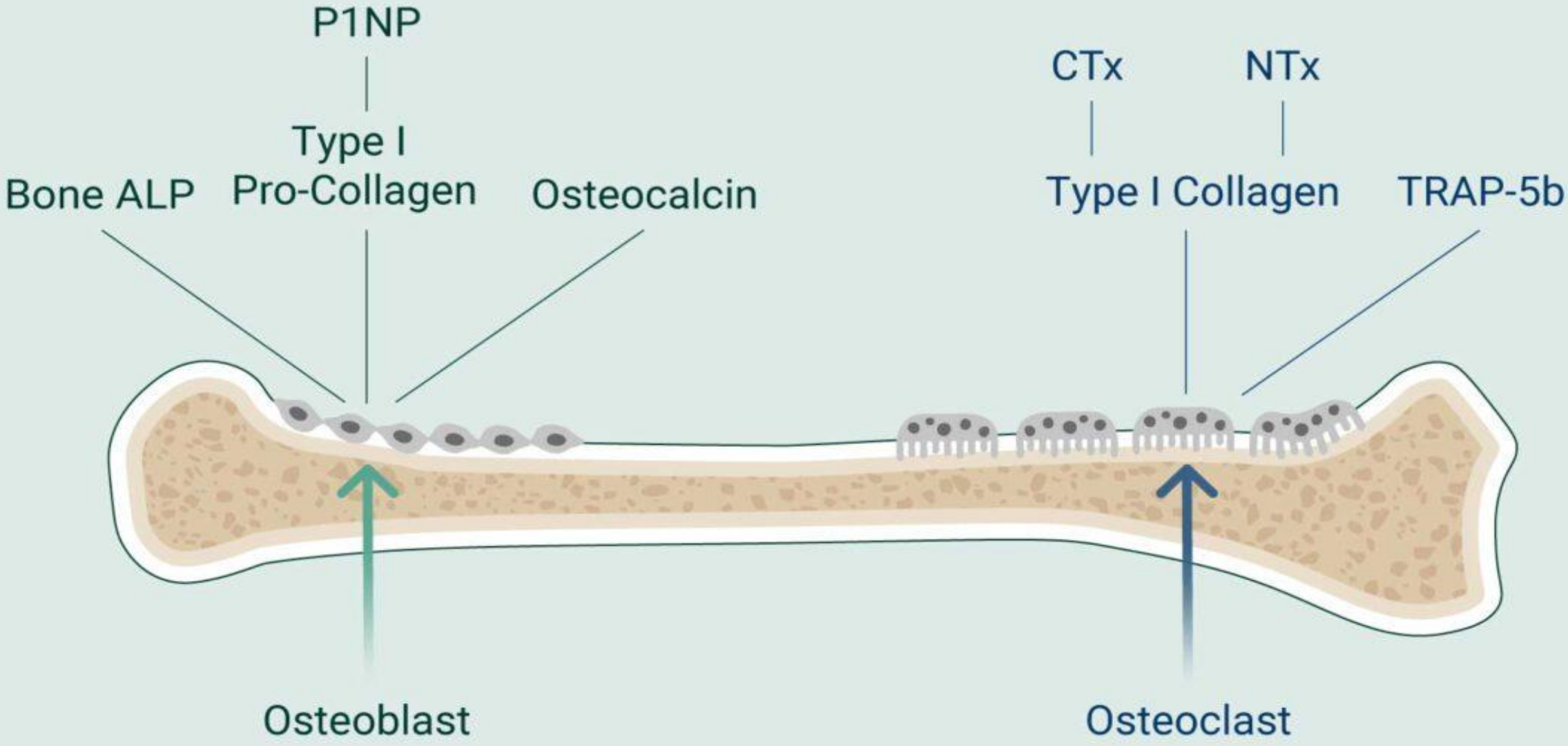
Immune system

New potential therapeutic targets


AP Spine Bone Density
L1
L2
L3
L4
Left Femur Bone Density
Densitometry Ref: L1-L4 (BMD)
MD (g/cm²)
YA T-score
42
30
18
06
94
82
70
58
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age (years)
Densitometry Ref: Total (BMD)
BMD (g/cm²)
YA T-scor
1.201
1.071
0.941
0.811
0.681
0.551
0.421
0.291
20 30 40 50 60 70 80 90 100
Age (years)

Bone Formation Markers

Bone Resorption Markers



In clinical practice …

Biomarker	Sample collection and assay	Predictor of histomorphometry	Predictor of fractures
PTH	Multiple assays and poor standardization between the various assays. High diurnal variation. Levels vary with temperature of plasma specimen. PTH assays detect variable amounts of circulating C-terminal fragments. Some fragments are potentially biologically active. Coefficient of variation within subject in hemodialysis patients is 25.6%.[63]	PTH levels higher with increased bone turnover than those with adynamic bone disease in CKD 3–5,[64] as well as CKD 5D.[65,a] No consistent relationship between PTH and bone formation rates or bone volume.[66] Racial differences.[67]	Inconsistent results for risk stratification between high or low PTH and fractures.[68–70] Decreased fracture risk after parathyroidectomy.[71]
Bone-specific alkaline phosphatase (b-alp)	Coefficient of variation within subject in hemodialysis patients is 12.5%.[72] Assay not widely available clinically. Crossreactivity of assay with the liver-derived alkaline phosphate fraction.	The b-alp levels are higher with higher bone turnover in CKD 5D.[22,73,a] No relationship of b-alp with bone volume.[22,74]	No prospective data on b-alp and risk of fractures in CKD. Higher risk of fractures in CKD 5D with high total alkaline phosphatase levels.[75]

Abbreviations: CKD, chronic kidney disease; PTH, parathyroid hormone.

[a]PTH measured by the intact assay (Elecsys PTH 91-84 assay; Roche Diagnostics, Indianapolis, IN) was equally predictive of bone-specific alkaline phosphatase (b-alp) of underlying bone turnover with a sensitivity of 0.58 versus 0.403, a positive predictive value of 0.373 versus 0.287, and a negative predictive value of 0.903 versus 0.877 (PTH vs. b-alp, respectively) for the detection of increased bone formation rates. The two together did not improve sensitivity or specificity.[45]

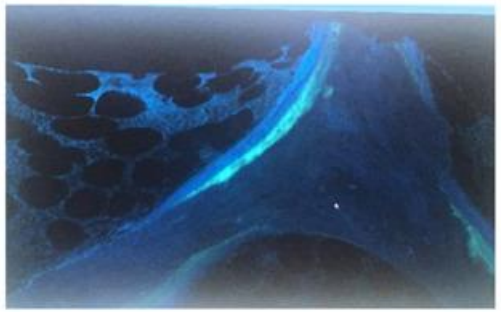
Diagnostic Accuracy of Noninvasive Bone Turnover Markers in Renal Osteodystrophy

Methods

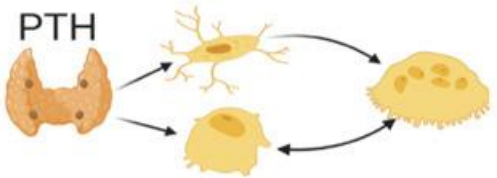
Participants

N = 199 kidney transplant candidates and recipients

Bone biopsy



Bone biomarkers

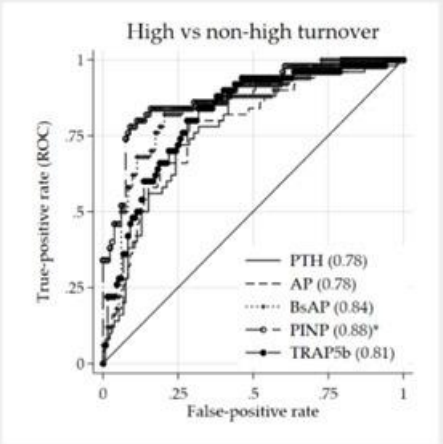


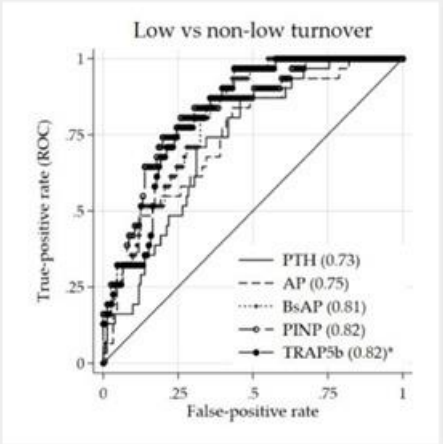
BsAP
P1NP

TRAP5b

Exploration Set (N = 100)

Optimal Diagnostic Cutoffs



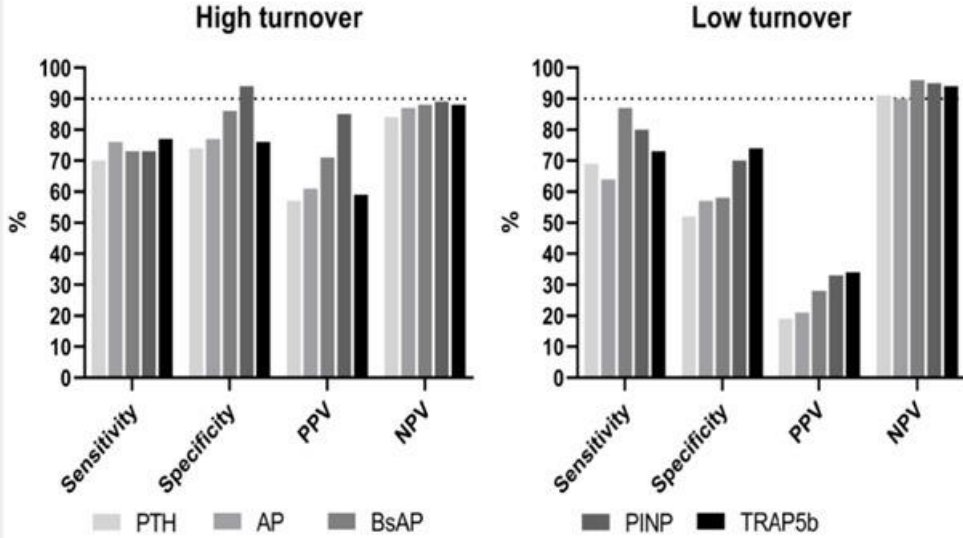


Two-step approach

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

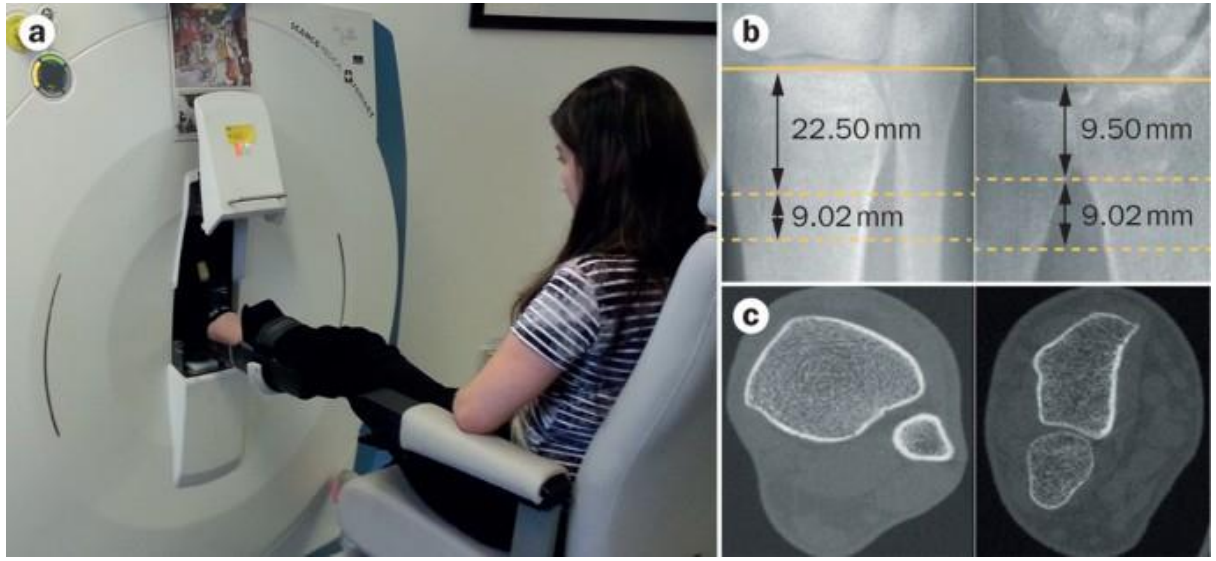
CONCLUSION: Circulating bone turnover markers show acceptable diagnostic performance for bone turnover and may be used to rule out high and low bone turnover.

