Le fratture da fragilità nel paziente in dialisi

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Regione Lombardia
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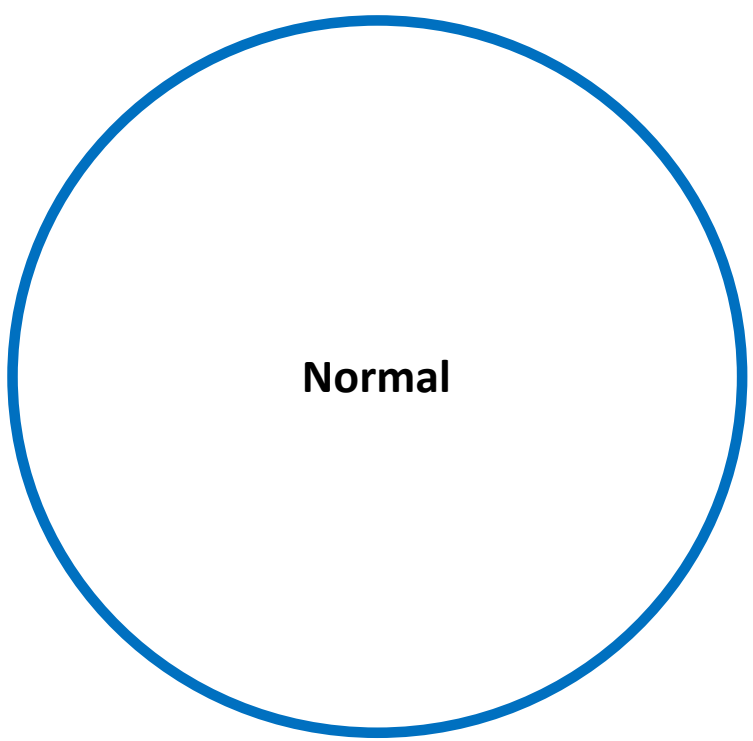
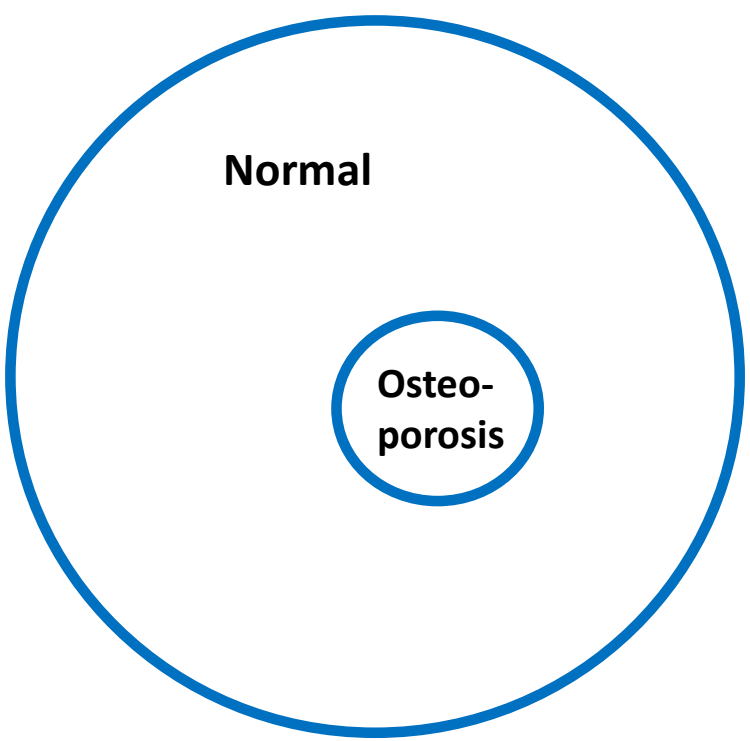
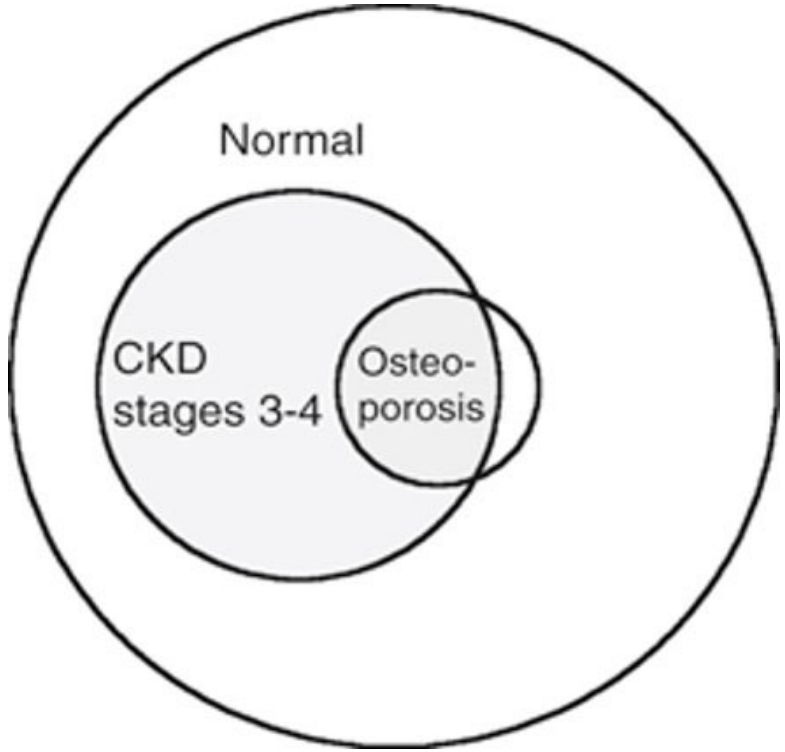
UNIMI SCUOLA DI NEFROLOGIA

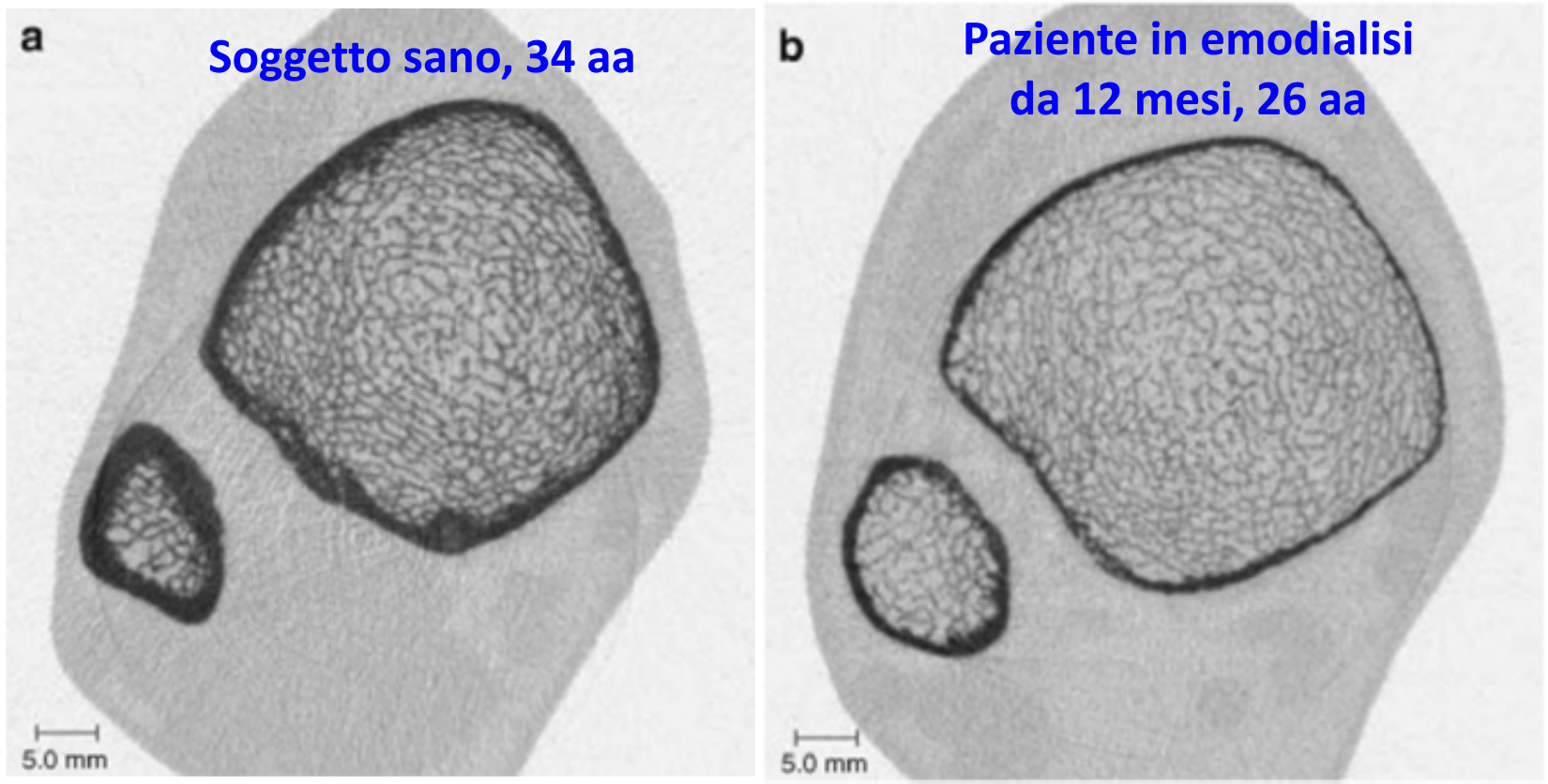
Overlap between osteoporosis and CKD stages 3–4.







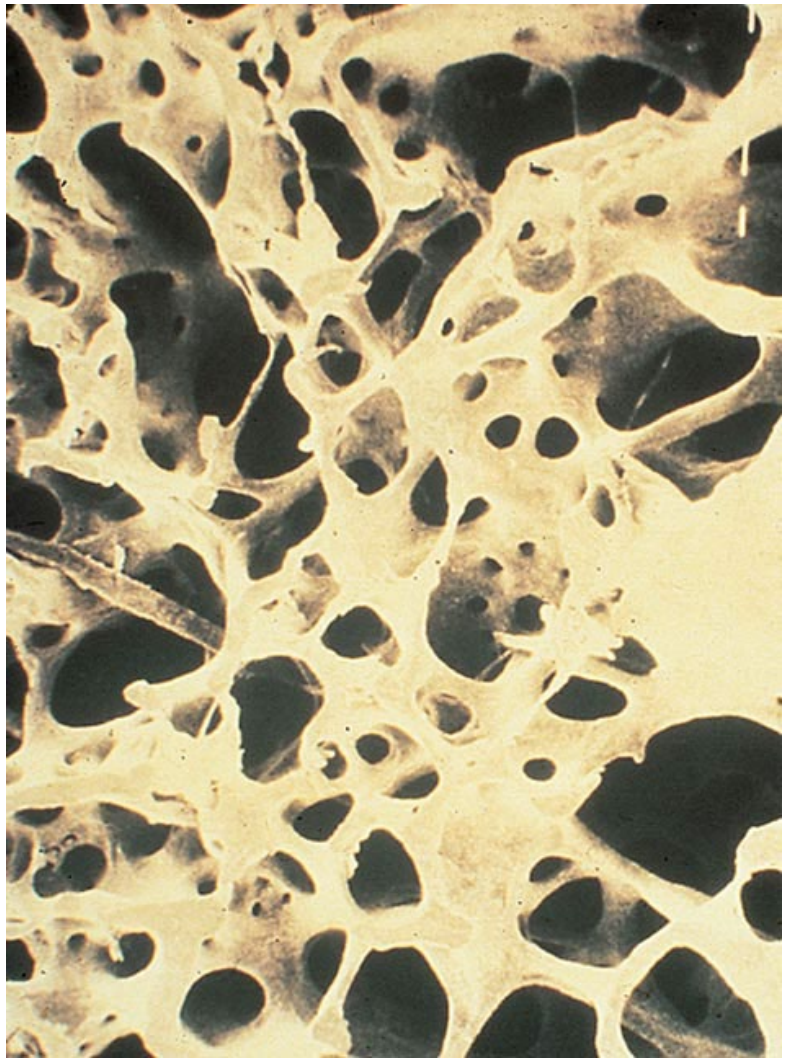
L'osteoporosi associata a CKD-MBD è un problema? Il rischio di fratture è significativamente elevato?

