



68° CONGRESSO NAZIONALE SIGG

Ritorno al futuro

FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI



IRC e osteoporosi, strategie terapeutiche preventive

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SAPIENZA
UNIVERSITÀ DI ROMA

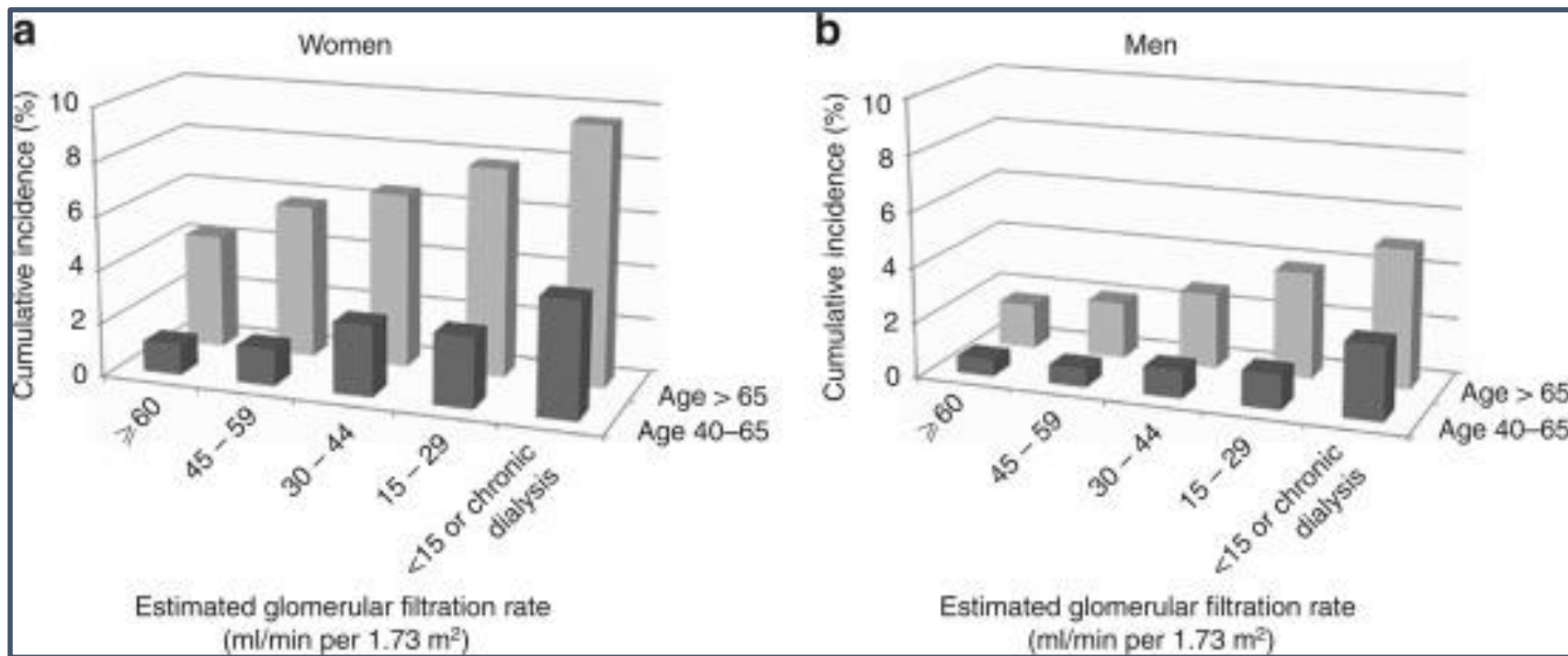
AZIENDA OSPEDALIERA
SANT' ANDREA
FACOLTÀ DI MEDICINA E
PSICOLOGIA





Incidenza di fratture e IRC

L'Incidenza cumulativa di fratture in tre anni su 679,114 è aumentato significativamente con la diminuzione del tasso di filtrazione glomerulare stimato (eGFR) sia per gli uomini che per le donne per entrambi i gruppi di età (40-65 anni e >65 anni; P per trend < 0,0001)