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

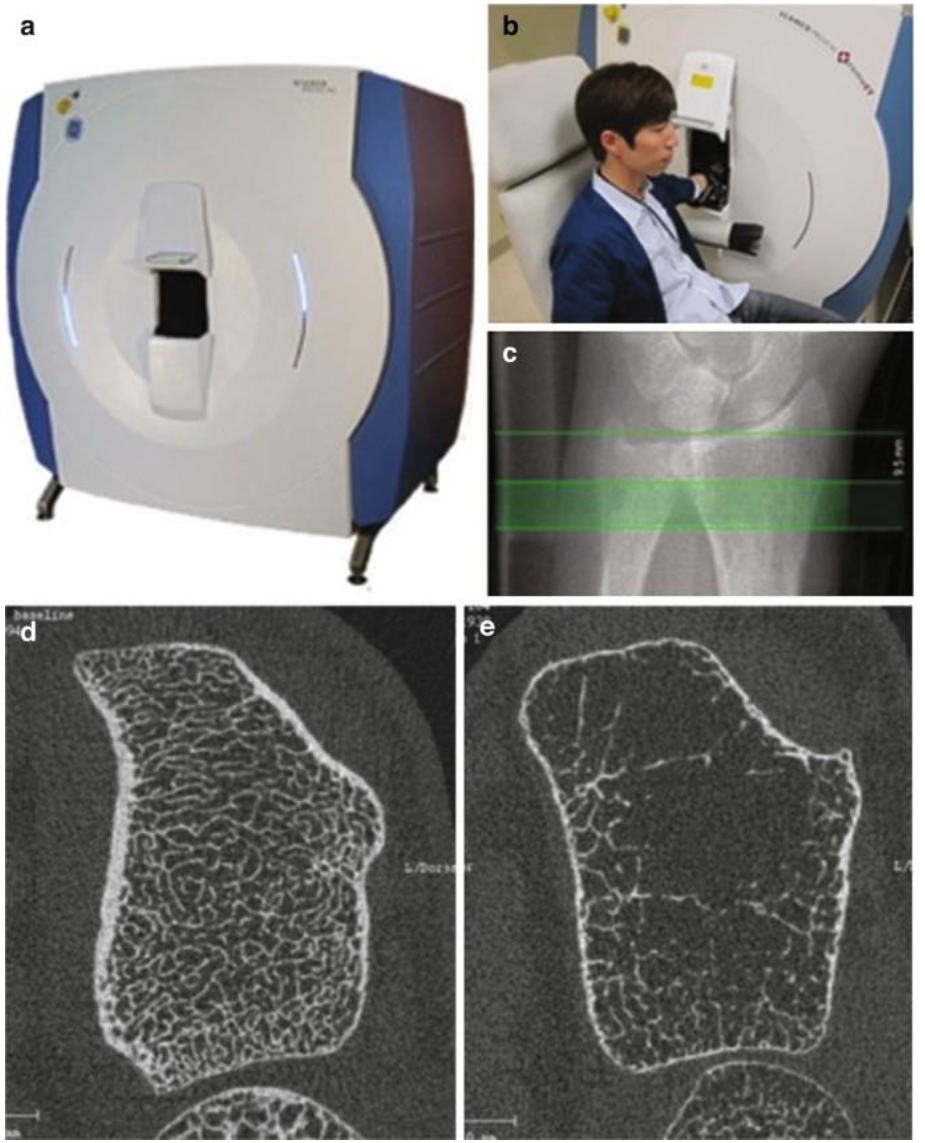
@AJKDonline | DOI: 10.1053/j.ajkd.2021.07.027

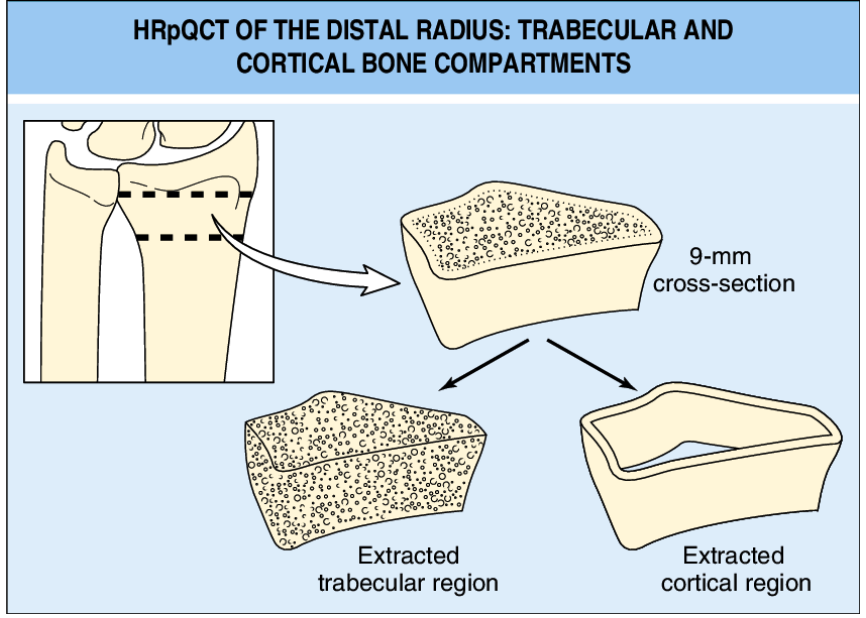
AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

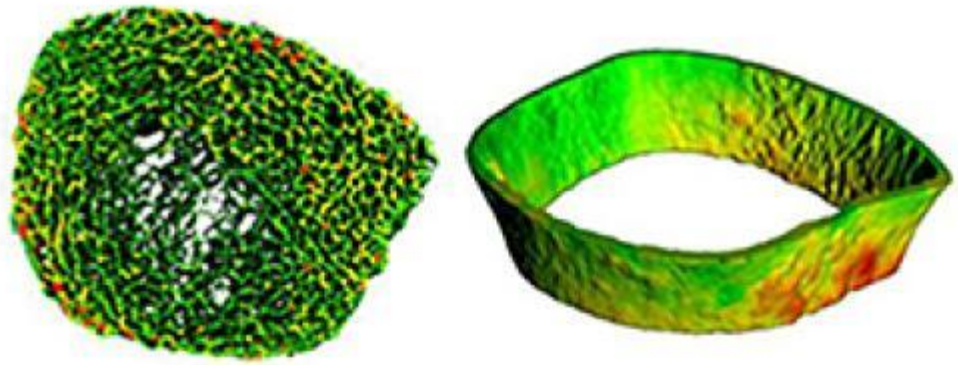
HR-pQCT

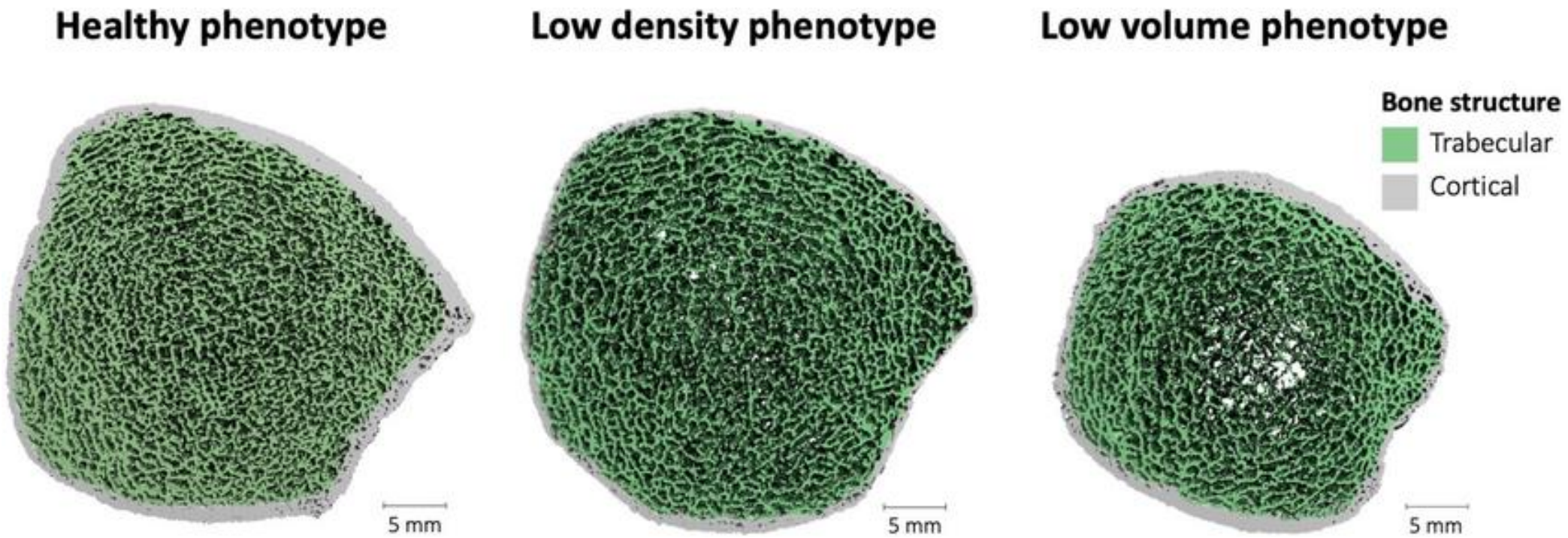


Quantifies both bone density & bone quality (micro-architecture)
Detects early changes in bone quality seen in **CKD**
Poor micro-architecture contributes to Fx risk
independently of BMD