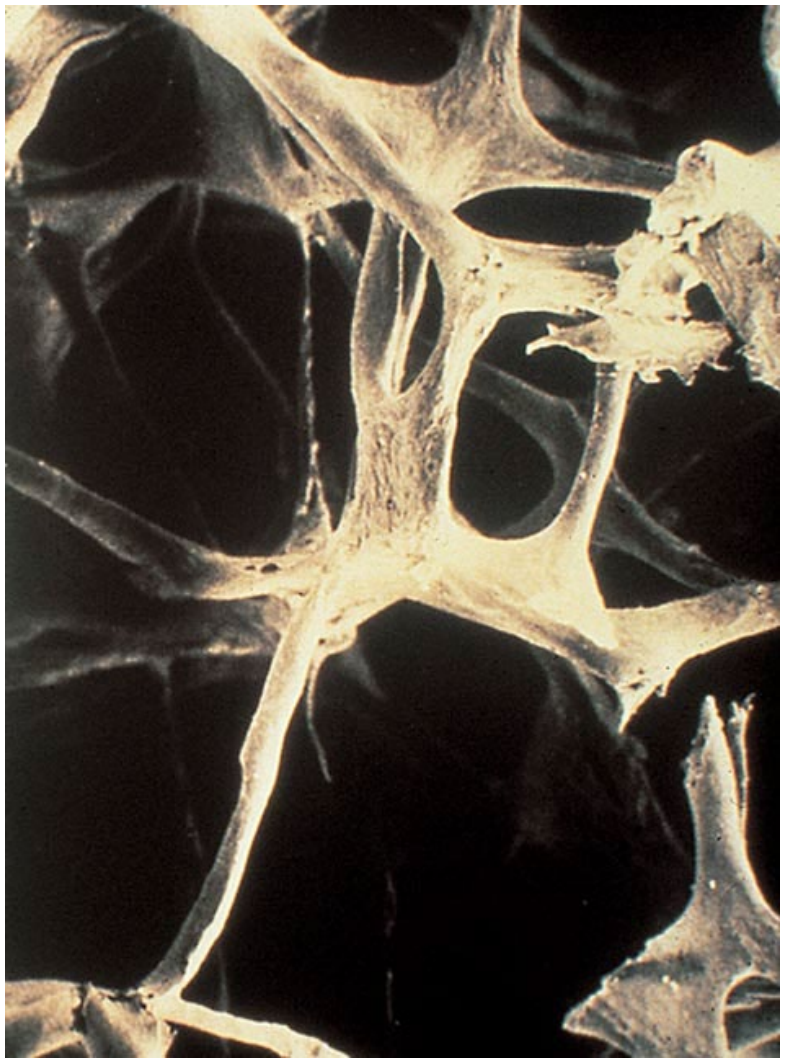


Images of distal tibia using high-resolution peripheral quantitative computed tomography (HR-pQCT). Compared with (A) a male 34-year-old control patient, the cortex of the distal tibia of (B) a 26-year-old male patient on hemodialysis for just over 1 year is thinner, and there is also qualitative impairment of the trabecular bone.

- Original images © 2012 International Society of Nephrology. Pelletier et al. Kidney Int 2012;82:581-588.

Scanning electron micrograph of normal and osteoporotic trabecular structures





Fattori di rischio per fratture in CKD

Bone-related risk factors

BMD abnormalities

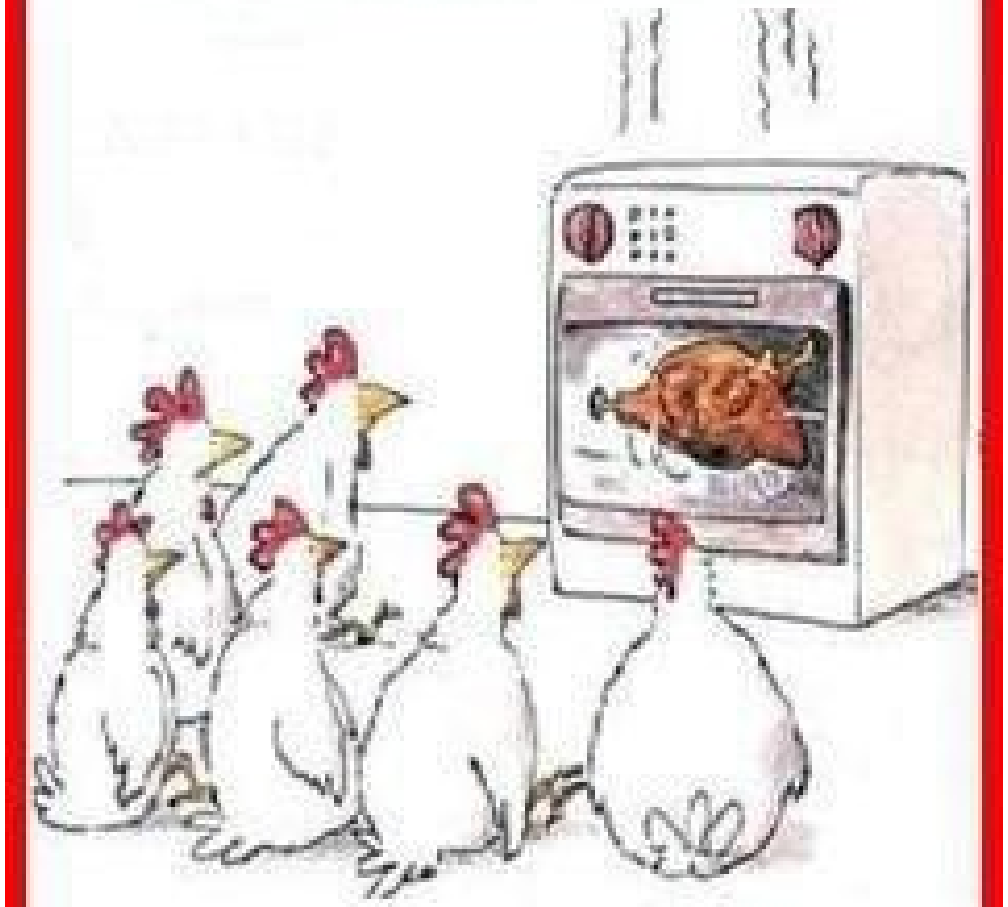
- Traditional risk factor is reduced BMD by DXA, t-score <2.5
- Reduced bone mass with alterations in bone microarchitecture, leading to trabecular and cortical thinning, cortical porosity and trabecularization, altered balance and orientation of newly formed and mature bone. Evaluated with trabecular bone score

Bone quality abnormalities

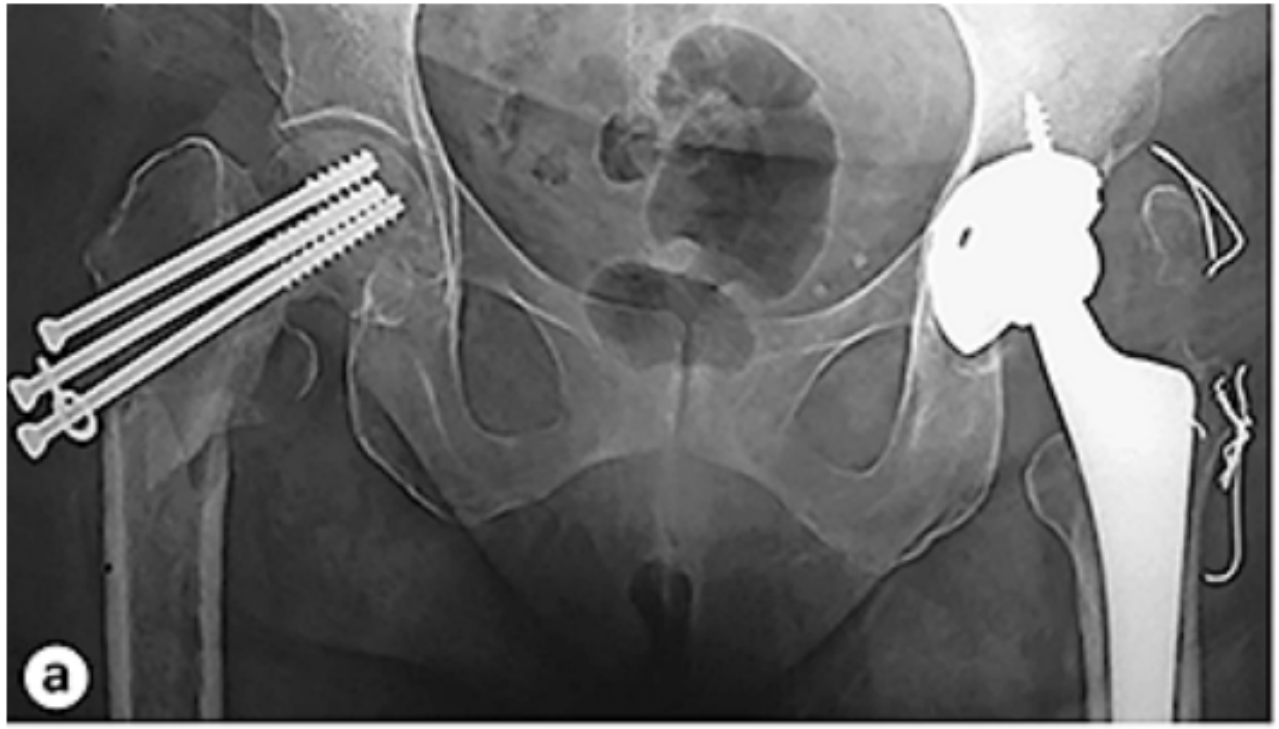
- Abnormal remodelling due to loss of normal repair processes, with either increased or decreased bone turnover
- Defective mineralization, leading to osteomalacia
- Progressive microdamage with reduced impact resistance
- Advanced glycation end products cross-linking, leading to bone tissue loss of elasticity and increased fragility

Fusaro et al. Nephrol Dial Transplant 2021; 36: 405–412

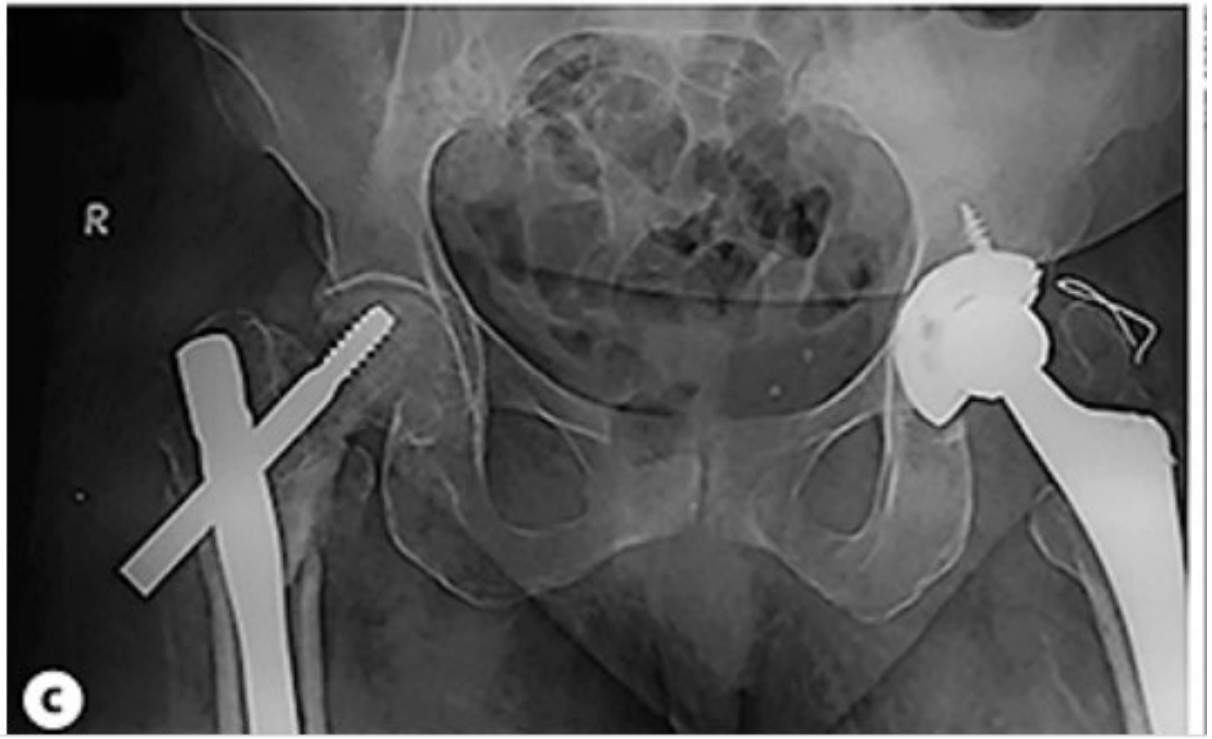
HORROR MOVIE



Le fratture nel paziente in dialisi sono molto problematiche.
Dopo la prima frattura si può osservare una «cascata» di eventi a causa del cedimento di un fragile equilibrio



Right subtrochanteric fracture of the femur distal to the last cannulated screw 24 weeks after fixation.