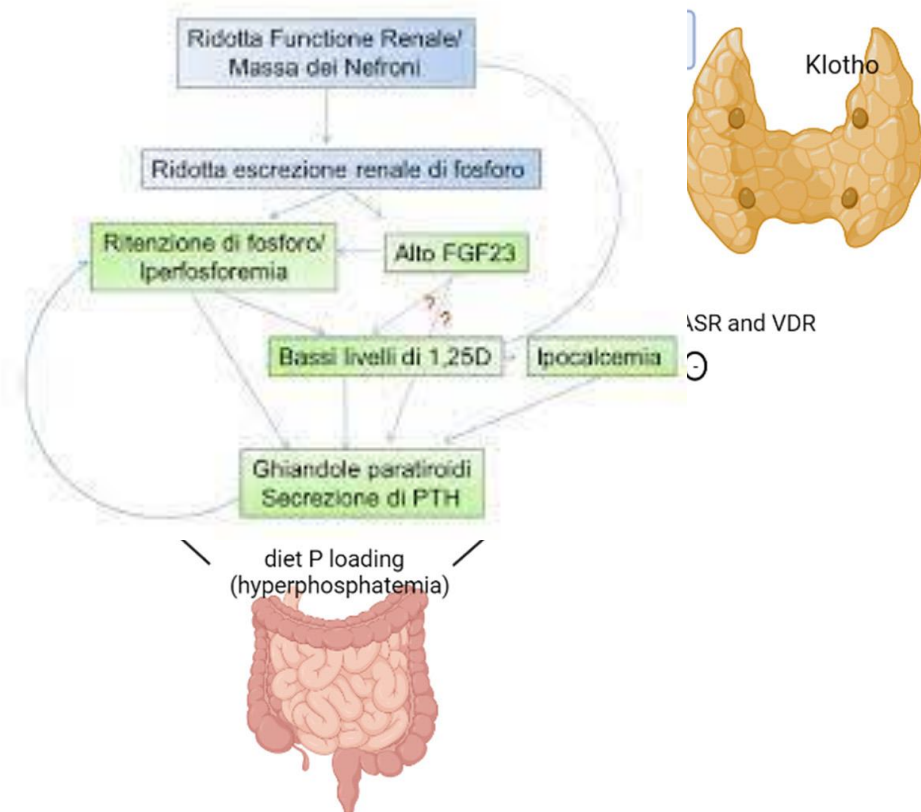
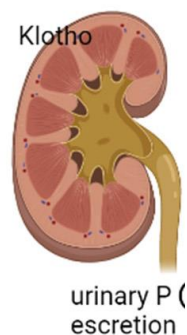


CKD-MBD: Bone Mineral Disorder –Chronic Kidney disease related Alterazione del metabolismo osseo

I normali livelli di Calcio e fosforo sono mantenuti da 3 ormoni:

- PTH
- Calcitriolo-1,25(OH) Vit D
- Proteina FGF23 (fattore di crescita dei fibroblasti)

Interazione tra rene, paratiroide, osso e intestino





CKD-MBD: Alterazione del metabolismo osseo

Stadio della CKD	GFR (mL/min/1,73 m ²)	P	Ca	PTH	Vitamina D
Stadio 1	≥ 90	N	N	↑	↓
Stadio 2	60–89			↑	↓
Stadio 3	30–59	↑	↓	↑	↓
Stadio 4	15–29			↑	↓
Stadio 5	< 15 o dialisi	↑ ↑	↓ o ↑	↑ ↑	↓ ↓



CKD-MBD: Anomalie nel turnover, nella mineralizzazione, nel volume dell'osso=alterazioni della qualità dell'osso



**Osteodistrofia renale ←
oppure
Osteoporosi Indotta da IRC?**

- **MACROARCHITETTURA (forma e geometria)**
- **MICROARCHITETTURA (organizzazione ed integrità delle trabecole)**
- **MICROCRACS**
- **MATRICE OSSEA (minerale e collagene)**



HR-pQCT provides images of bone geometry and microarchitecture

Decreased bone density and microarchitecture

- Cortical porosity
- Cortical thinning and trabecularization
- Trabecular thinning and dropout