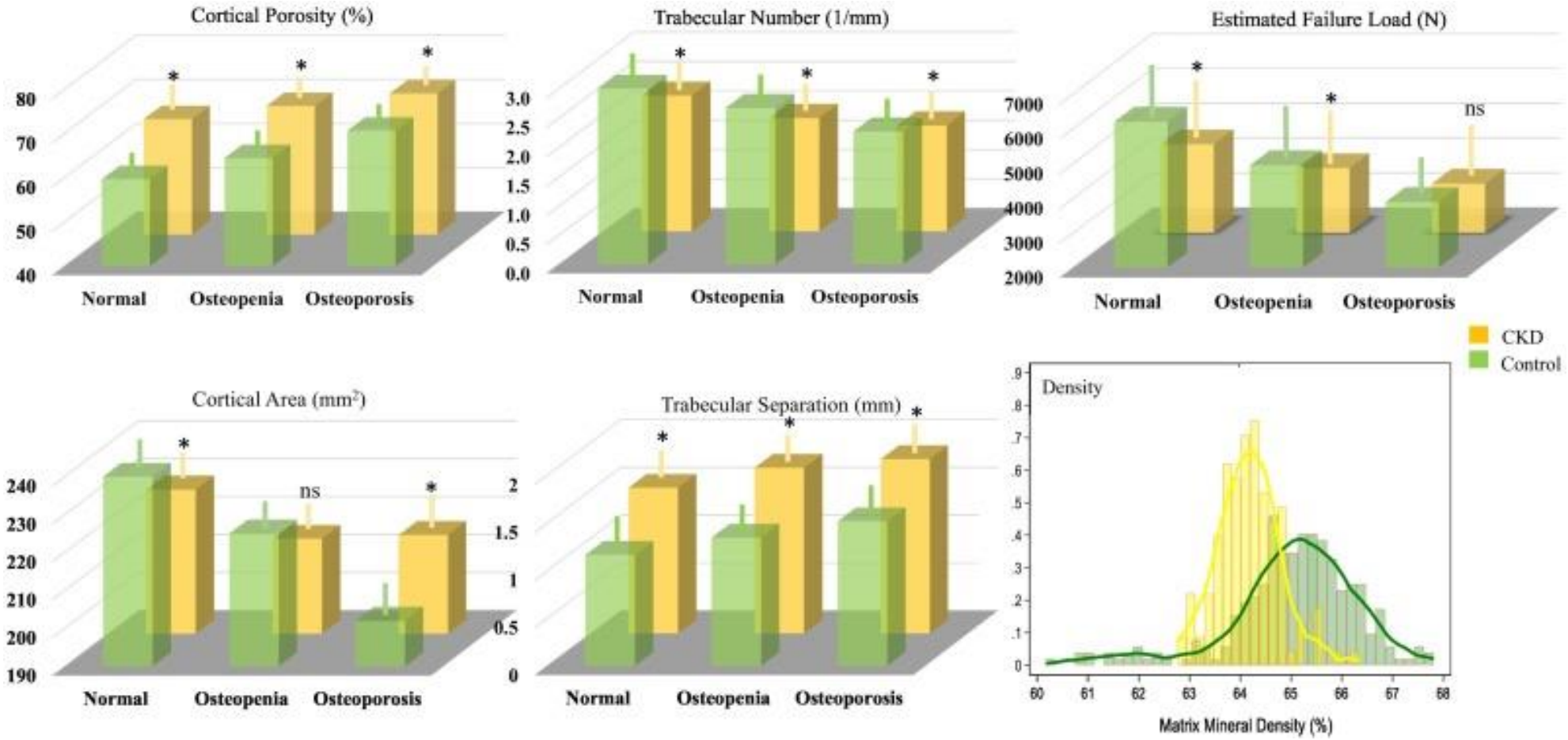

HRpQCT OF THE DISTAL RADIUS: TRABECULAR AND CORTICAL BONE COMPARTMENTS
9-mm cross-section
Extracted trabecular region
Extracted cortical region

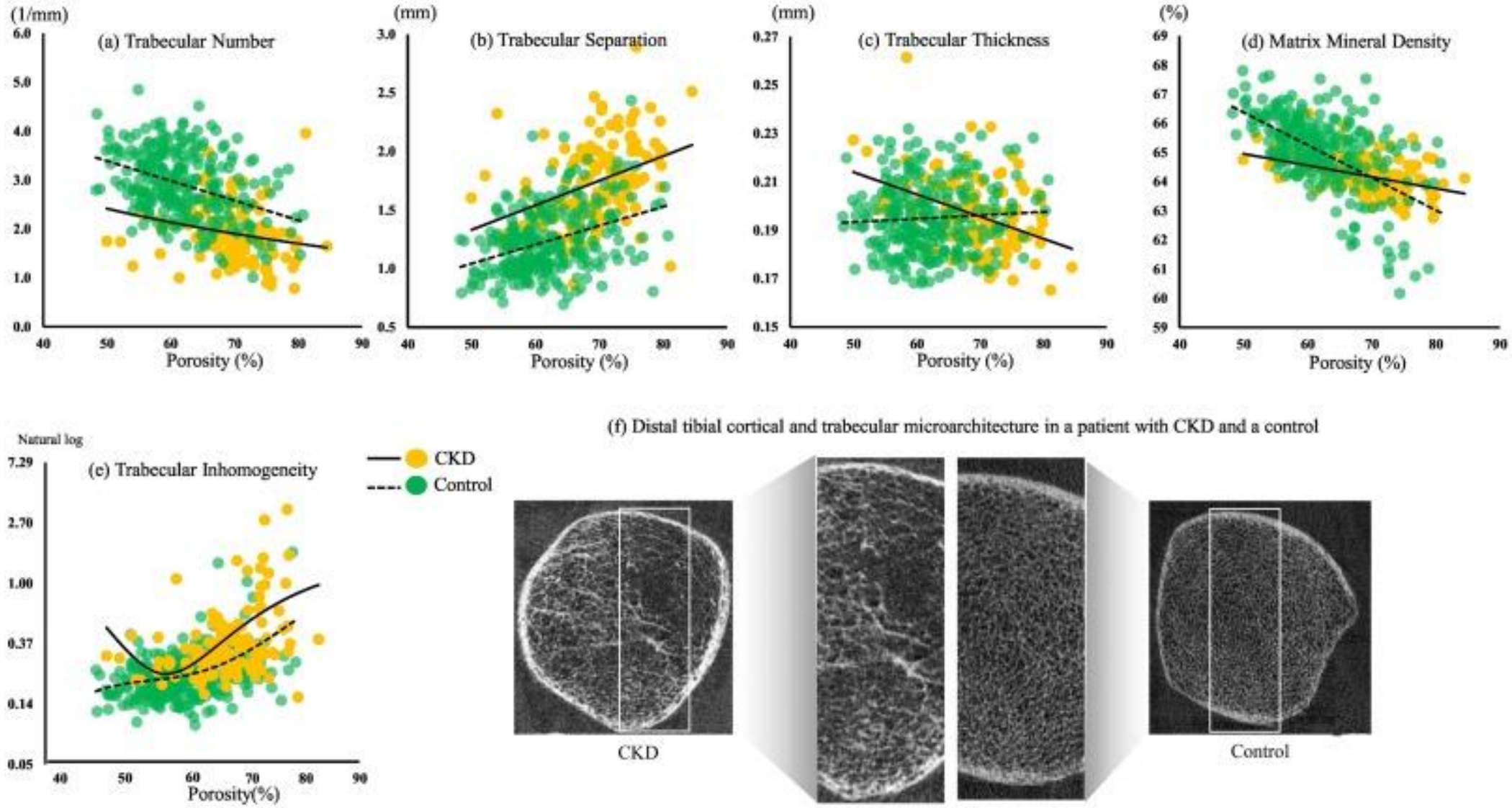


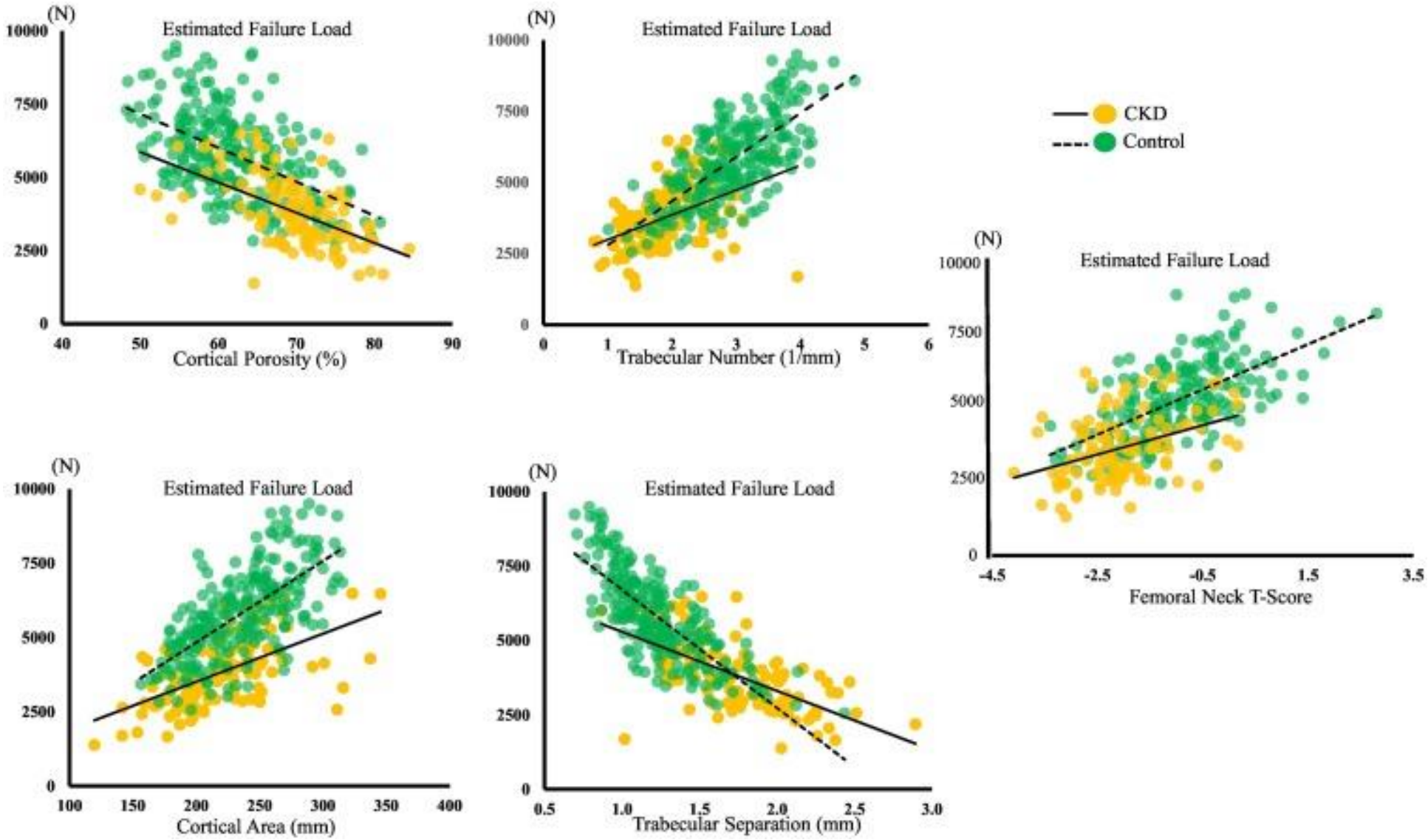

Healthy phenotype
Low density phenotype
Low volume phenotype
Bone structure
Trabecular
Cortical
5 mm
5 mm
5 mm