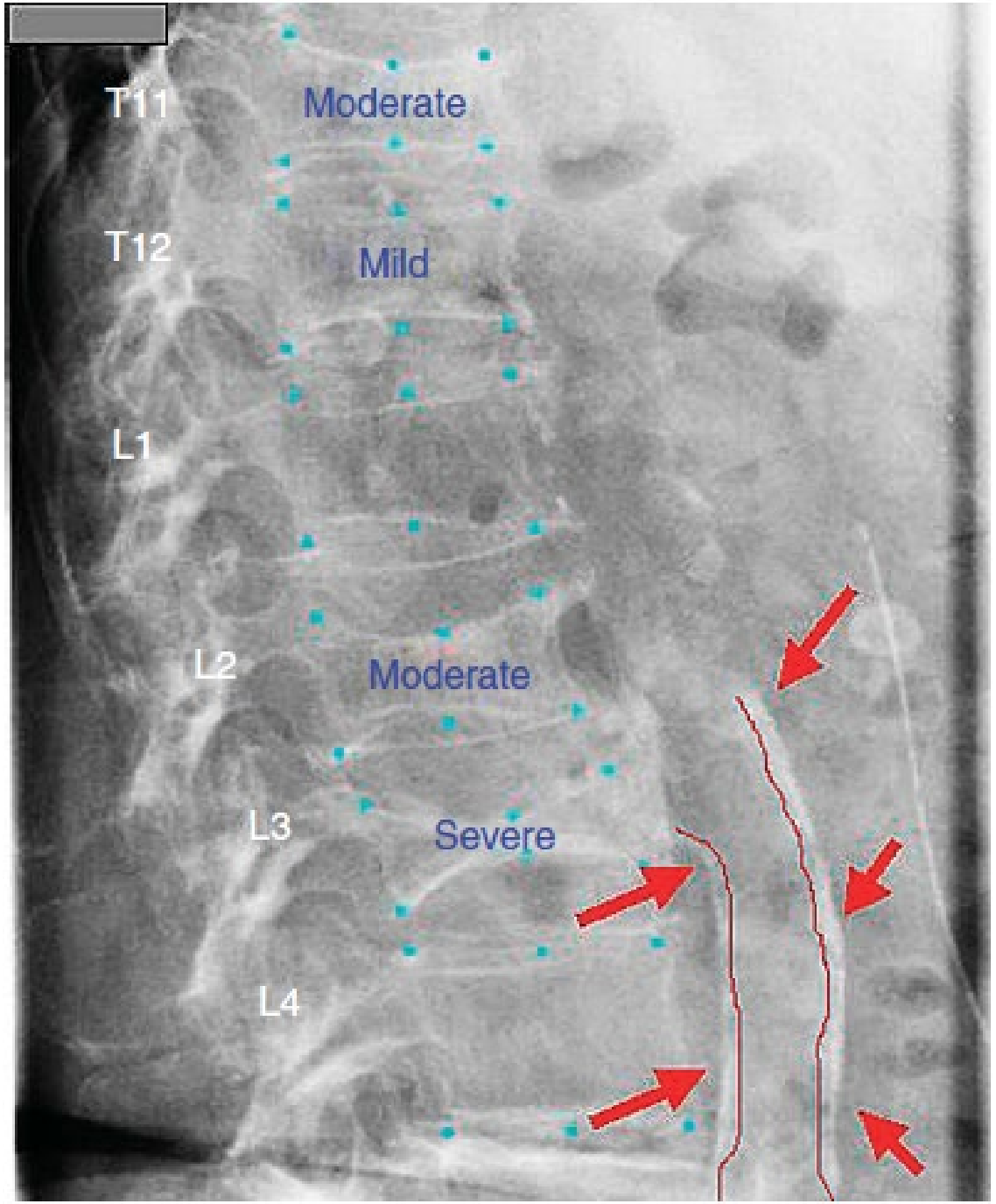


Immediate postoperative radiographs showing fixation of the right subtrochanteric fracture with a long Gamma nail.

Samy TM et al. Fracture Cascade in ESRD Patients. Case Rep Orthop Res 2018

L’incidenza e la prevalenza di fratture vertebrali sono sottostimate

Esempio di valutazione di fratture vertebrali con l'ausilio di morfometria vertebrale quantitativa (MVQ).
In questa figura, sono stati identificate le seguenti fratture : T11, biconcava, moderata; T12, biconcava, lieve; L2, biconcava, moderata; L3, biconcava, grave.
La MVQ è un prezioso strumento clinico e di ricerca che consente una più caratterizzazione precisa delle fratture vertebrali, rispetto ai metodi semiquantitativi, che sono più dipendenti dall'operatore.

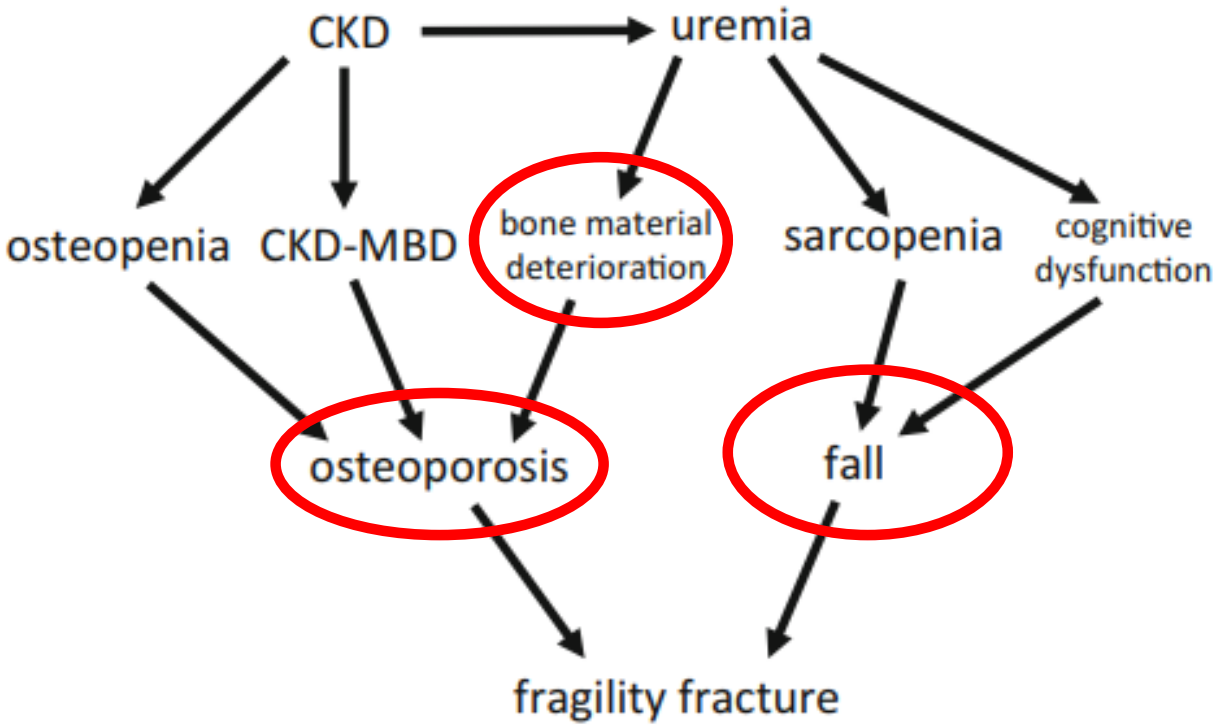


Fusaro et al. Kidney Int 2013; 85: 20–22.

CKD/MBD osteoporosis

- **Patients with chronic kidney disease (CKD) experience a several-fold increased risk of fracture.**
- **Despite the high incidence and the associated excess morbidity and premature mortality, bone fragility in CKD, or CKD-associated osteoporosis, remains a blind spot in nephrology with an immense treatment gap.**
- **Defining the bone phenotype is a prerequisite for the appropriate therapy of CKD-associated osteoporosis at the patient level.**

Le fratture in CKD/dialisi hanno cause multifattoriali



- **Direct cause of fragility fracture is osteoporosis. Generally, the major cause of osteoporosis is osteopenia (reduced bone quantity), and osteopenia is common in CKD patients. CKD-MBD can also potentially cause osteoporosis.**
- **Uremia is likely to deteriorate bone material properties (reduced bone quality).**
- **The frequency of the fall is another major risk of fragility fracture, and uremia also increases the risk of fall, because of sarcopenia and cognitive impairment.**

Kazama. CKD and fragility fracture. Clin Exp Nephrol 2017

Fratture in dialisi

È stato possibile osservare fratture ossee in pazienti dializzati indipendentemente dalla patologia ossea istologica sottostante, specialmente quando è presente osteoporosi. 1

Nei pazienti con CKD-MBD, la frequenza delle fratture vertebrali e dell'anca è fino a quattro volte maggiore rispetto alla popolazione generale. 2-4

1. Hruska KA, Seifert M. Pathophysiology of chronic kidney disease mineral bone disorder (CKD-MBD). In: Rosen CJ, ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Wiley; 2013:632-639.
2. Aleksova J, Rodriguez AJ, McLachlan R, Kerr P, Milat F, Ebeling PR. Gonadal hormones in the pathogenesis and treatment of bone health in patients with chronic kidney disease: a systematic review and meta-analysis. Curr Osteoporos Rep. 2018;16(6):674-692.
3. Tentori F et al. High rates of death and hospitalization follow bone fracture among hemodialysis patients. Kidney Int 2013; 85, 166–173;
4. Sidibé A et al. Fracture Risk in Dialysis and Kidney Transplanted Patients: A Systematic Review. JBMR Plus 2019; 3:45-55.

Fratture in dialisi

clinical investigation

http://www.kidney-international.org

see commentary on page 20

High rates of death and hospitalization follow bone fracture among hemodialysis patients

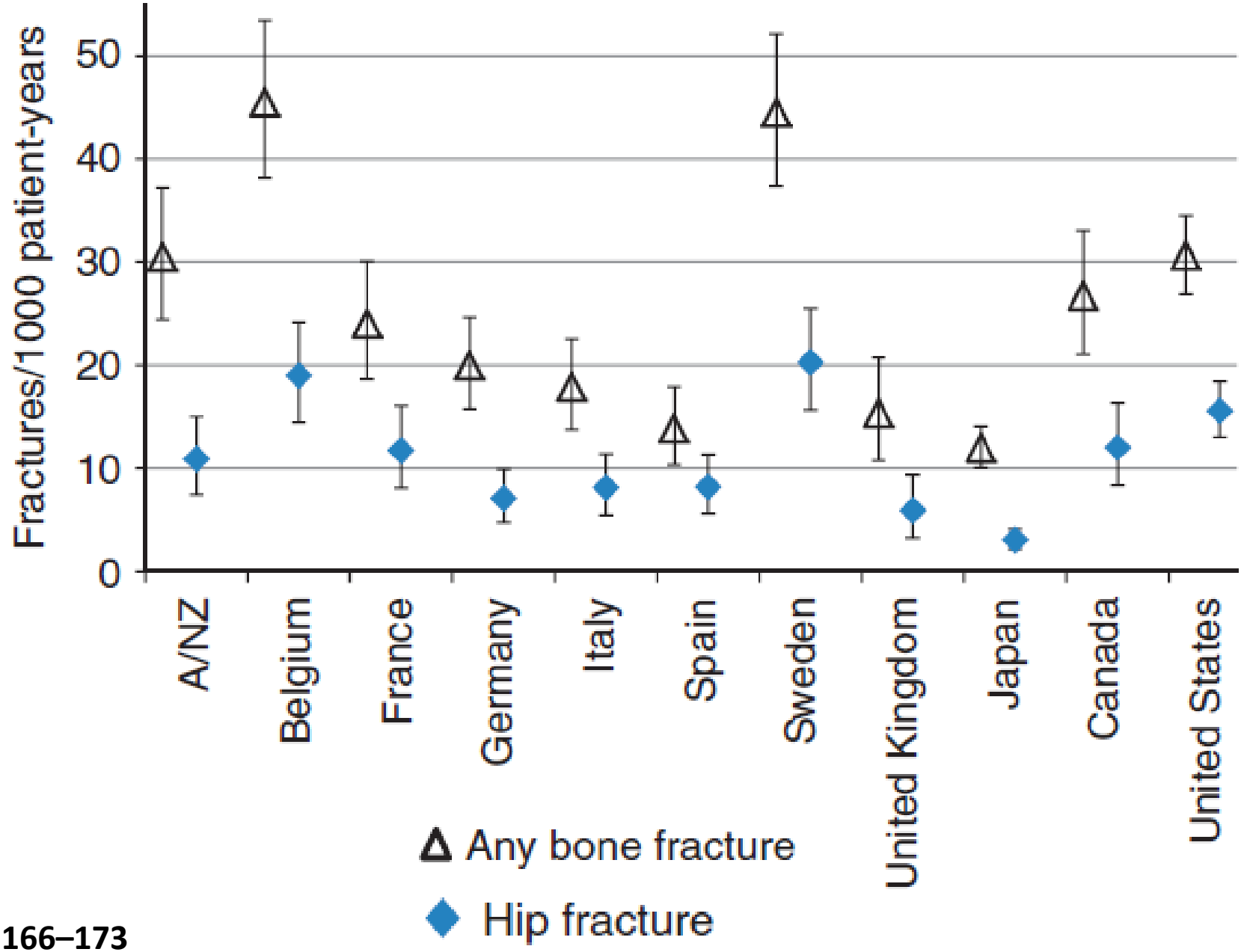
Francesca Tentori[1,2], Keith McCullough[1], Ryan D. Kilpatrick[3], Brian D. Bradbury[3,4], Bruce M. Robinson[1,5], Peter G. Kerr[6] and Ronald L. Pisoni[1]

[1]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [2]Vanderbilt University Medical Center, Nashville, Tennessee, USA; [3]Center for Observational Research, Amgen, Thousand Oaks, California, USA; [4]Department of Epidemiology, University of California, Los Angeles, Los Angeles, California, USA; [5]University of Michigan, Ann Arbor, Michigan, USA and [6]Monash Medical Centre and Monash University, Clayton, Australia

Using the international DOPPS cohort, we demonstrate that bone fractures are relatively common among hemodialysis patients in many countries and pose a significant health burden.