Decreased bone quality

- Mineralization (osteomalacia)
- Abnormal remodeling

adynamic bone disease

low turnover

high turnover

- Microdamage accumulation
- AGE crosslinking

Donna in post-menopausa senza fratture

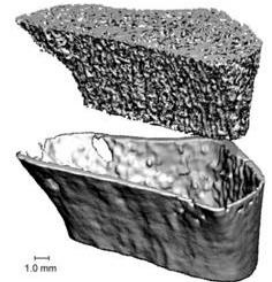
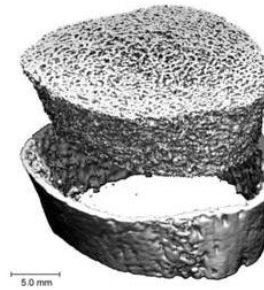
Donna in predialisi senza fratture

Donna in predialisi con fratture

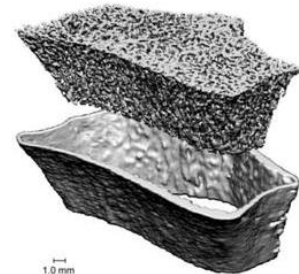
radius

tibia

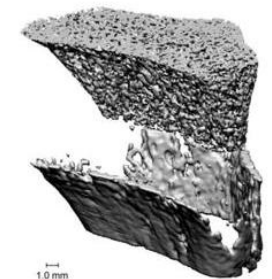
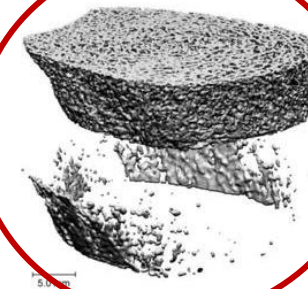
B