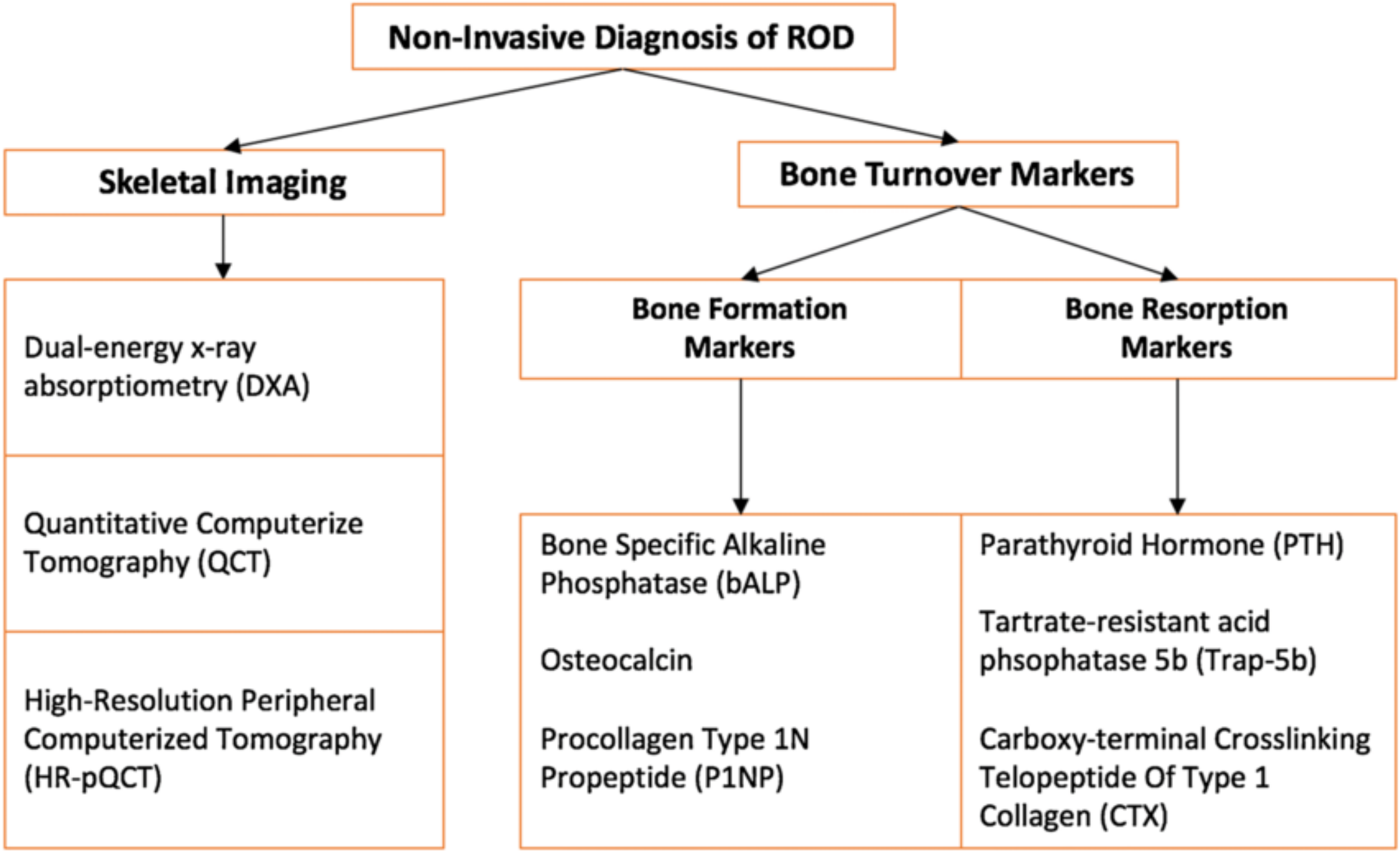
At any level of DEXA-defined bone density (Osteopen or Osteopor), if there is **concomitant CKD**, bone **quality will be worse**

Normal & CKD pts imaging with DEXA & HR-QCT & failure load = strength of bone stratified by: whether DEXA is Nl, Osteopen, Osteopor

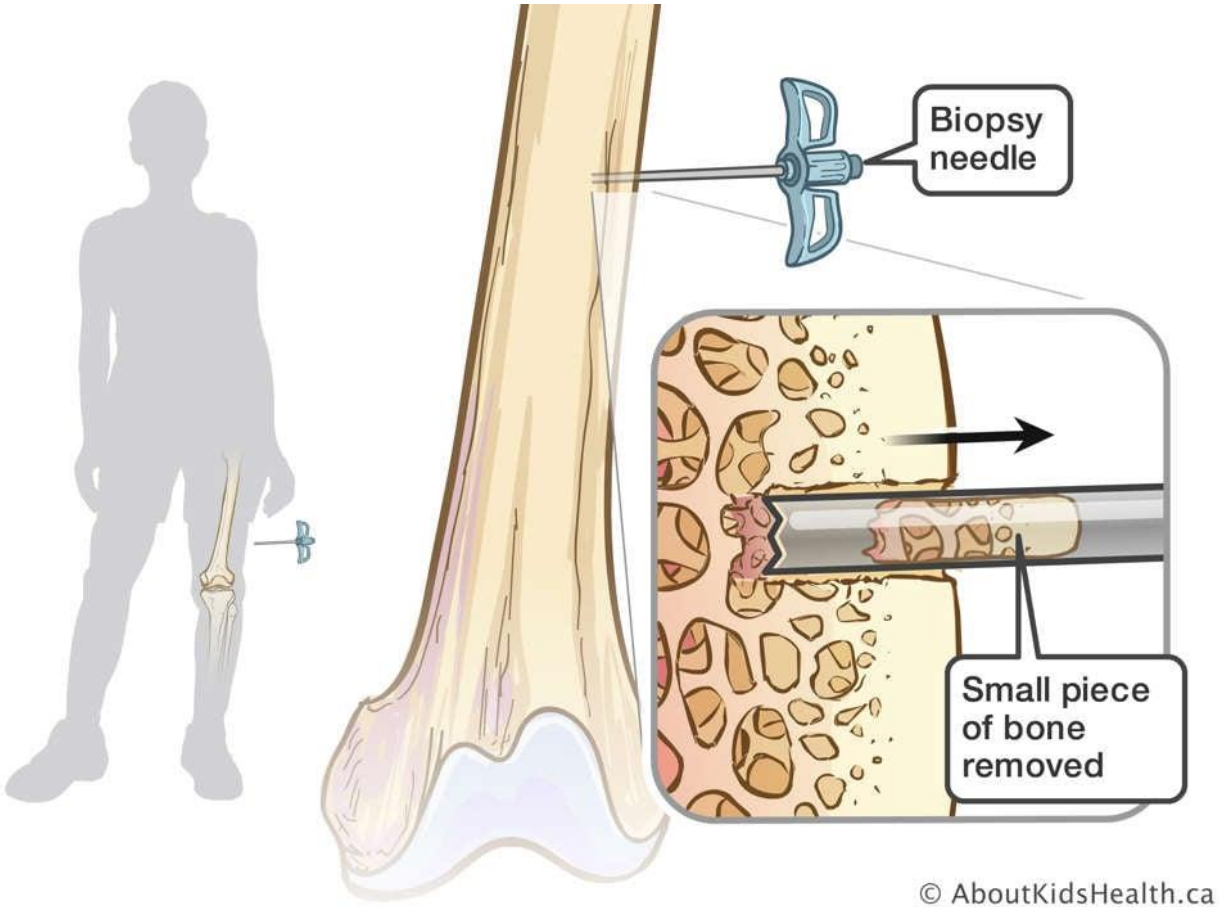


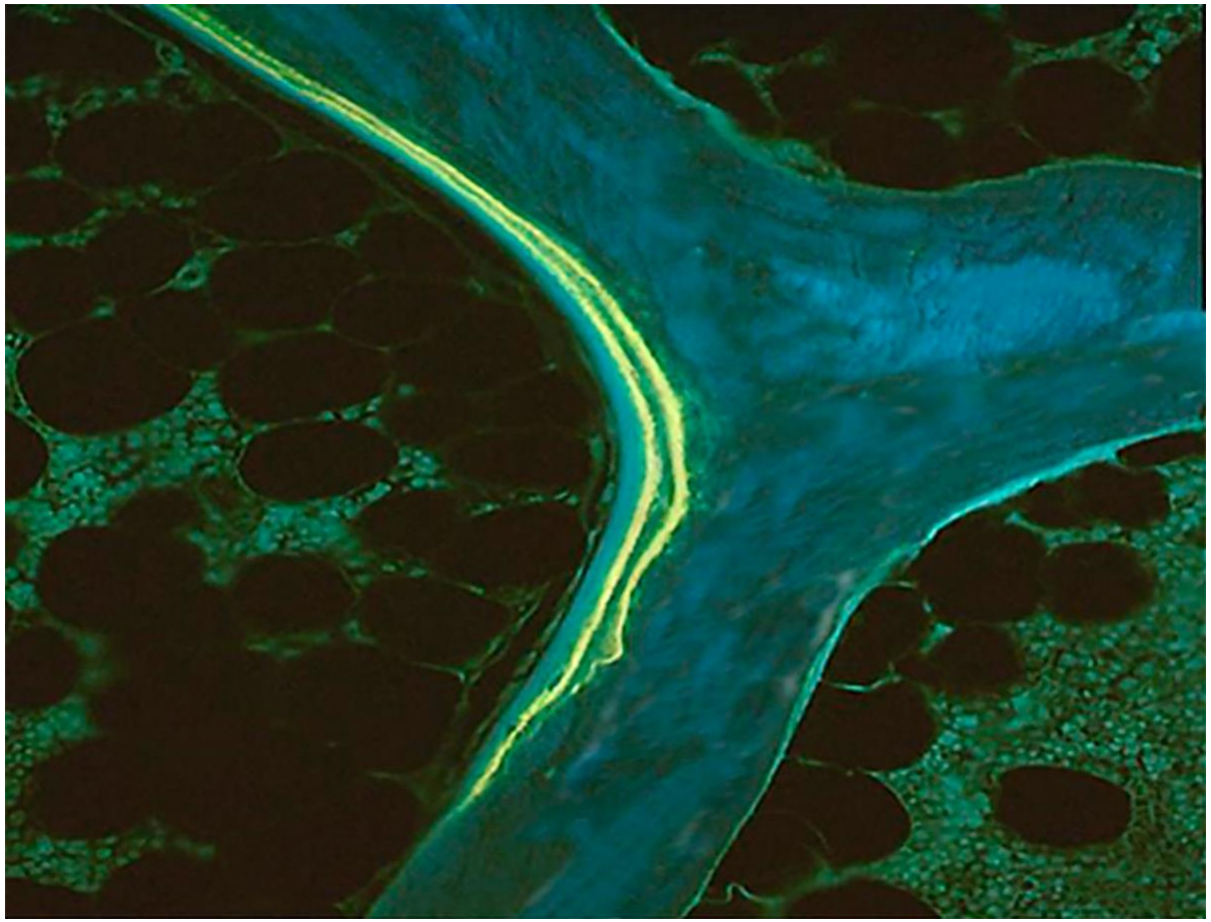

(1/mm)
(a) Trabecular Number
Porosity (%)
(mm)
(b) Trabecular Separation
Porosity (%)
(mm)
(c) Trabecular Thickness
Porosity (%)
(%)
(d) Matrix Mineral Density
Porosity (%)
Natural log
(e) Trabecular Inhomogenicity
Porosity(%)
CKD
Control
(f) Distal tibial cortical and trabecular microarchitecture in a patient with CKD and a control
CKD
Control