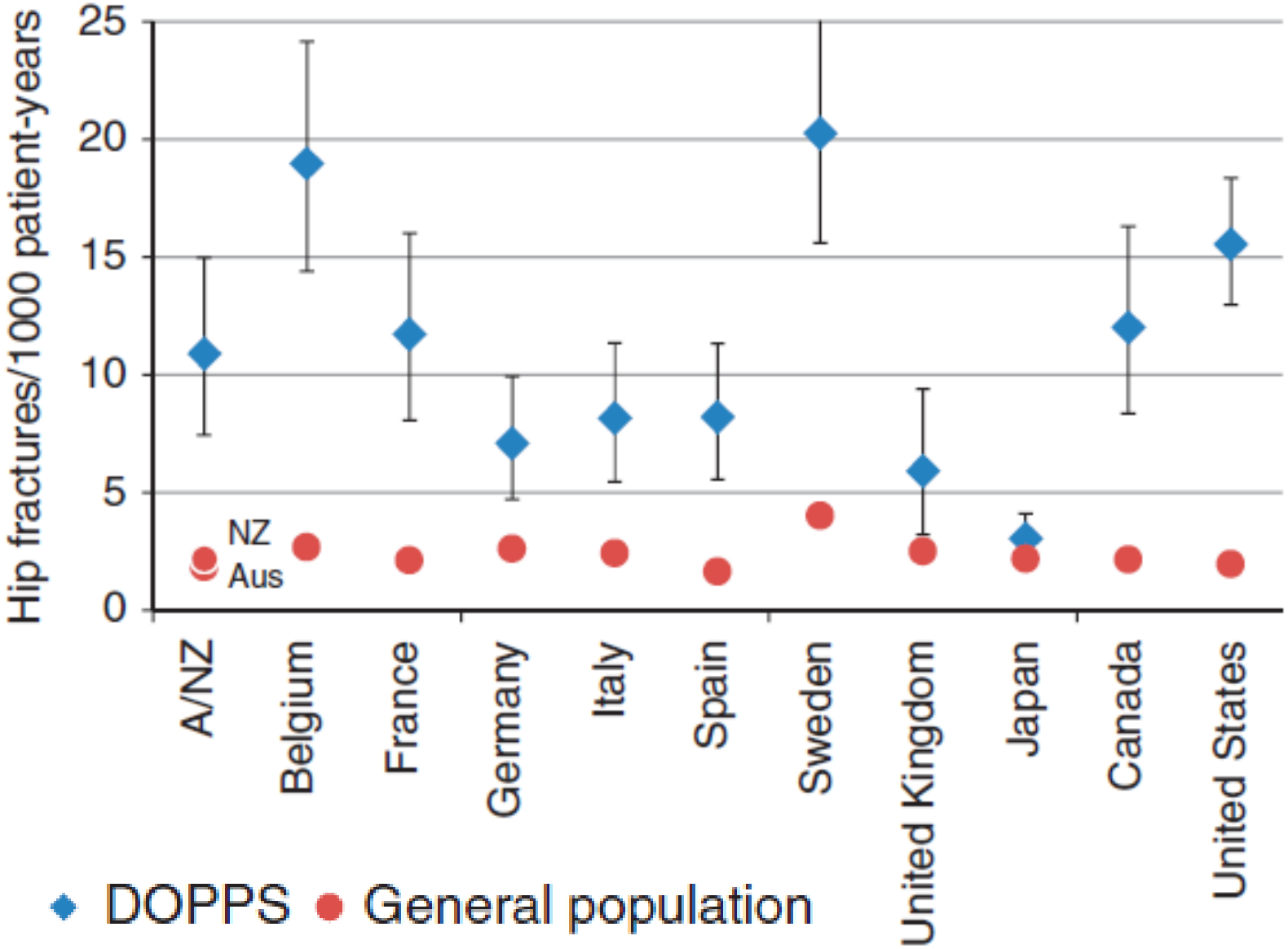
Tentori et al. Kidney Int 2013; 85, 166–173

Incidence of fractures resulting in a hospital admission among participants of DOPPS, by country.



Tentori et al. Kidney Int 2013; 85, 166–173

Hip fracture rates among participants of DOPPS, by country.



Tentori et al. Kidney Int 2013; 85, 166–173

*E*pidemiological *VER*tebral *FRAC*tures i*T*alian Study in Dialysis Patients: (*EVERFRACT* Study)

Calcif Tissue Int
DOI 10.1007/s00223-013-9722-x

ORIGINAL RESEARCH

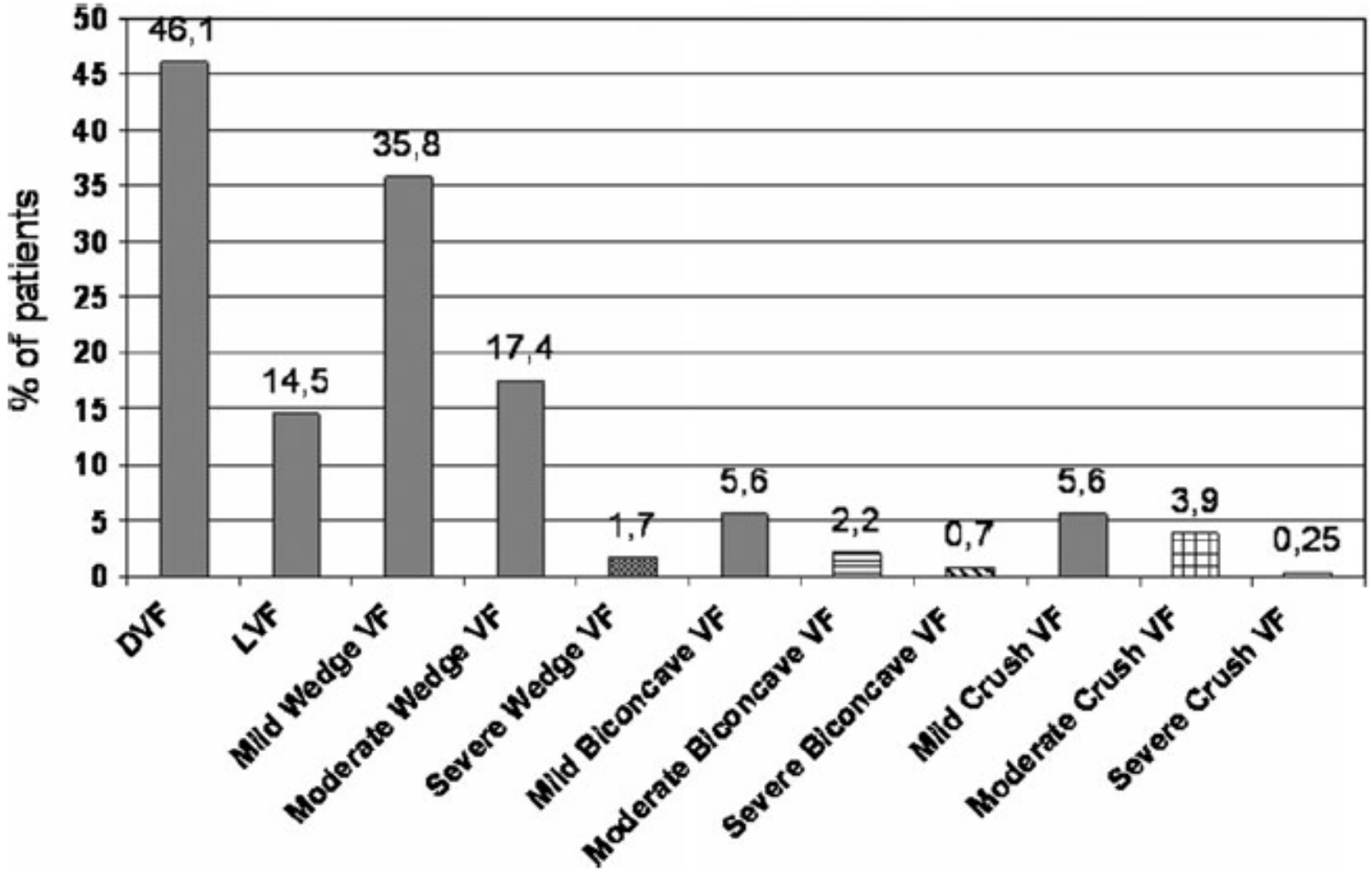
High Prevalence of Vertebral Fractures Assessed by Quantitative Morphometry in Hemodialysis Patients, Strongly Associated with Vascular Calcifications

Maria Fusaro · Giovanni Tripepi · Marianna Noale · Nicola Vajente · Mario Plebani · Martina Zaninotto · Giuseppe Guglielmi · Diego Miotto · Luca Dalle Carbonare · Angela D'Angelo · Daniele Ciurlino · Riccarda Puggia · Davide Miozzo · Sandro Giannini · Maurizio Gallieni

Received: 26 November 2012 / Accepted: 9 February 2013

Studio EVERFRACT

VF in 214/387 (55,3%) di Pazienti ED



Prevalenza di fratture vertebrali con MORFOMETRIA QUANTITATIVA

Persistent Secondary Hyperparathyroidism and Vertebral Fractures in Kidney Transplantation: Role of Calcium-Sensing Receptor Polymorphisms and Vitamin D Deficiency

Sandro Giannini , Stefania Sella , Fatima Silva Netto et al

125 patients: *Prevalence VF **57%***

JBMR, April 2010

Prevalence of vertebral fracture in postmenopausal women with lumbar osteopenia using MorphoXpress® (OSTEOXPRESS Study)

Luis Arboleya, Manuel Díaz-Curiel, Luis del Río et al.

289 postmenopausal women. **MorphoXpress® revealed that 50% of postmenopausal women with osteopenic lumbar densitometry showed VF. This result is relevant since only 7% of all evaluated subjects had been previously diagnosed with VF.**

Aging Clin Exp Res January 28, 2010

ORIGINAL ARTICLE

Fratture in dialisi

2019

JBMR PLUS Open Access ASBMR

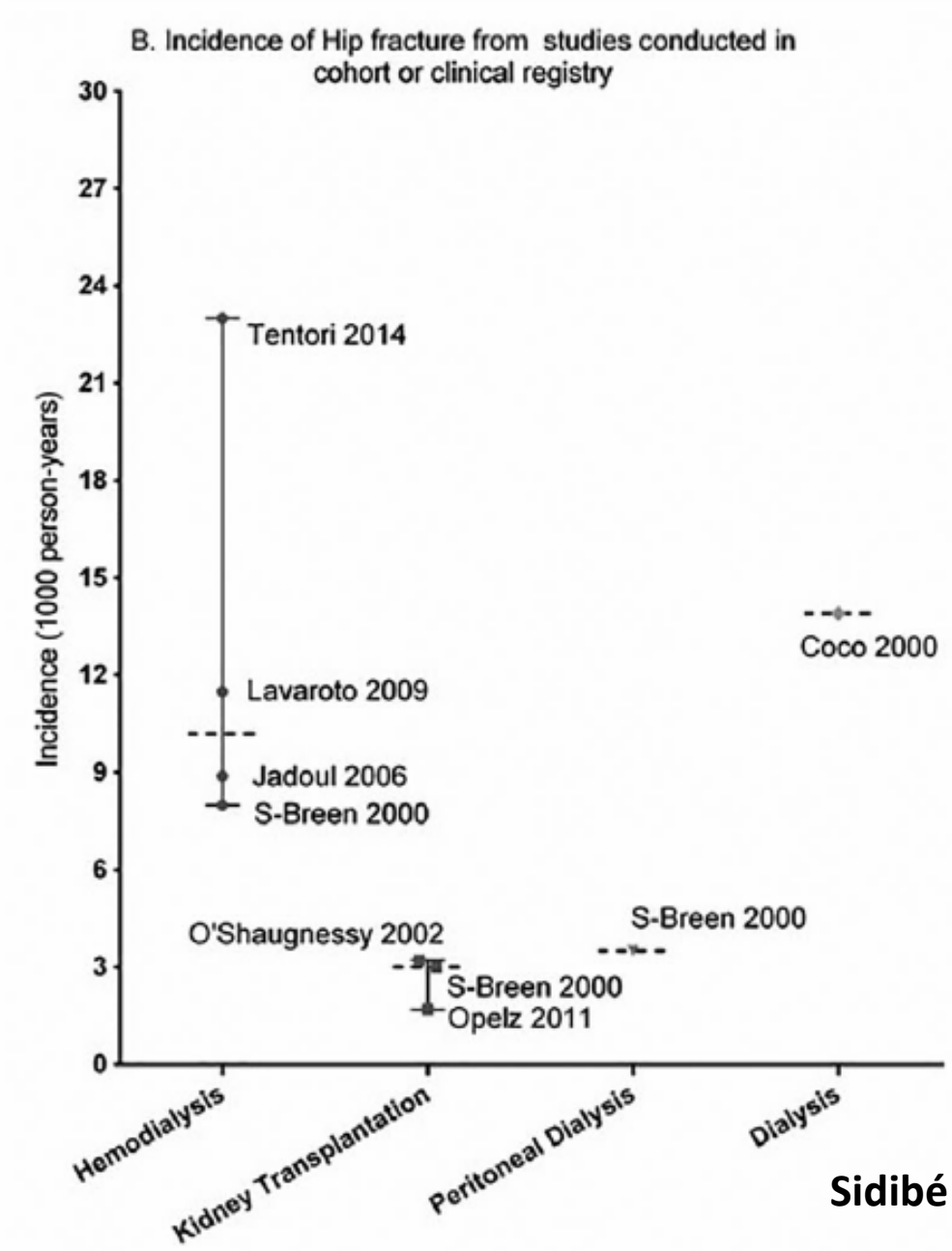
Fracture Risk in Dialysis and Kidney Transplanted Patients: A Systematic Review