C



D

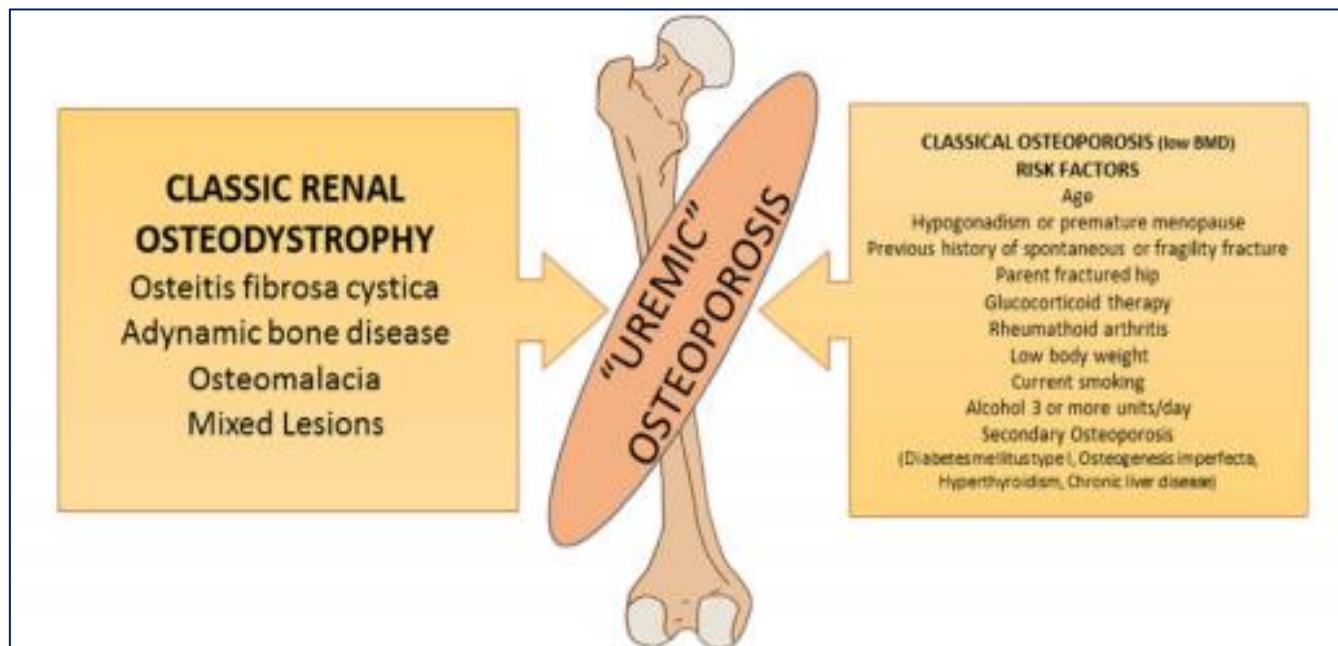




Uremic osteoporosis

Junichiro J. Kazama¹, Yoshiko Iwasaki² and Masafumi Fukagawa³

¹Division of Blood Purification Therapy, Niigata University Medical and Dental Hospital, Niigata, Japan; ²Department of Health Sciences, Oita University of Nursing and Health Sciences, Oita, Japan and ³Division of Nephrology and Metabolism, Tokai University School of Medicine, Kanagawa, Japan

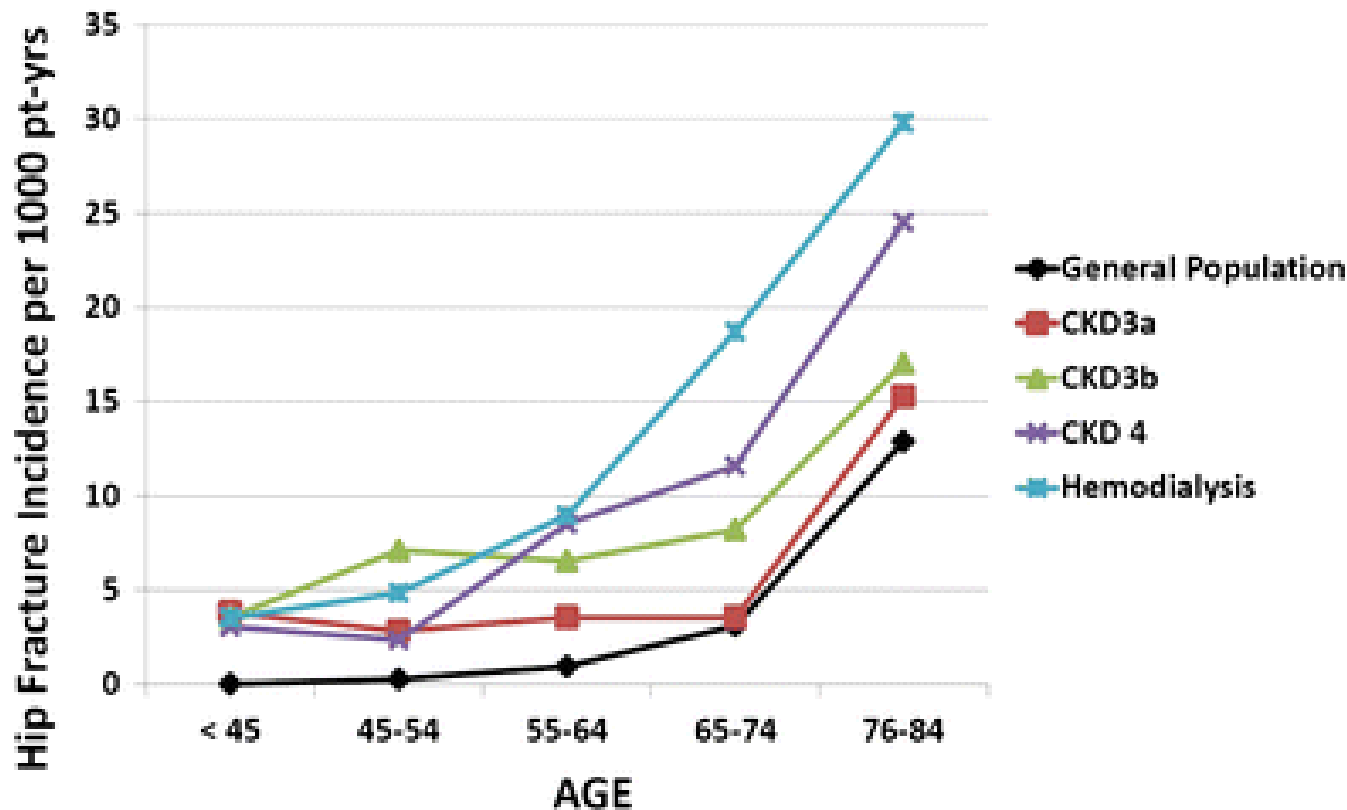


Kidney International Supplements (2013) 3, 446-450

Lo stato uremico si presenta anche nei pazienti con IRC acuta o cronica pre-renale