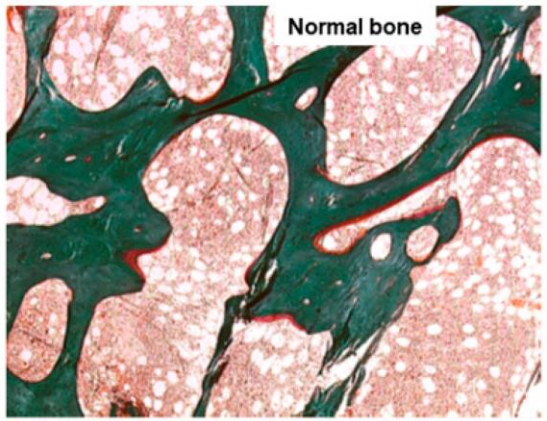

(N)
Estimated Failure Load
10000
7500
5000
2500
0
40
50
60
70
80
90
Cortical Porosity (%)
(N)
Estimated Failure Load
10000
7500
5000
2500
0
0
1
2
3
4
5
6
Trabecular Number (1/mm)
CKD
Control
(N)
Estimated Failure Load
10000
7500
5000
2500
0
-4.5
-2.5
-0.5
1.5
3.5
Femoral Neck T-Score
(N)
Estimated Failure Load
10000
7500
5000
2500
0
100
150
200
250
300
350
400
Cortical Area (mm)
(N)
Estimated Failure Load
10000
7500
5000
2500
0
0.5
1.0
1.5
2.0
2.5
3.0
Trabecular Separation (mm)

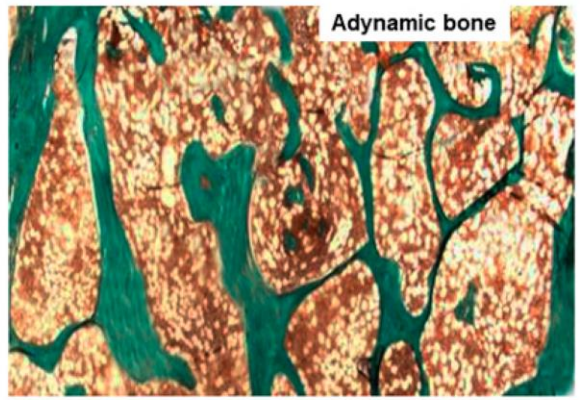

Non-Invasive Diagnosis of ROD
Skeletal Imaging
Bone Turnover Markers
Dual-energy x-ray absorptiometry (DXA)
Quantitative Computerize Tomography (QCT)
High-Resolution Peripheral Computerized Tomography (HR-pQCT)
Bone Formation Markers
Bone Resorption Markers
Bone Specific Alkaline Phosphatase (bALP)
Osteocalcin
Procollagen Type 1N Propeptide (P1NP)
Parathyroid Hormone (PTH)
Tartrate-resistant acid phsophatase 5b (Trap-5b)
Carboxy-terminal Crosslinking Telopeptide Of Type 1 Collagen (CTX)

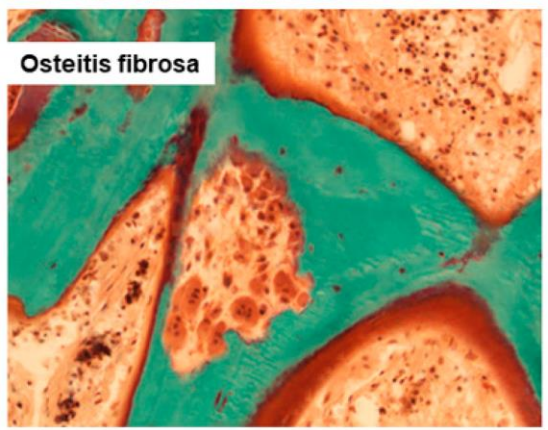
Bone Biopsy is the Gold Standard @ the iliac crest

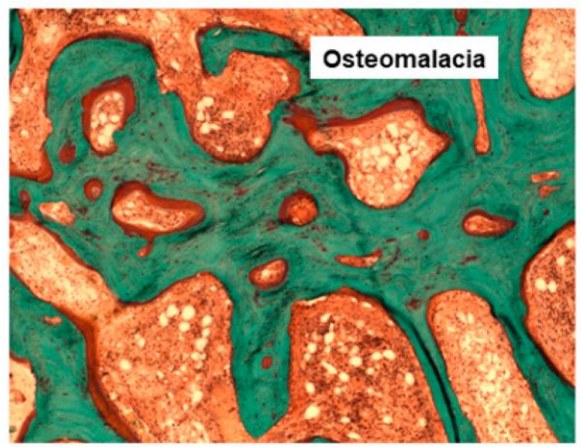


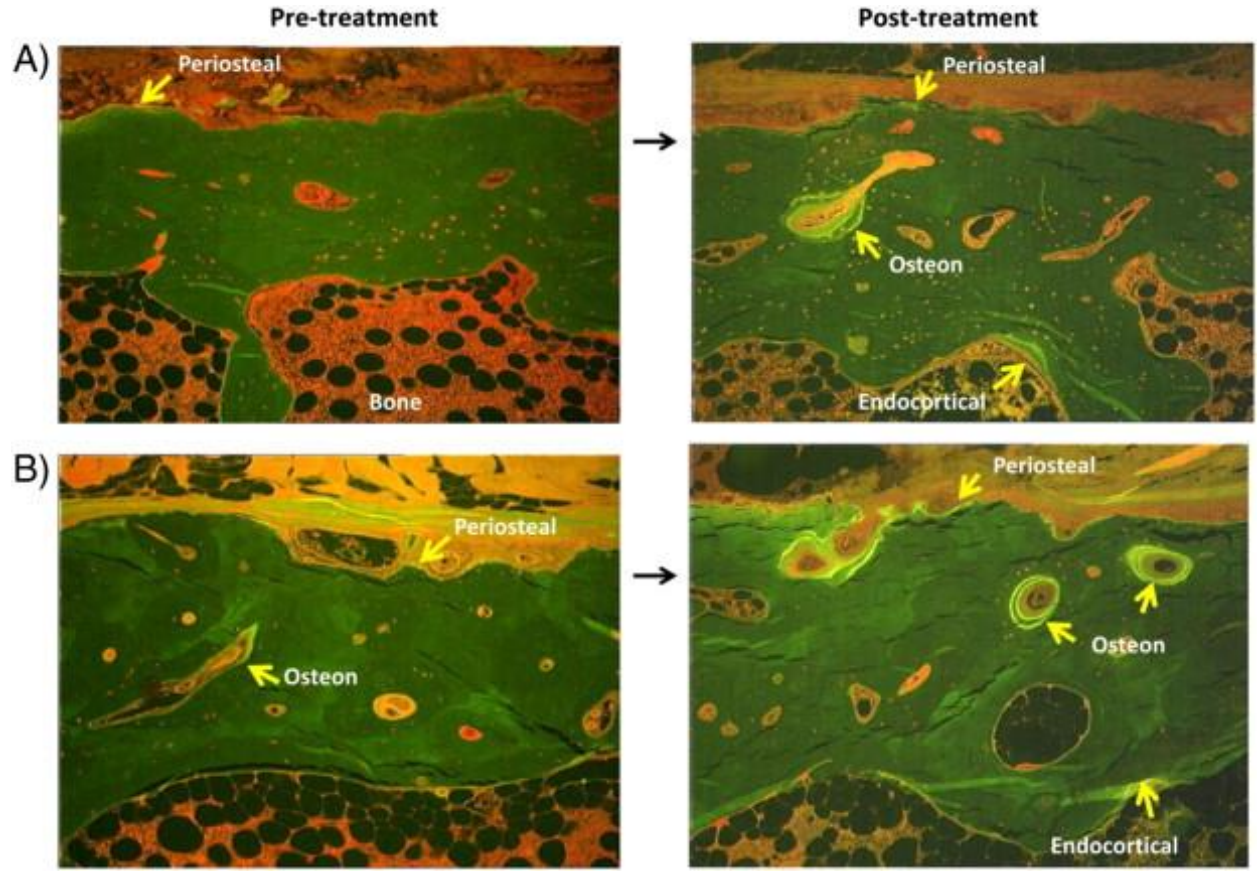



Normal bone


Adynamic bone


Osteitis fibrosa


Osteomalacia


Pre-treatment
Post-treatment
A)
Periosteal
Bone
Periosteal
Osteon
Endocortical
B)
Periosteal
Osteon
Periosteal
Osteon
Endocortical