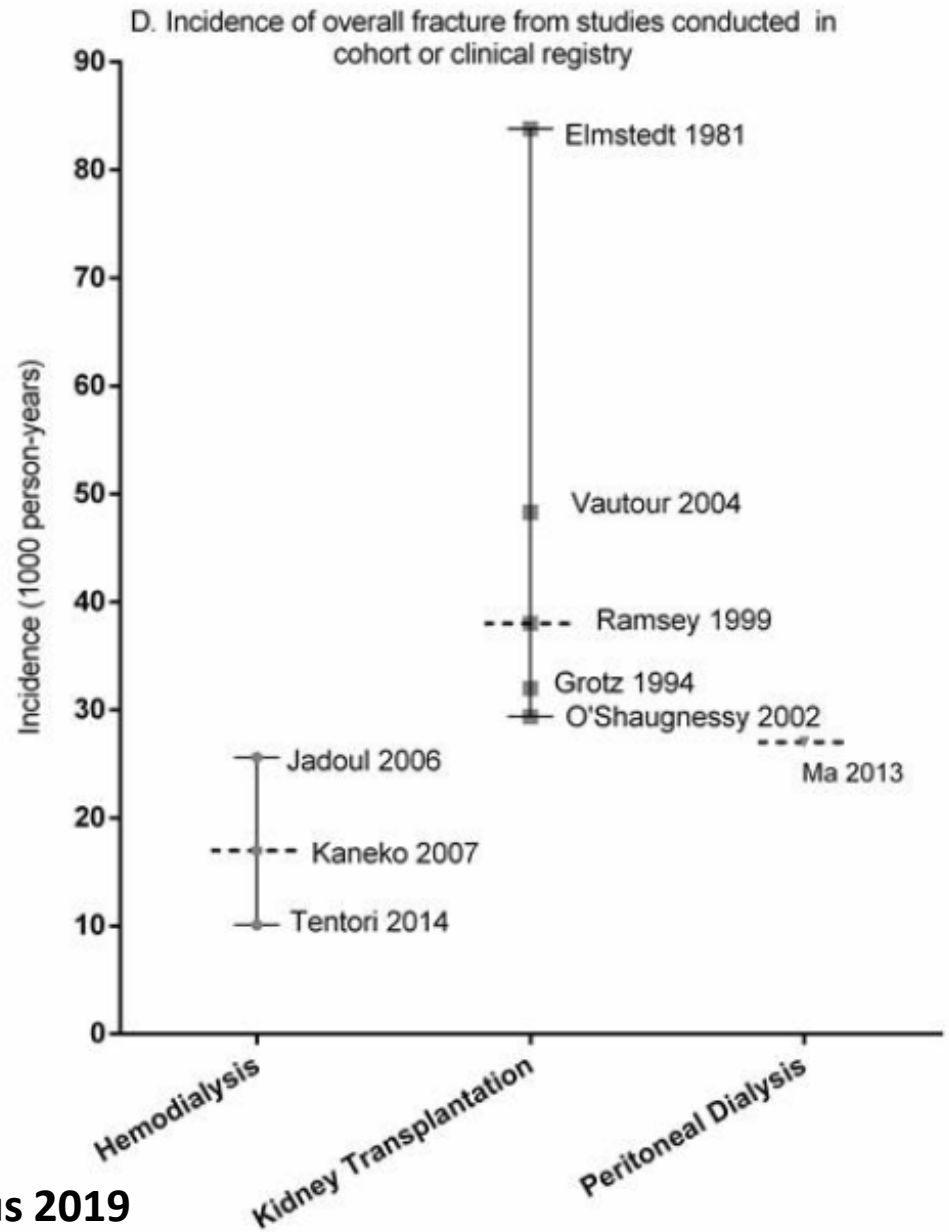
Aboubacar Sidibé,[1] David Auguste,[2] Louis-Charles Desbiens,[3] Catherine Fortier,[3] Yue Pei Wang,[3] Sonia Jean,[4] Lynne Moore,[5] and Fabrice Mac-Way[3]

[1]Centre de Recherche du CHU de Québec, Hôpital Hôtel-Dieu de Québec, Division of Nephrology, Endocrinology, and Nephrology Axis, Faculty of Medicine, Department of Social and Preventive Medicine, Laval University, Quebec, Canada

- **47 studi che hanno valutato il rischio di frattura nelle popolazioni ED, PD e Trapianto (KT).**
- **L'incidenza di frattura dell'anca in ED (mediana 11,45 per 1000 anni-persona, range 9,3 - 13,6 era maggiore rispetto al trapianto (mediana 2,6 per 1000 p-y; intervallo da 1,5 a 3,8) o in PD (mediana 5,2 per 1000 p-y; intervallo da 4,1 a 6,3).**
- **La maggior parte di questi studi si è concentrata sulla frattura dell'anca o complessiva, mentre la frattura vertebrale è stata raramente affrontata.**
- **In contrasto con l'incidenza di fratture, la prevalenza della frattura vertebrale o complessiva sembra essere simile tra la popolazione ED KT.**
- **I risultati rafforzano l'importanza della fragilità ossea come uno dei principali problemi di salute nella popolazione CKD.**

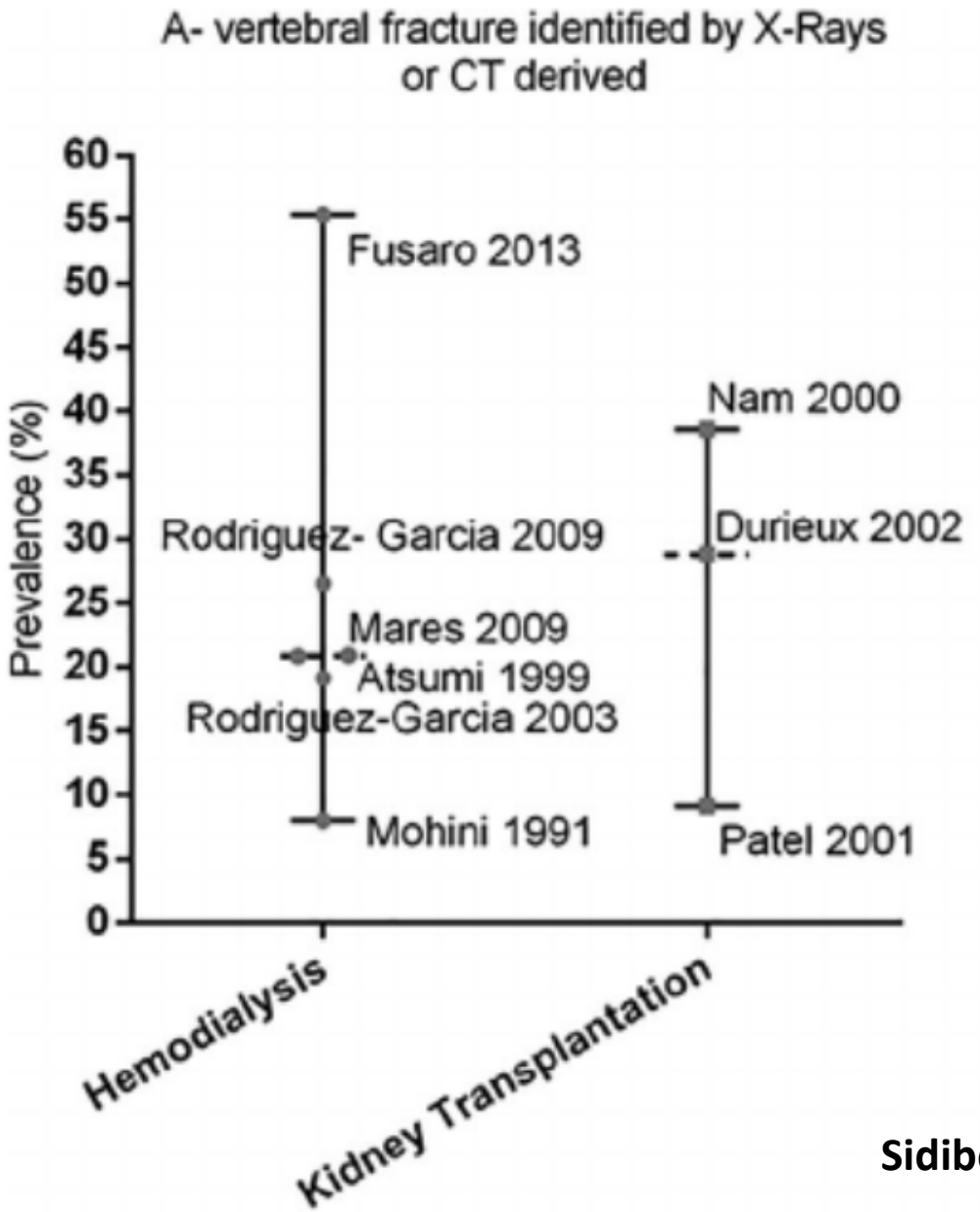
Incidenza di frattura dell'anca (sin) e globale di frattura (dx) in ED, PD e Trapianto.

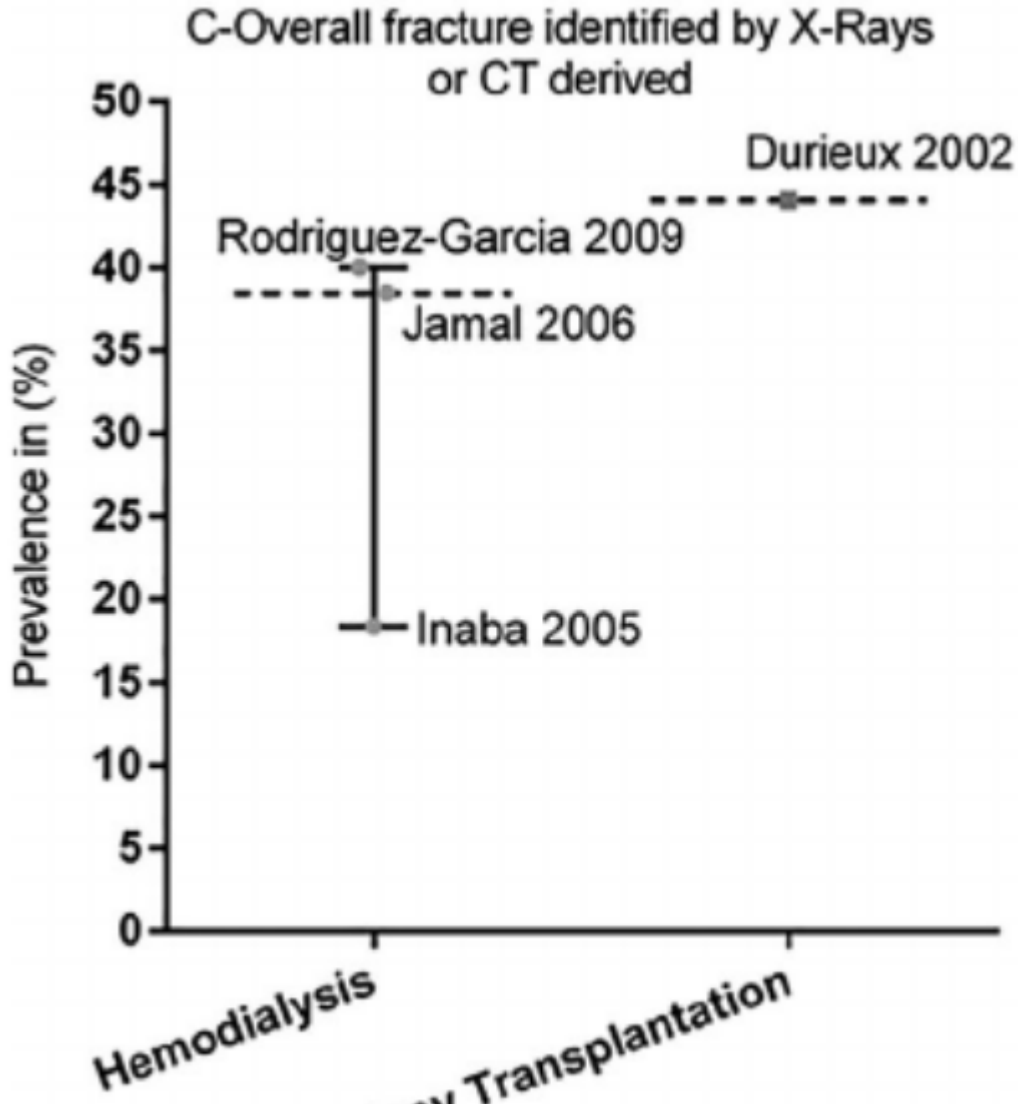




Sidibé et al. JBMR Plus 2019

Prevalenza di fratture vertebrali (sin) e globale di frattura (dx) in ED e Trapianto





Sidibé et al. JBMR Plus 2019

Clinical Kidney Journal

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Abstract

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JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Ten tips on how to assess bone health in patients with chronic kidney disease

Hanne Skou Jørgensen, Maria Jesús Lloret, Alexander D Lalayiannis, Rukshana Shroff, Pieter Evenepoel ✉ on behalf of the European Renal Osteodystrophy (EUROD) initiative of the CKD-MBD working group of the European Renal Association (ERA), and the CKD-MBD and Dialysis working groups of the European Society of Pediatric Nephrology