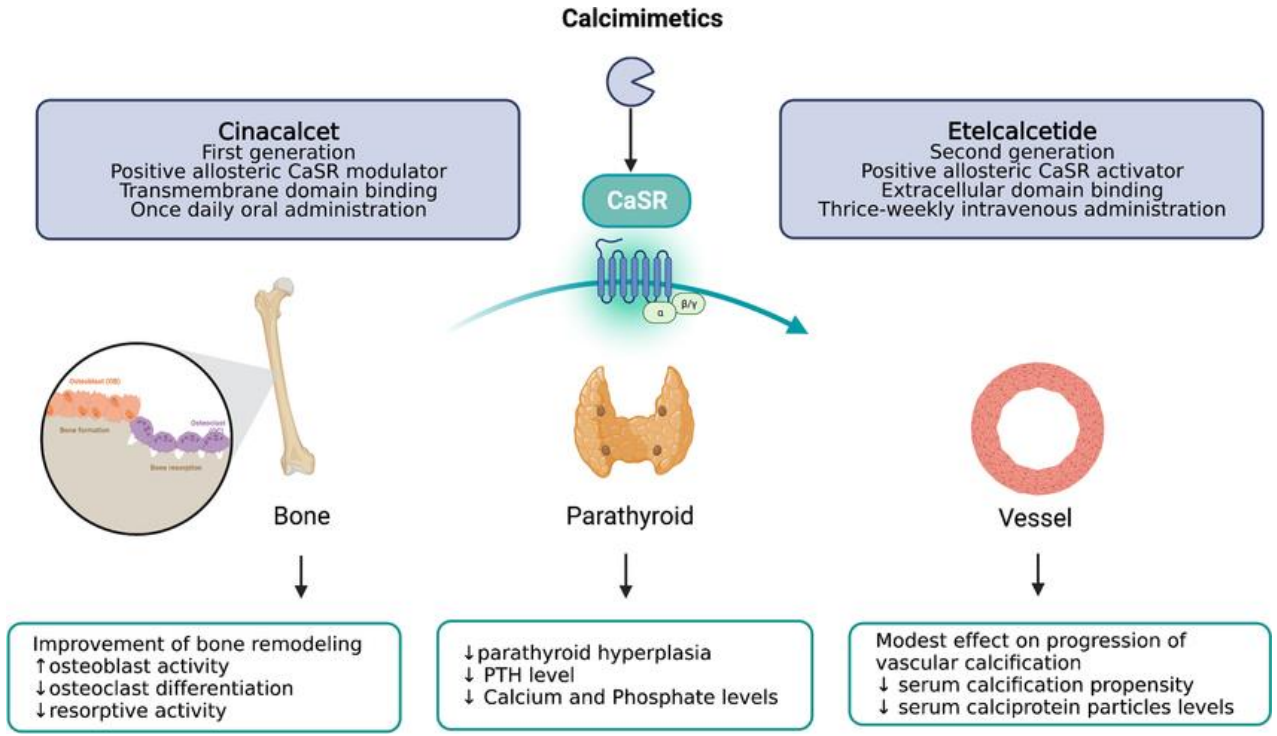
Vit D

Improves mineralization and treats high turnover bone disease

Table 26. Recommended Supplementation f… in Patients with C… …sy/Insufficiency

Serum 25(OH)D (ng/mL) [nmol/L]	Definition	Ergo…		Comment
<5 [12]	Severe vit… D…		…months	Measure 25(OH)D levels after 6 months
		…I.M.		Assure patient adherence; measure 25(OH)D at 6 months
5-15 [12-37]		…0/wk x 4 weeks, …en 50,000 IU/month orally	6 months	Measure 25(OH)D levels after 6 months
16-30 [40-75]	…D …ficiency	50,000 IU/month orally	6 months	

No data from well-powered trials to show they improve Fx risk in CKD/ESRD

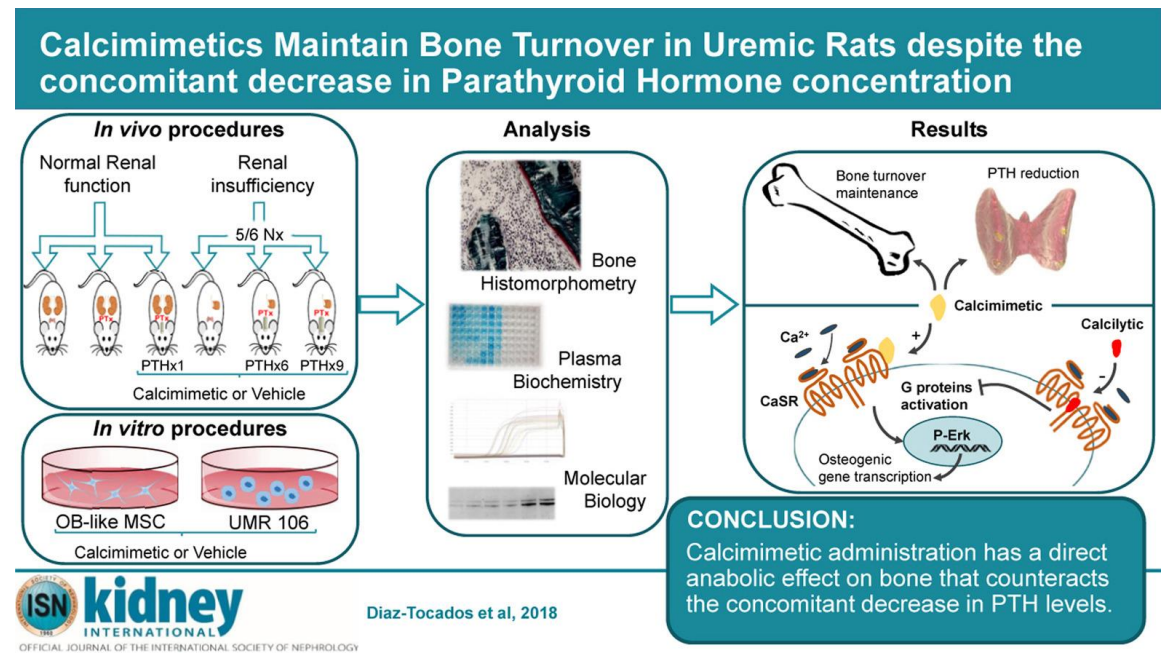


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

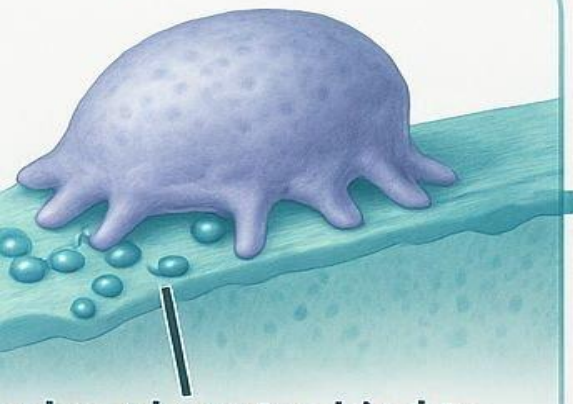
The EVOLVE Trial Investigators*



Mechanism of Action of Bisphosphonates

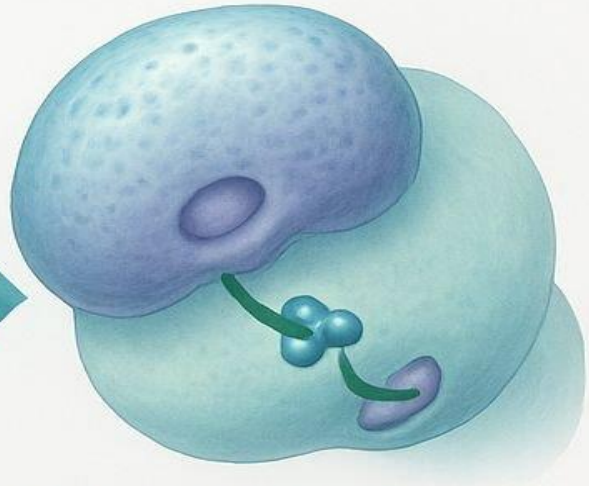
Bone Context

Bisphosphonates



sphosphonates bind to
ne mineral (hydroxapatite)

Osteoclast



Osteoclast takes up
Bisphosphonate

Cellular Mechanisms

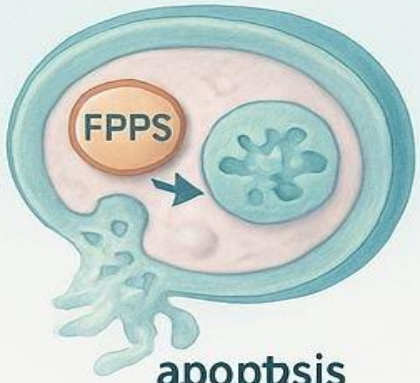
Non-Nitrogen:
Toxic ATP Analogs

steoclast

Osteoclast apoptosis

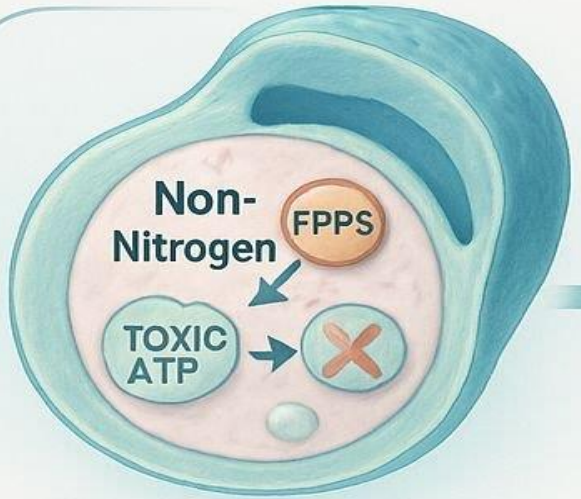
Nitrogen:
Inhibits FPPS

↓ Protein
Prenylation

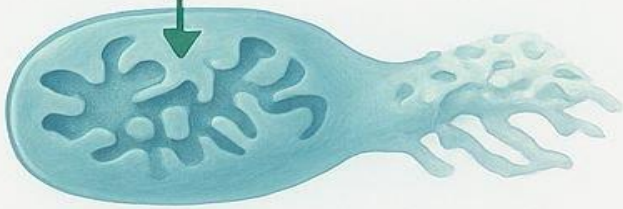


apoptsis

Net Bone Effect



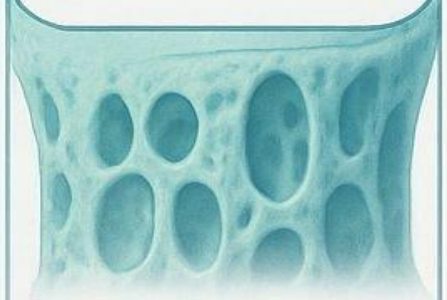
Non-Nitrogen:
Inhibits FPPS
↓ Protein Prenylation