Clinical Kidney Journal, sfae093, https://doi.org/10.1093/ckj/sfae093

Jørgensen. CKJ 2024

Clinical Kidney Journal

10 tips: Bone health in CKD

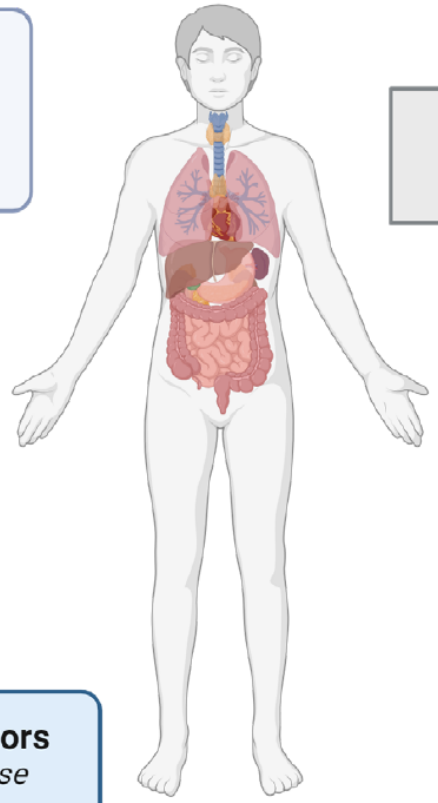
Define the individual fracture risk profile

Traditional risk factors
Age-related osteoporosis
LIfe-style (diet, exercise)
Hypogonadism

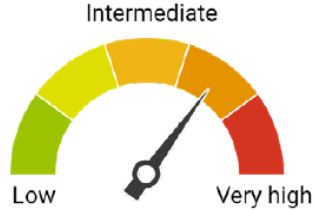
Systemic illness
Cause of CKD
Comorbidities

Polypharmacy
Immunosuppressants
Drugs affecting mineral metabolism
Falls risk

CKD-associated risk factors
Debut and duration of disease
Chronic inflammation
Metabolic acidosis
Mineral metabolism disturbances



Use a fracture risk assessment tool
FRAX, QFracture, Garvan



Take action
Communicate risk
Consider intervention threshold

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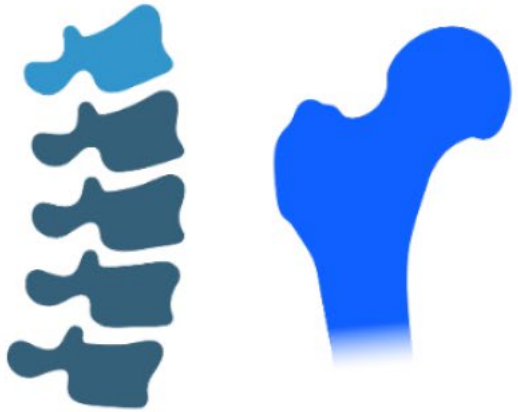
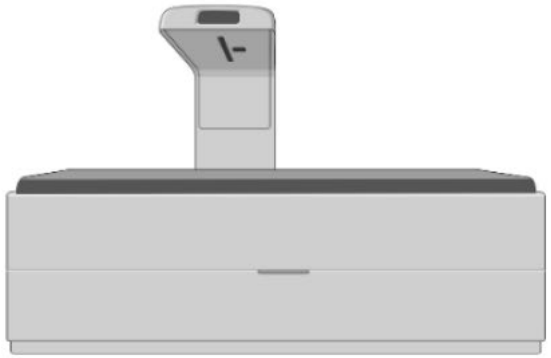
10 tips: Bone health in CKD

Assess bone mineral density by dual energy X-ray absorptiometry





- ✓ Widely available
  Low-radiation exposure
  Clinical standard for osteoporosis
- ✗ Susceptible to artifacts
  No separation of cortical/trabecular bone
  Does not provide measure of bone quality

No evidence for routine use in children

Should not be repeated unless clinically indicated (~2 yrs)

Screen all patients >50 yrs or postmenopausal

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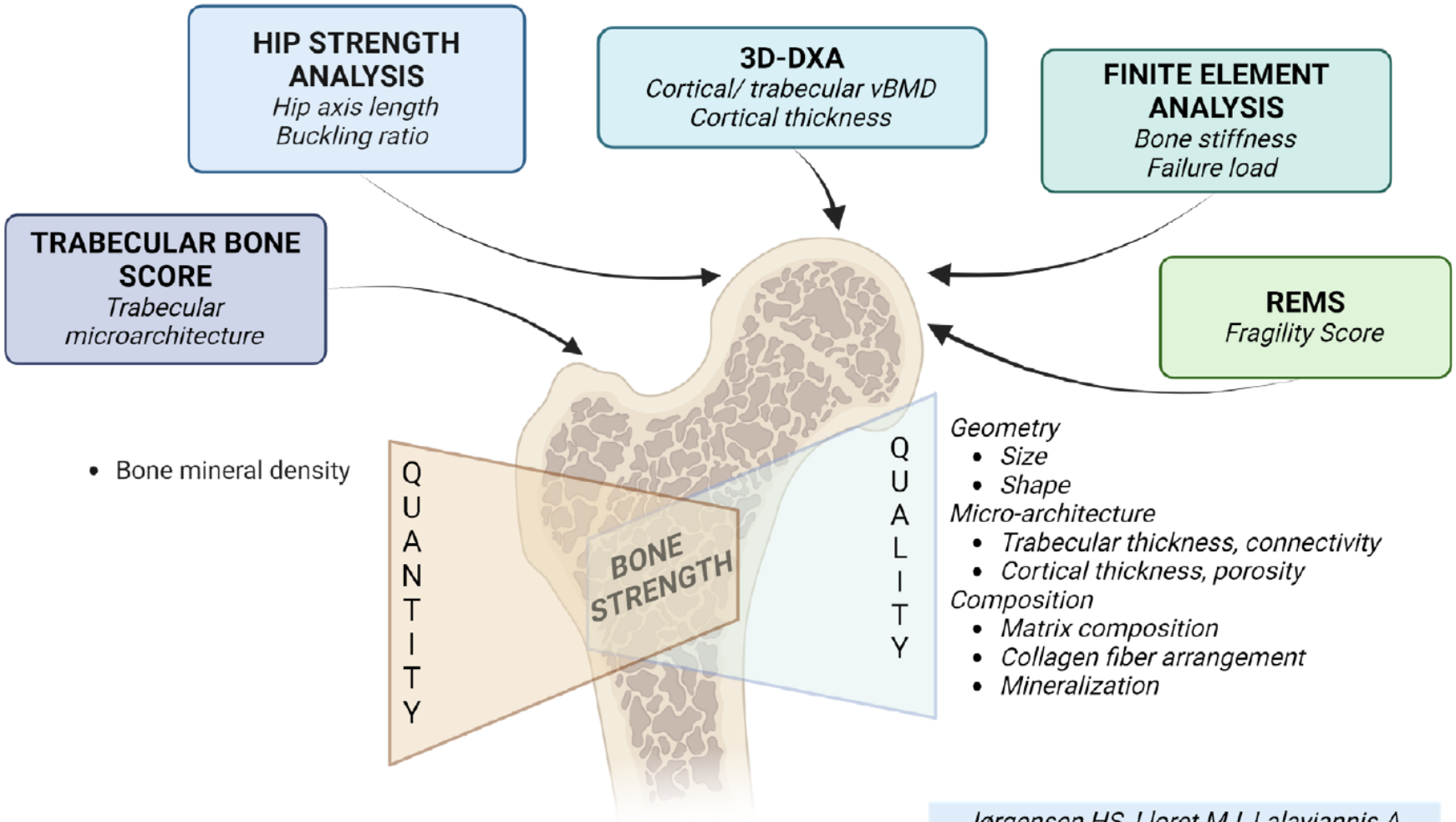
10 tips: Bone health in CKD

Consider novel imaging techniques and analyses of bone strength



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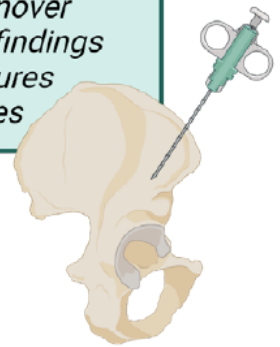
10 tips: Bone health in CKD

Consider a bone biopsy in complex cases

BONE BIOPSY
- *Not a mandatory step in the evaluation of CKD-associated osteoporosis*
- *Consider in complex cases*

INDICATIONS
- *Suspicion of a mineralization defect (bone pain, low vit D, Ca, P)*
- *Suspicion of low bone turnover*
- *Discrepancies in biomarker findings*
- *Multiple or atypical fractures*
- *Important comorbidities*

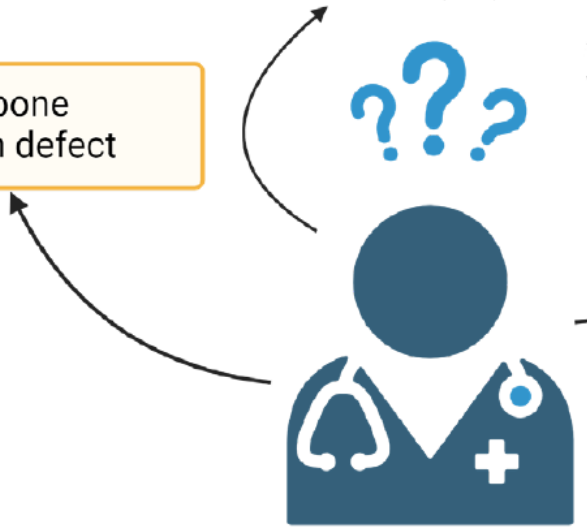


Reasonable to perform to:

Confirm suspicions of low bone turnover

Exclude a bone mineralization defect

Rule out atypical bone pathology



...if results will impact your therapeutic approach.

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Nephrol Dial Transplant (2021) 36: 405–412
doi: 10.1093/ndt/gfz196
Advance Access publication 17 October 2019

Phosphate and bone fracture risk in chronic kidney disease patients

Maria Fusaro[1,2], Rachel Holden[3], Charmaine Lok[4], Giorgio Iervasi[1], Mario Plebani[5], Andrea Aghi[6], Maurizio Gallieni[7,*] and Mario Cozzolino[8,*]

[1]National Research Council, Institute of Clinical Physiology, Pisa, Italy, [2]Department of Medicine, University of Padova, Padova, Italy, [3]Department of Medicine, Division of Nephrology, Queen's University, Kingston, Ontario, Canada, [4]Department of Medicine, Division of Nephrology, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada, [5]Department of Medicine, Laboratory Medicine Unit, University of Padova, Padova, Italy, [6]Department of Medicine, Clinica Medica 1, University of Padova, Padova, Italy, [7]Department of Biomedical and Clinical Sciences 'L. Sacco', Nephrology and Dialysis Unit, ASST Fatebenefratelli-Sacco, Università di Milano, Milan, Italy and [8]Department of Health Sciences, ASST Santi Paolo and Carlo, University of Milan and Renal Division, Milan, Italy

Whether phosphate has an independent role in determining bone fractures has been poorly explored

Facts about P and Bone

- Phosphate accumulates in bone in the form of hydroxyapatite
- Low phosphorus availability causes defective mineralization of bone (e.g. rickets/osteomalacia)
- High phosphate may induce osteoblast apoptosis and reduce bone formation
- Phosphate has been shown to suppress 1-alpha-hydroxylase activity contributing to calcitriol deficiency

Fusaro et al. Nephrol Dial Transplant (2021) 36: 405–412

Campos-Obando et al. J Bone Miner Res. 2017;32:1182-1193

ORIGINAL ARTICLE

JBMR®

Serum Phosphate Is Associated With Fracture Risk: The Rotterdam Study and MrOS

Natalia Campos-Obando,[1*] W Nadia H Koek,[1*] Elizabeth R Hooker,[2] Bram CJ van der Eerden,[1] Huibert A Pols,[1,3] Albert Hofman,[3] Johannes PTM van Leeuwen,[1] Andre G Uitterlinden,[1,3] Carrie M Nielson,[2,4] and M. Carola Zillikens[1,3]

[1]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands
[2]Bone and Mineral Unit, Oregon Health & Science University, Portland, OR, USA
[3]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands
[4]School of Public Health, Oregon Health & Science University, Portland, OR, USA

Our findings suggest that increased Phosphate levels, even within normal range, might be deleterious for bone health in the normal population.