Osteoporosis:
↓ Fractures

Prevents
Skeletal Events

↑ Bone Resorption
↑ Bone Density



Treats
Hypercalcemia
of Malignancy

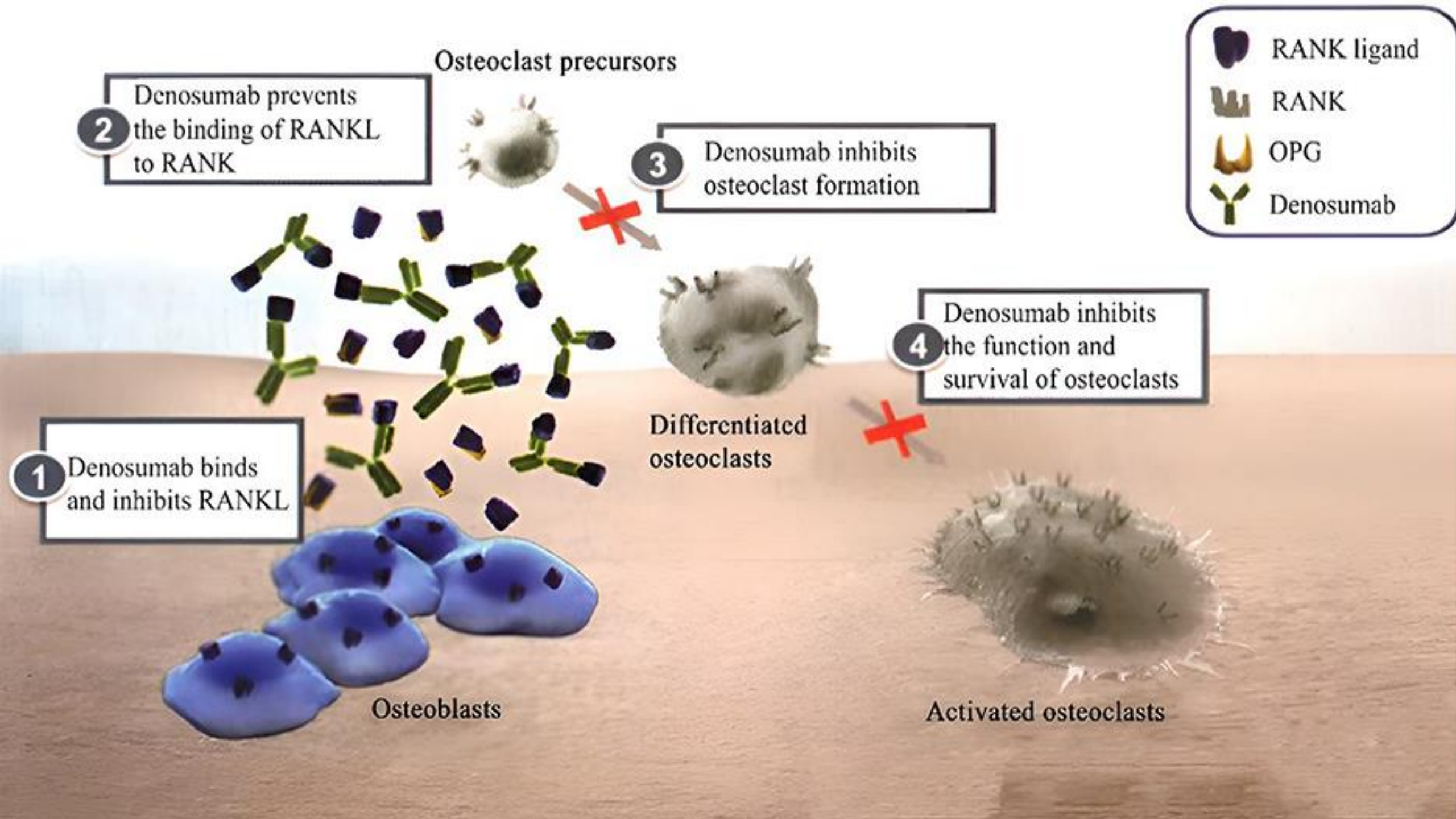
Table 1. Bisphosphonate Summary Data

Drug	Approved Indications	Dosing Frequency	Dosage Adjustment for Renal Function[a]	Clinical Trial Notes
Zoledronic acid (Reclast, Zometa)	Osteoporosis, PD, GIO, HM, osteolytic lesions of MM, osteolytic bone met of BC	Every 3–4 wk annually/ biannually, depending on indication	CrCl <35 mL/min: not indicated	Data lacking in CKD pts; nephrotoxicity reported in pts with normal renal function
Risedronate (Actonel)	Osteoporosis, GIO, PD	Daily/wkly	CrCl <30 mL/min: not indicated	5 mg/day for ≤3 y studied in =4,500 PM pts with mild, moderate, severe renal impairment; no major ADEs
Alendronate (Fosamax)	Osteoporosis, GIO, PD	Daily/wkly	CrCl <35 mL/min: not indicated	No ADEs on renal function; pts with CrCl <45 mL/min received ≤10 mg/day; no ADEs
Etidronate (Didronel)	PD, heterotrophic ossification	Daily	Adjustment recommended but not defined; SCr >5 mg/dL: not indicated	Data lacking in CKD pts
Ibandronate (Boniva)	PM osteoporosis	Daily/monthly/ every 3 mo	CrCl <30 mL/min: not indicated	Small studies in HD pts; no ADEs on renal function
Pamidronate (Aredia)	PD, osteolytic lesions of MM, osteolytic bone met of BC, HM	Every 3–4 wk	Max 90 mg/mo	ARF reported, even at standard doses
Tiludronate (Skelid)	PD	400 mg/day for 3 mo	CrCl <30 mL/min: not indicated	Data lacking in CKD pts

[a] *As per manufacturer.*

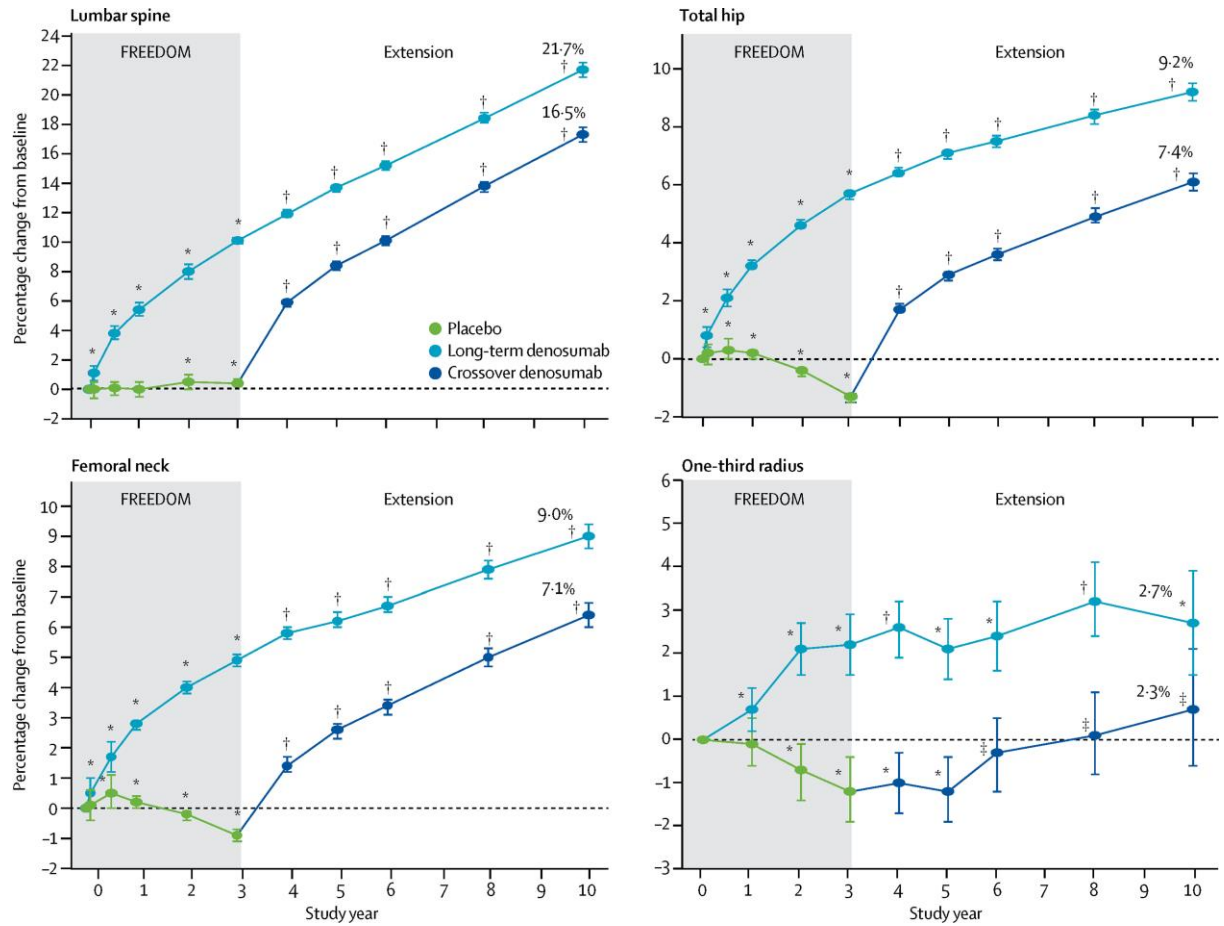
ADE: adverse drug event; ARF: acute renal failure; BC: breast cancer; CKD: chronic kidney disease; CrCl: creatinine clearance; GIO: glucocorticoid-induced osteoporosis; HD: hemodialysis; HM: hypercalcemia of malignancy; max: maximum; met: metastasis; MM: multiple myeloma; PD: Paget's disease; PM: postmenopausal; pt: patient; SCr: serum creatinine.

Source: References 6-14, 17, 24, 34, 40-41.


RANK ligand
RANK
OPG
Denosumab
Osteoclast precursors
2 Denosumab prevents the binding of RANKL to RANK
3 Denosumab inhibits osteoclast formation
1 Denosumab binds and inhibits RANKL
Differentiated osteoclasts
4 Denosumab inhibits the function and survival of osteoclasts
Osteoblasts
Activated osteoclasts

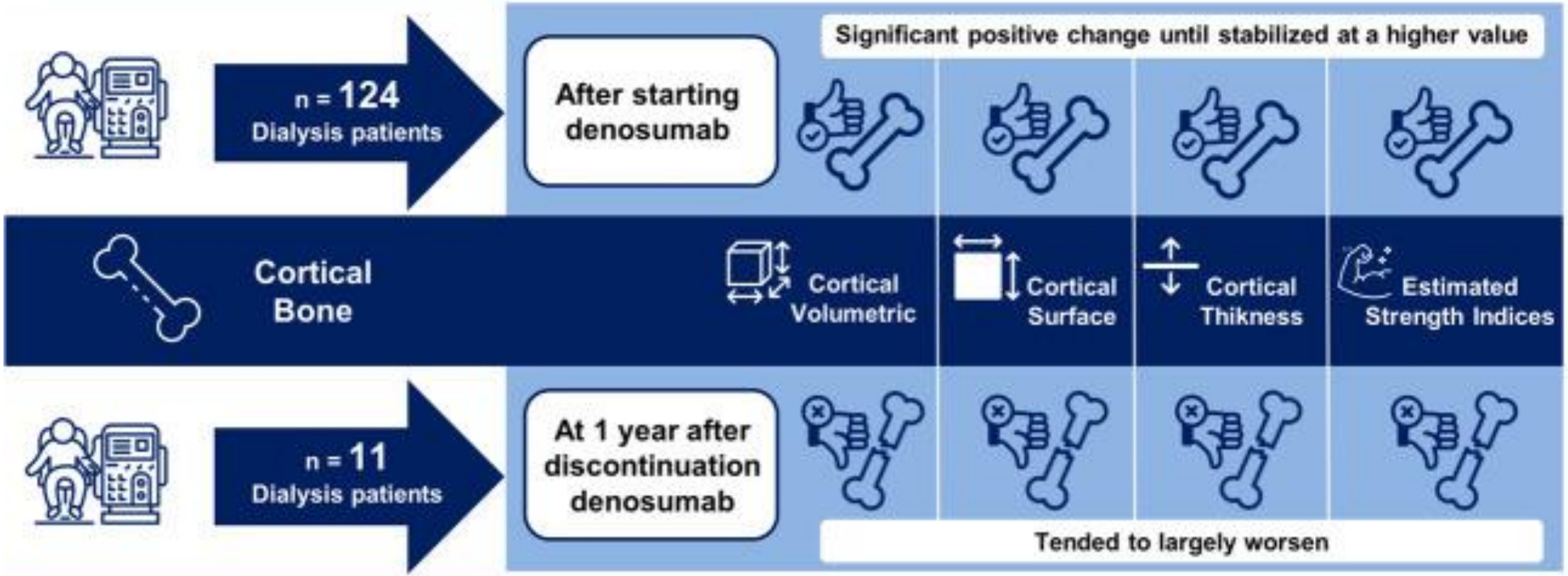
10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension

Henry G Bone, Rachel B Wagman, Maria L Brandi, Jacques P Brown, Roland Chapurlat, Steven R Cummings, Edward Czerwiński, Astrid Fahrleitner-Pammer, David L Kendler, Kurt Lippuner, Jean-Yves Reginster, Christian Roux, Jorge Malouf, Michelle N Bradley, Nadia S Daizadeh, Andrea Wang, Paula Dakin, Nicola Pannacciulli, David W Dempster, Socrates Papapoulos



Long-term effect of denosumab on bone disease in patients with chronic kidney disease

CJASN
Clinical Journal of the American Society of Nephrology



Conclusions: The cortical and trabecular components in the hip region were significantly higher following denosumab therapy. However, these exhibited a trend of declining substantially after denosumab discontinuation.