ORIGINAL ARTICLE

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Serum Phosphate Is Associated With Fracture Risk: The Rotterdam Study and MrOS

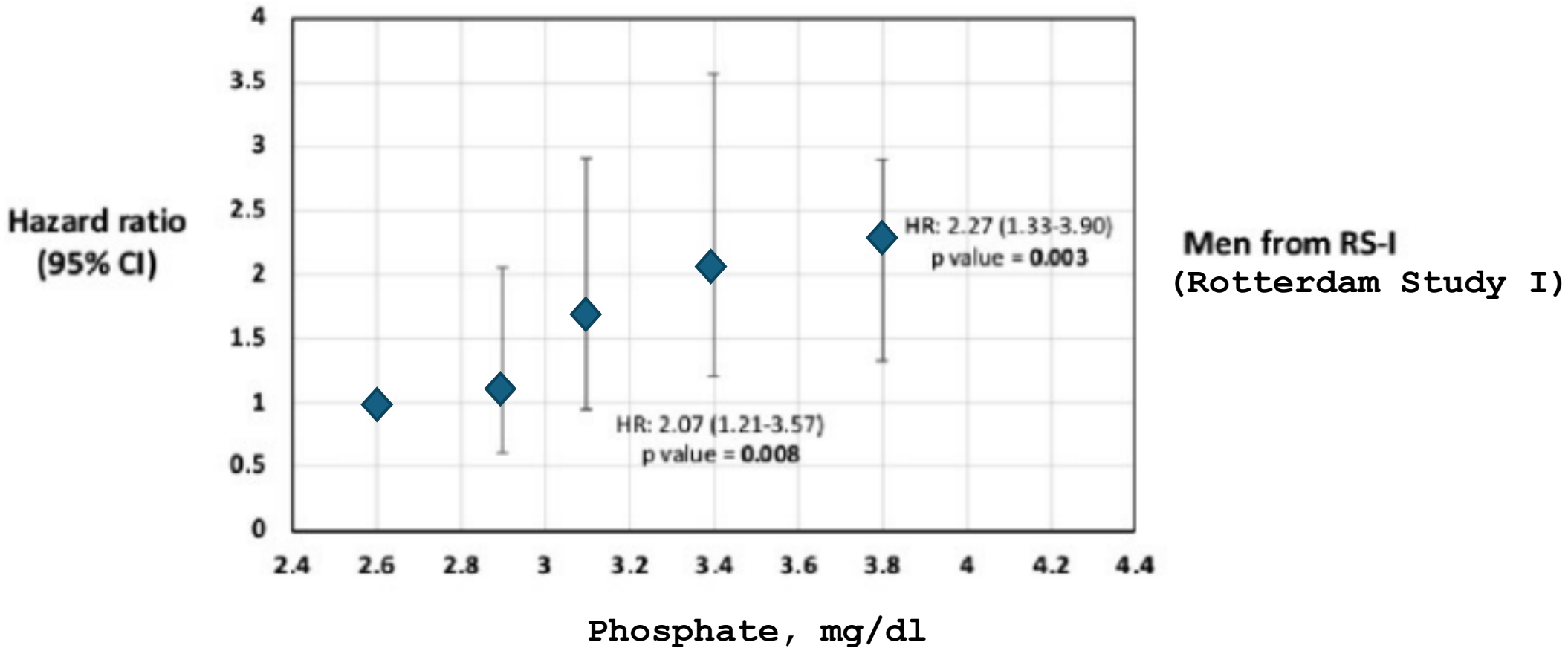
Natalia Campos-Obando,[1*] W Nadia H Koek,[1*] Elizabeth R Hooker,[2] Bram CJ van der Eerden,[1] Huibert A Pols,[1,3] Albert Hofman,[3] Johannes PTM van Leeuwen,[1] Andre G Uitterlinden,[1,3] Carrie M Nielson,[2,4] and M. Carola Zillikens[1,3]

The study reports results from large prospective observational trials in two population-based cohorts:

- **the Dutch Rotterdam Study (RS: n.6791)**
- **the US Osteoporotic Fractures in Men (MrOS: n.5425) study**
- **Follow-up of 8.6 and 10.9 years, respectively**

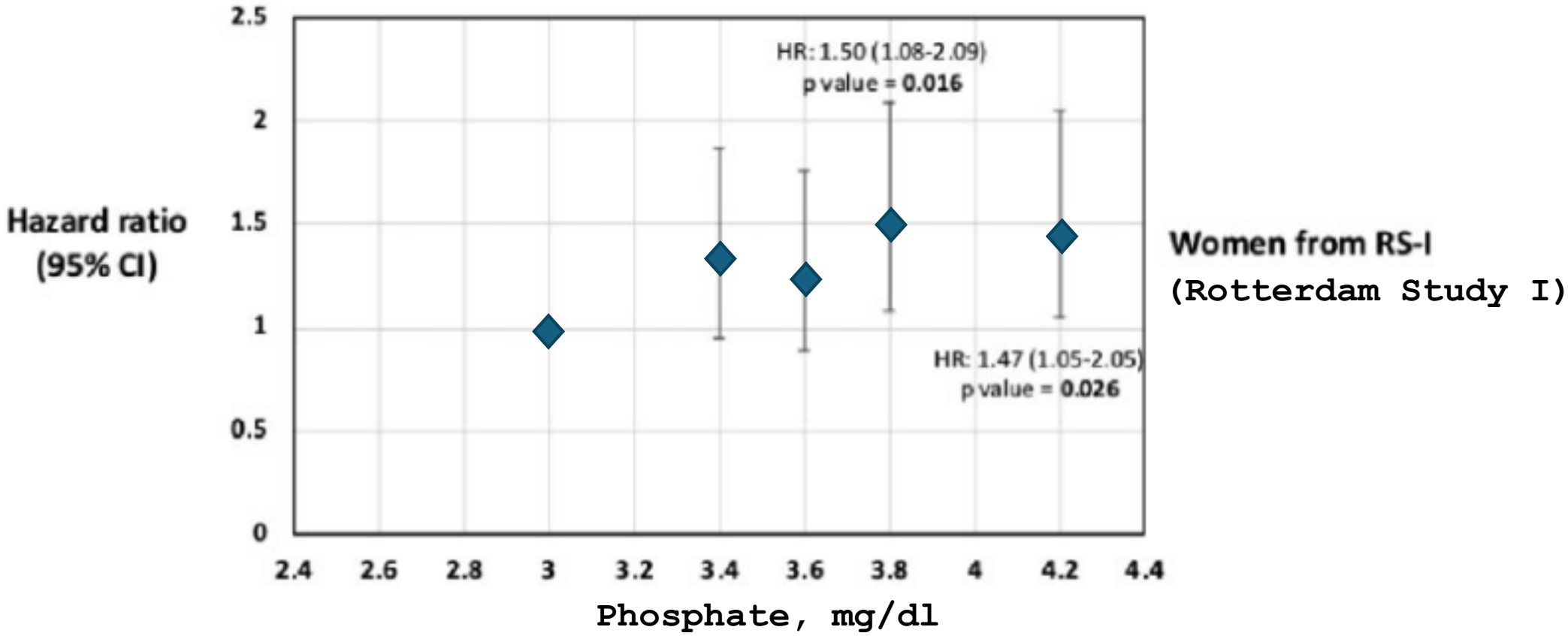
Campos-Obando et al. J Bone Miner Res. 2017;32:1182-1193

Phosphate levels and risk of incidence of bone fractures in patients (men) with normal renal function. RS-I



Fusaro et al. NDT 2021; 36: 405–412; Data from the RS study: Campos-Obando N et al. Serum phosphate Is associated with fracture risk: the Rotterdam Study and MrOS. J Bone Miner Res. 2017;32:1182-1193.

Phosphate levels and risk of incidence of bone fractures in patients (women) with normal renal function. RS-I



Fusaro et al. NDT 2021; 36: 405–412; Data from the RS study: Campos-Obando N et al. Serum phosphate Is associated with fracture risk: the Rotterdam Study and MrOS. J Bone Miner Res. 2017;32:1182-1193.

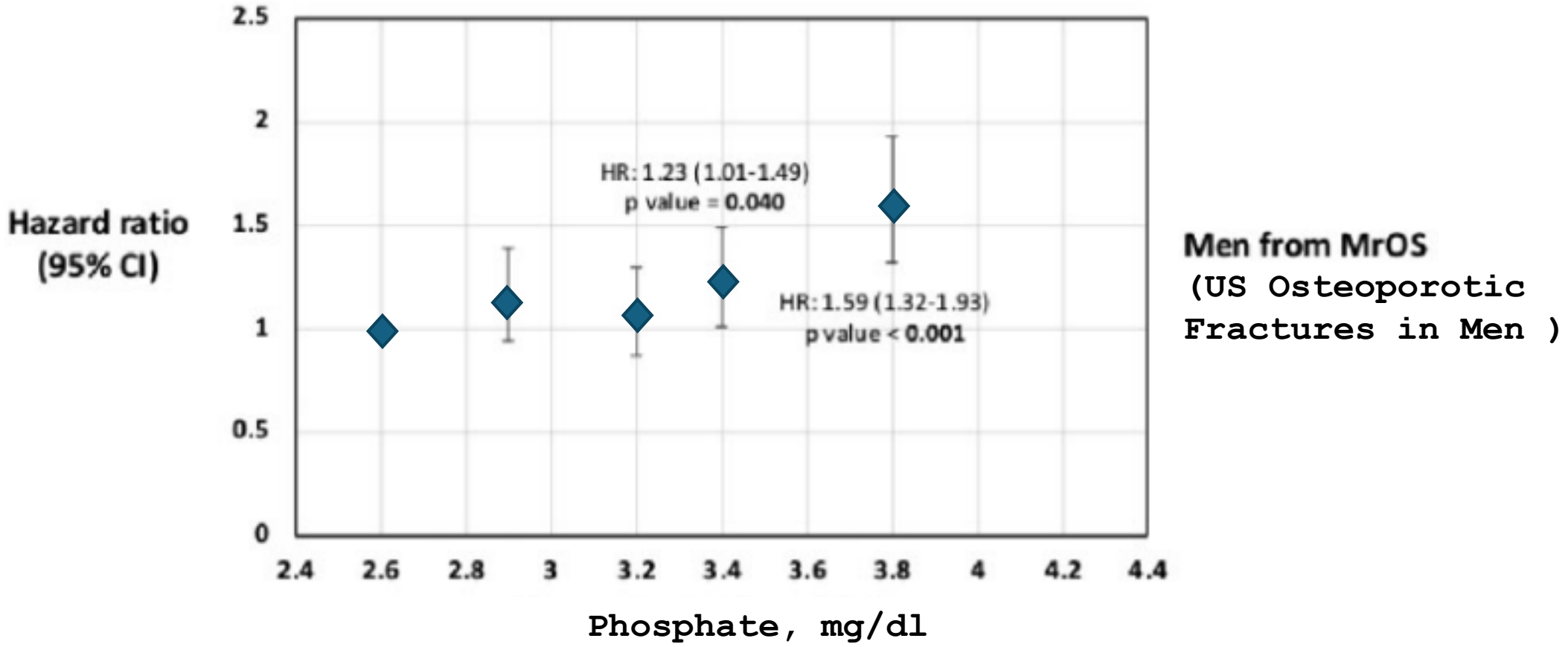
Risk of incidence of all types of fractures as a function of phosphate levels in men from MrOS

Table 7. Risk of Incidence of All Types of Fractures as a Function of Phosphate Levels Categorized in Quintiles in Men From MrOS

	Men		
P levels[a] mean (range)	Events/no. risk	HR[b,c] (95% CI)	*p*
2.6 (1.8–2.8)	188/1085	1.00 (reference)	
2.9 (2.8–3.0)	206/1081	1.14 (0.94–1.39)	0.194
3.2 (3.1–3.3)	190/1081	1.06 (0.87–1.30)	0.558
3.4 (3.3–3.5)	213/1083	**1.23** (1.01–1.49)	0.040
3.8 (3.5–6.8)	249/1079	**1.59** (1.32–1.93)	<0.001
		p_{trend} <**0.001**	

Campos-Obando et al. J Bone Miner Res. 2017;32:1182-1193

Phosphate levels and risk of incidence of bone fractures in patients (men) with normal renal function. MrOS study



Fusaro et al. NDT 2021; 36: 405–412; MrOS study summarized in: Cawthon PM et al. Osteoporosis in men: findings from the Osteoporotic Fractures in Men Study (MrOS). Ther Adv Musculoskelet Dis. 2016;8(1):15-27.

ORIGINAL ARTICLE

JBMR®

Serum Phosphate Is Associated With Fracture Risk: The Rotterdam Study and MrOS

Natalia Campos-Obando,[1*] W Nadia H Koek,[1*] Elizabeth R Hooker,[2] Bram CJ van der Eerden,[1] Huibert A Pols,[1,3] Albert Hofman,[3] Johannes PTM van Leeuwen,[1] Andre G Uitterlinden,[1,3] Carrie M Nielson,[2,4] and M. Carola Zillikens[1,3]

- The positive association between phosphate level and fracture risk was independent of BMD
- A stronger association between phosphate levels and fracture risk was found in CKD patients, which remained significant after adjustment for FGF-23 and PTH levels in the MrOS, suggesting that high phosphate itself and no other mechanisms may explain the increased fracture risk in this population
- Lowering phosphate levels to within normal levels could reduce the fracture risk: if proved with an RCT, such a hard outcome could lead to a revision of the current guidelines

http://www.kidney-international.org clinical investigation

The three-year incidence of fracture in chronic kidney disease

Kyla L. Naylor[1,2], Eric McArthur[3], William D. Leslie[4], Lisa-Ann Fraser[5], Sophie A. Jamal[6], Suzanne M. Cadarette[3,7], Jennie G. Pouget[8], Charmaine E. Lok[9], Anthony B. Hodsman[1], Jonathan D. Adachi[10] and Amit X. Garg[1,2,3]

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Naylor KL et al. Kidney Int 2014