Ken Iseri, Masahide Mizobuchi, Renaud Winzenrieth, et al. ***Effect of Long-Term Denosumab Therapy on Cortical Bone in CKD Patients***. CJASN doi: 10.2215/CJN.0000000000000213. **Visual Abstract by Ana Flávia Moura, MD, FASN**

Annals of Internal Medicine

ORIGINAL RESEARCH

Cardiovascular Safety and Fracture Prevention Effectiveness of Denosumab Versus Oral Bisphosphonates in Patients Receiving Dialysis

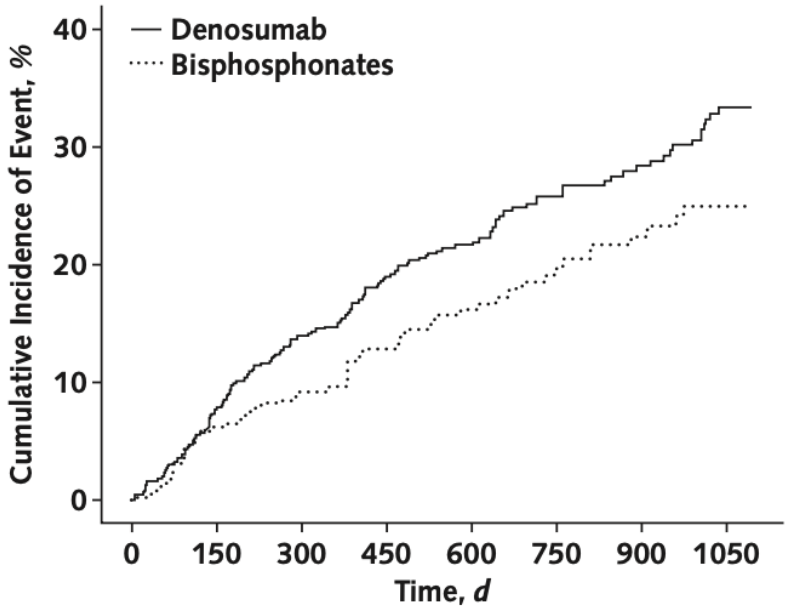
A Target Trial Emulation

Soichiro Masuda, MD, PhD; Toshiki Fukasawa, PhD; Shuichi Matsuda, MD, PhD; and Koji Kawakami, MD, PhD

Differences in risk with denosumab vs. oral bisphosphonates for adults on dialysis:

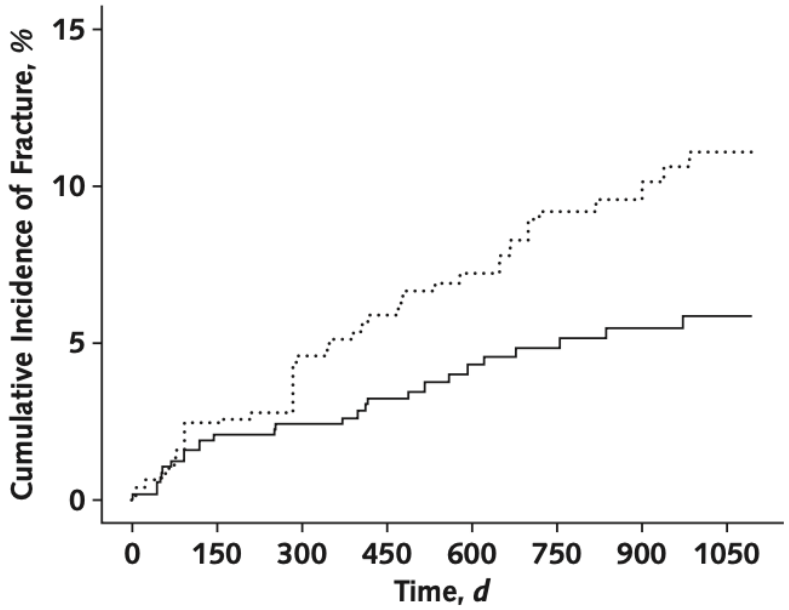
Fracture risk	Cardiovascular risk
↓ 45% LOWER	↑ 36% HIGHER

Major Adverse Cardiac Events



At risk, *weighted n*								
Denosumab	656	525	422	345	265	213	170	120
Bisphosphonates	373	305	253	199	155	124	98	82

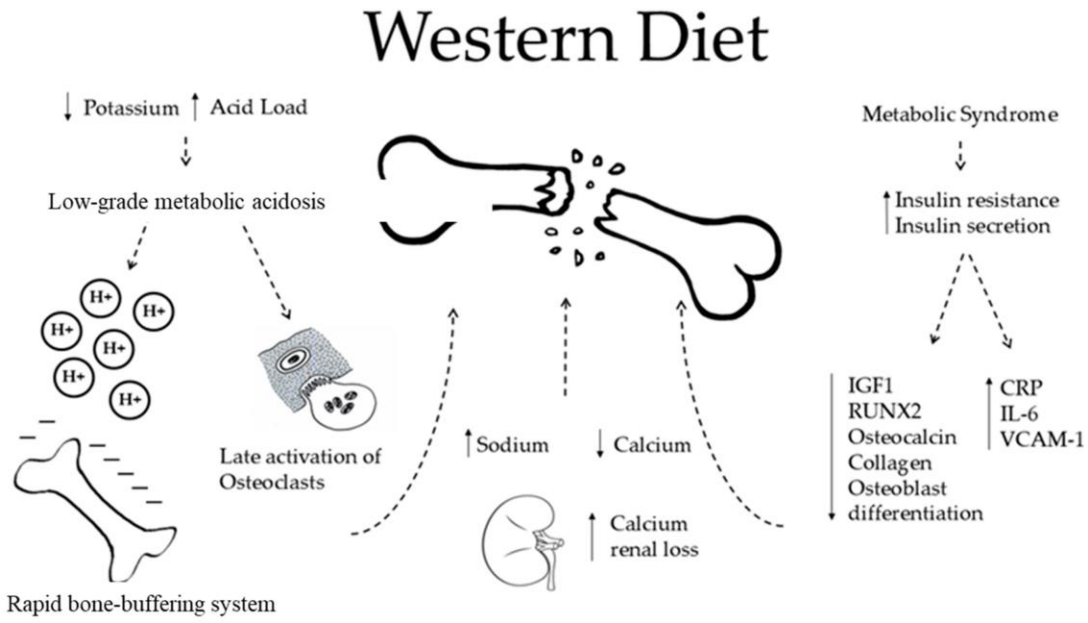
Composite Fracture



At risk, *weighted n*								
Denosumab	656	556	481	417	337	299	260	216
Bisphosphonates	373	319	267	223	182	153	130	116

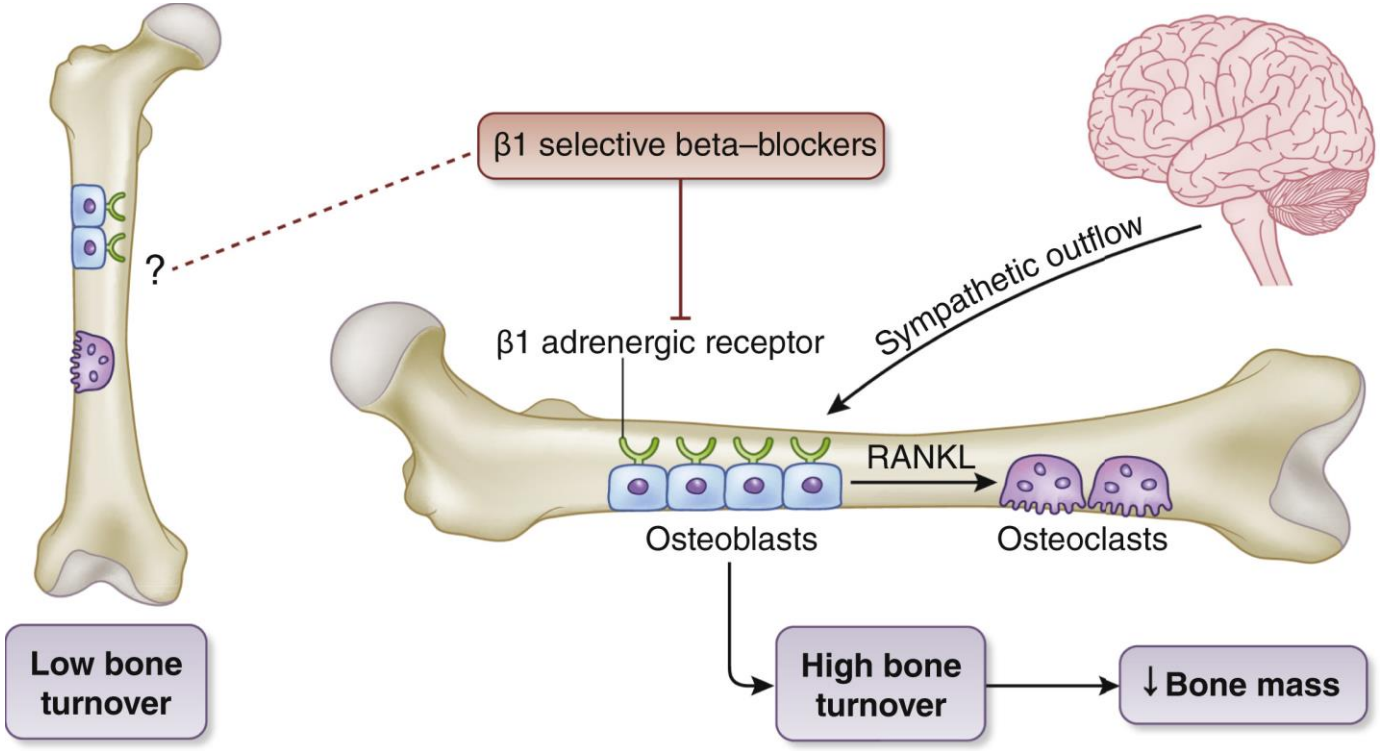
K+-Citrate

- Based on that >>> western diet are high in acid
- The bone is the biggest buffer of acid in the body
- When we eat a high acid diet >>> we leach the Ca out of the bone to mobilize the alkali
- If we give Na-Alkali >>> we will induce Hyper-Ca uria
- 3-4% increase in BMD & suppression of bone resorption & increase in bone formation
- K+-Citrate >>> protective effects from >>> Alkali loading + may be an anabolic effect



Beta-blockers

- Bone is regulated by the SNS
- SNS results in an increase in bone resorption & suppresses bone formation
- Use of beta blockers to protect the skeleton
- Atenolol as a bone protecting agent !



- 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
- So if PTH & bs Alp are not low >>> we would be comfortable to say that we don't have ABD
- The mean barriers is expertise and reading the pathology and not the techniques !

MERCI