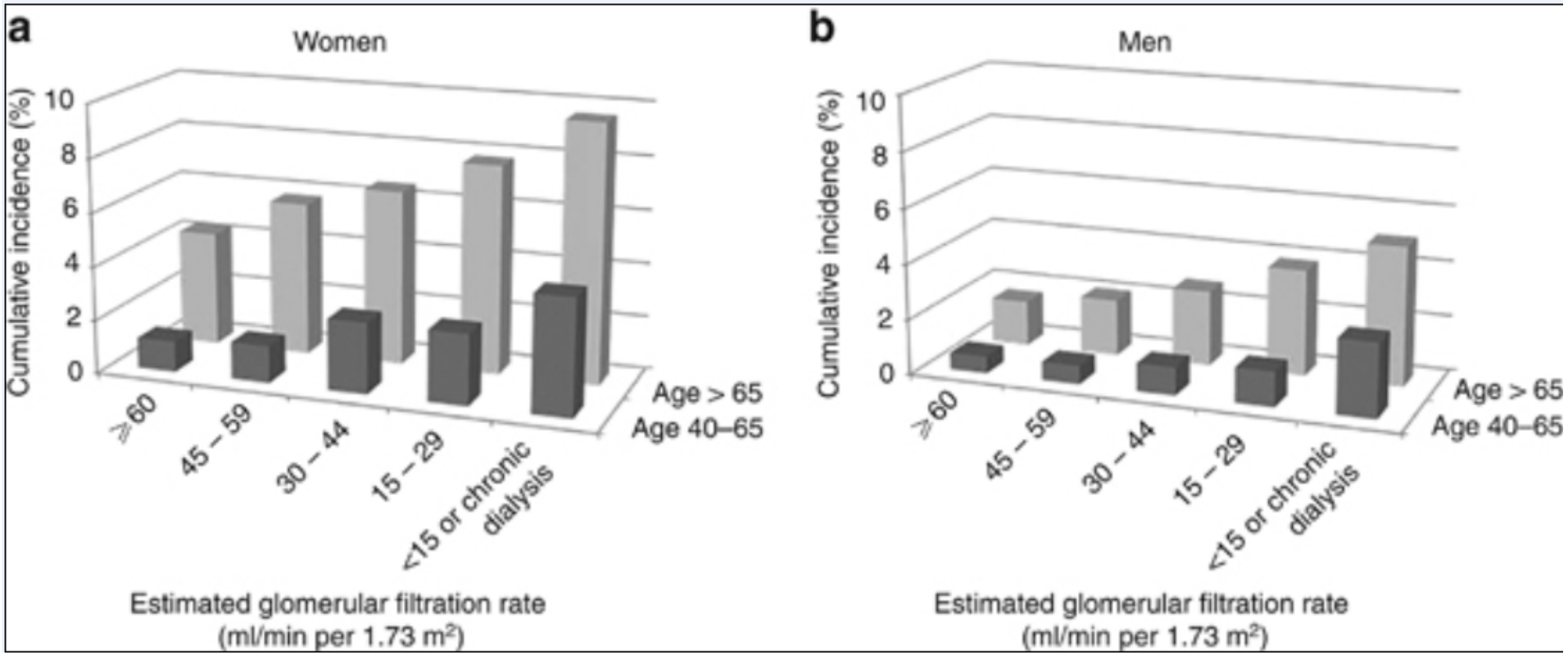
Cohort study of 679,114 adults of 40 years and over (mean age 62 years) stratified at cohort entry by:

- eGFR (60 and over, 45–59, 30–44, 15–29, and under 15ml/min per 1.73 m^2)
- Gender
- Age (40–65 and over 65 years)

The primary outcome was the 3-year cumulative incidence of fracture (proportion of adults who fractured (hip, forearm, pelvis, or proximal humerus) at least once within 3-years of follow-up).

Naylor KL et al. Kidney Int 2014

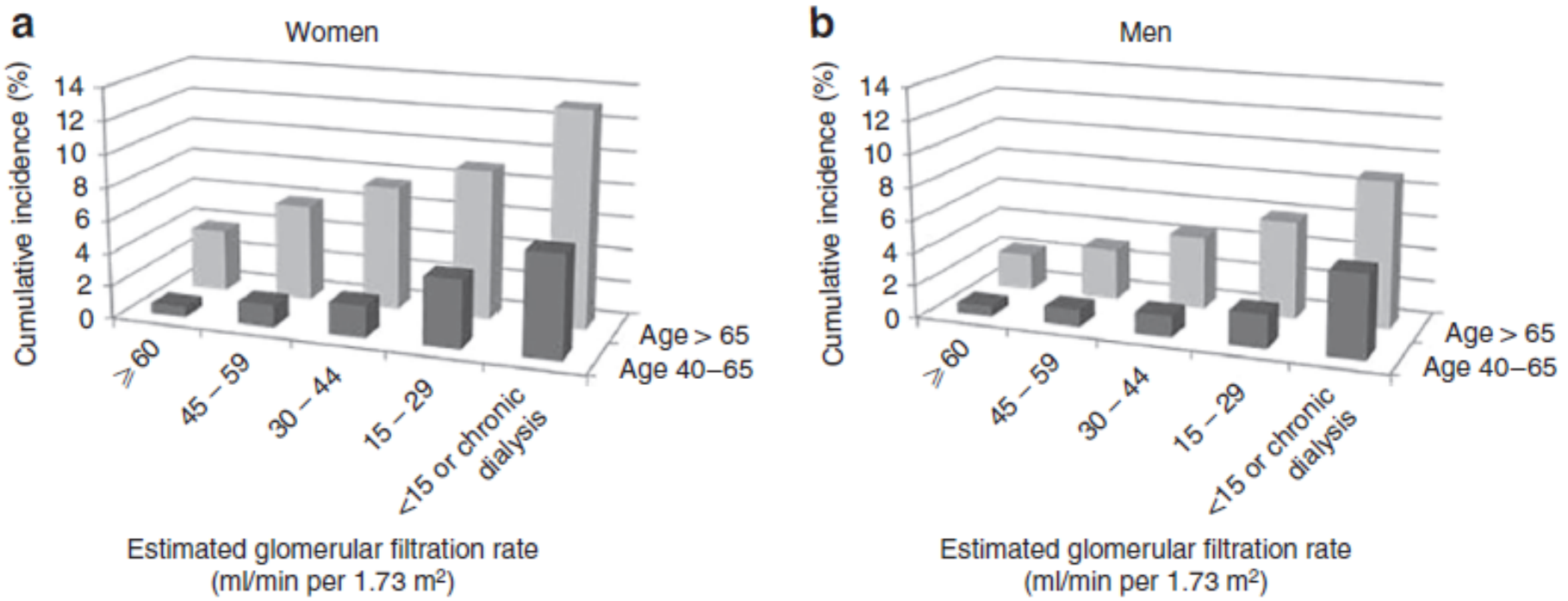
Three-year cumulative incidence of fracture.



Three-year cumulative incidence of fracture for (a) women and (b) men. The number of fracture (hip, forearm, pelvis, or proximal humerus) events increased significantly with decreasing eGFR for both men and women for both age groups (40–65 years and > 65 years).

Naylor KL et al. Kidney Int 2014

3-year cumulative incidence of falls with hospitalization



Three-year cumulative incidence of falls with hospitalization for (a) women and (b) men. The number of falls with hospitalization events increased significantly with decreasing eGFR for both men and women for both age groups (40–65 years and >65 years).

Naylor KL et al. Kidney Int 2014

Table 3 | Location of the first fracture in follow-up according to kidney function

	eGFR (ml/min per 1.73 m^2)				
Fracture location	⩾60	45–59	30–44	15–29	<15 or chronic dialysis
Hip (%)	27.2	46.3	47.9	54.3	54.2
Forearm (%)	47.6	28.4	22.7	20.6	19.2
Proximal humerus (%)	15.0	13.5	13.8	11.4	8.4
Pelvis (%)	10.2	11.8	15.6	13.7	18.2

Abbreviation: eGFR, estimated glomerular filtration rate.

Naylor KL et al. Kidney Int 2014

CONCLUSIONS (Naylor KI 2014)

Many adults with chronic kidney disease will fall and fracture.

Results can be used for prognostication and guidance of sample size requirements for fracture prevention trials.

Results are a call to develop and test interventions to reduce the burden of fracture in this population

Le fratture da fragilità nel paziente in dialisi
Sintesi e conclusioni

- **L'osteoporosi può essere considerata una condizione di alterazione della resistenza ossea dovuta a due fattori principali:**
  - **Ridotta densità minerale ossea (BMD = bone mineral density)**
  - **Compromessa qualità dell'osso**
- **L'osteoporosi si caratterizza per un aumento del rischio di fratture ossee**
- **Un altro importante fattore di rischio per l'evento frattura è la propensione a cadere**

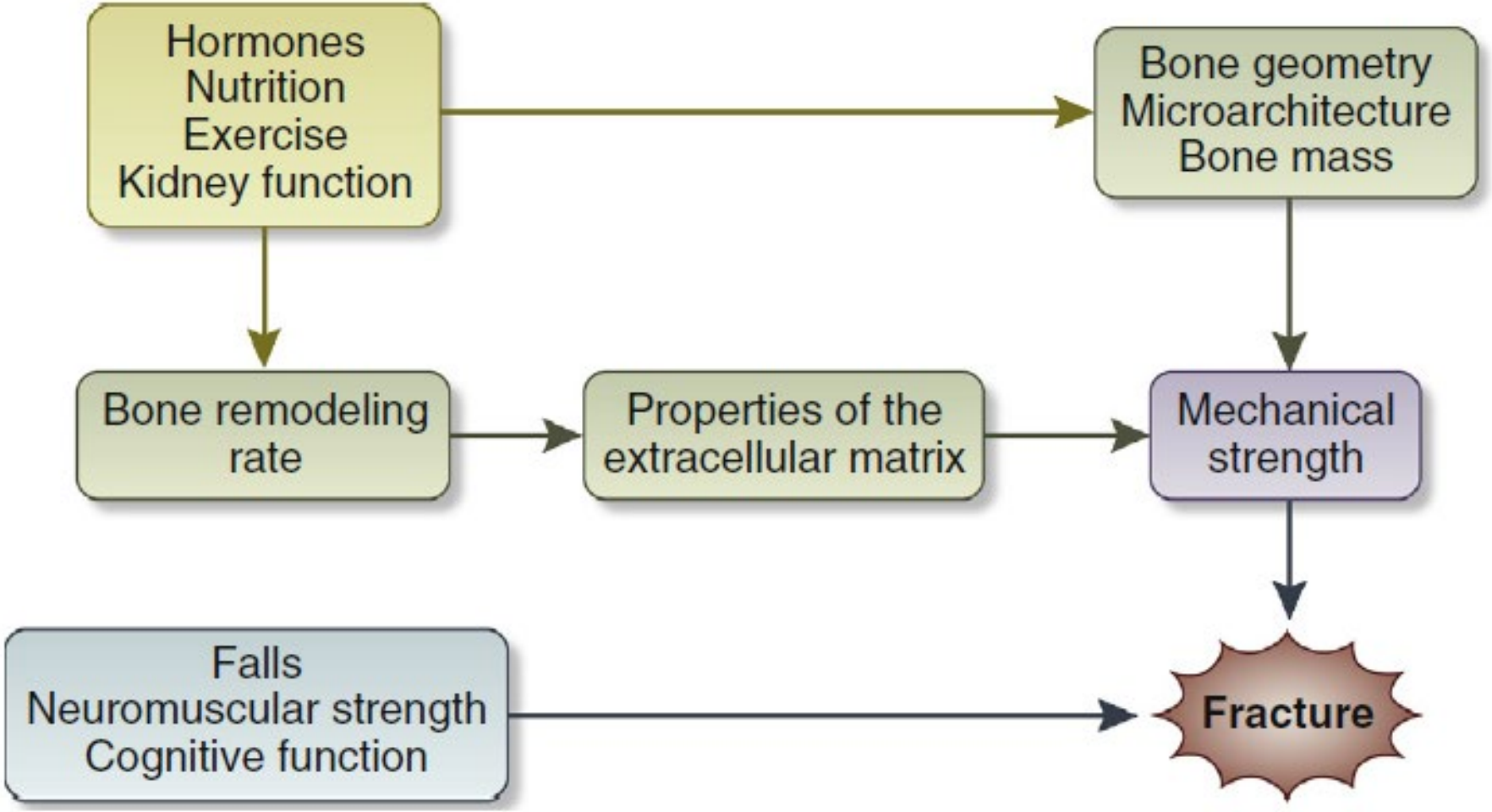
Le fratture da fragilità nel paziente in dialisi
Sintesi e conclusioni

- **L'osteoporosi può coesistere con la CKD-MBD (chronic kidney disease - mineral and bone disorder)**
- **Fratture osteoporitche si possono osservare in tutti gli stadi di malattia renale cronica.**
- **Il trattamento dell'osteoporosi deve tenere in considerazione la fisiopatologia di entrambi I disordini ossei.**

Le fratture da fragilità nel paziente in dialisi
Sintesi e conclusioni

- **Le due componenti della malattia ossea (osteoporosi e CKD-MBD) possono essere valutate al meglio con la biopsia ossea e l'istomorfometria ossea quantitativa**
- **Anche alcuni marcatori biochimici, in particolare il PTH e la fosfatasi alcalina, possono dare delle indicazioni utili**
- **La valutazione scheletrica, in particolare la valutazione delle fratture vertebrali, è importante per identificare pazienti che meritano un trattamento in prevenzione secondaria.**

Fattori che influenzano quantità e qualità dell'osso influenzano il rischio di frattura



Pimentel A et al. Kidney Int 2017; 92: 1343-55

Clinical Kidney Journal

10 tips: Bone health in CKD

Be aware of the fracture burden in CKD

Fractures in CKD

Risk increases as kidney function declines
Integrates reduced bone strength and high falls risk

Consequences

Long hospital stays
Loss of physical function
Reduced quality of life
Excess mortality

Screen
Age > 50 years
Postmenopausal
Systemic glucocorticoids

Risk assessment

DXA scan

Spine imaging

History of clinical fracture

High risk (FRAX score)

Low BMD (T-score<-2.5)

Vertebral fracture

Intervention threshold

Take action
Optimize CKD-MBD therapy
Advise lifestyle modification
Initiate non-pharmacological interventions
Consider pharmalogical therapy

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Le fratture da fragilità nel paziente in dialisi

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