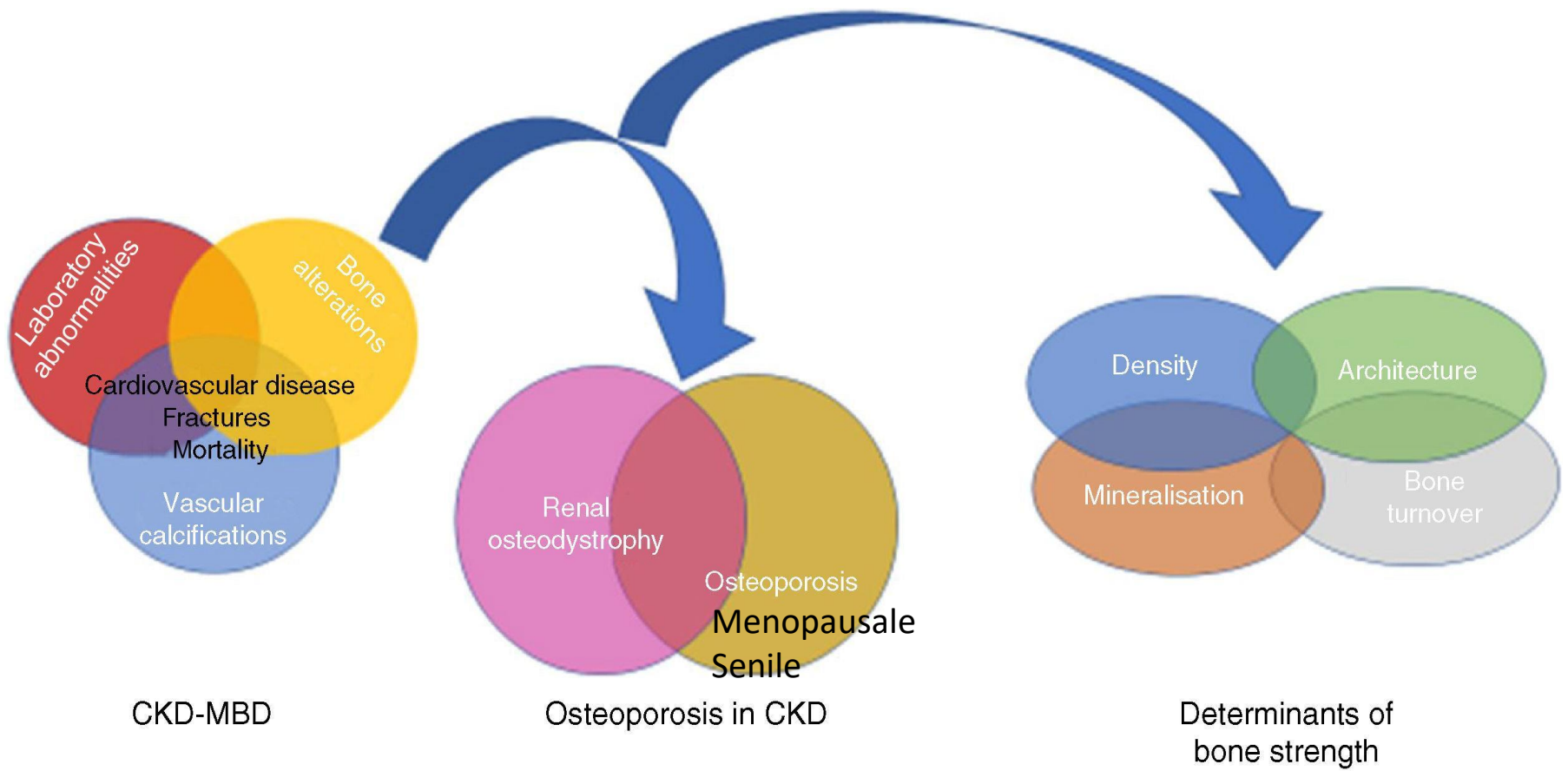


L'incidenza delle fratture dell'anca aumenta con la progressione della malattia renale cronica e con l'aumentare dell'età dei pazienti





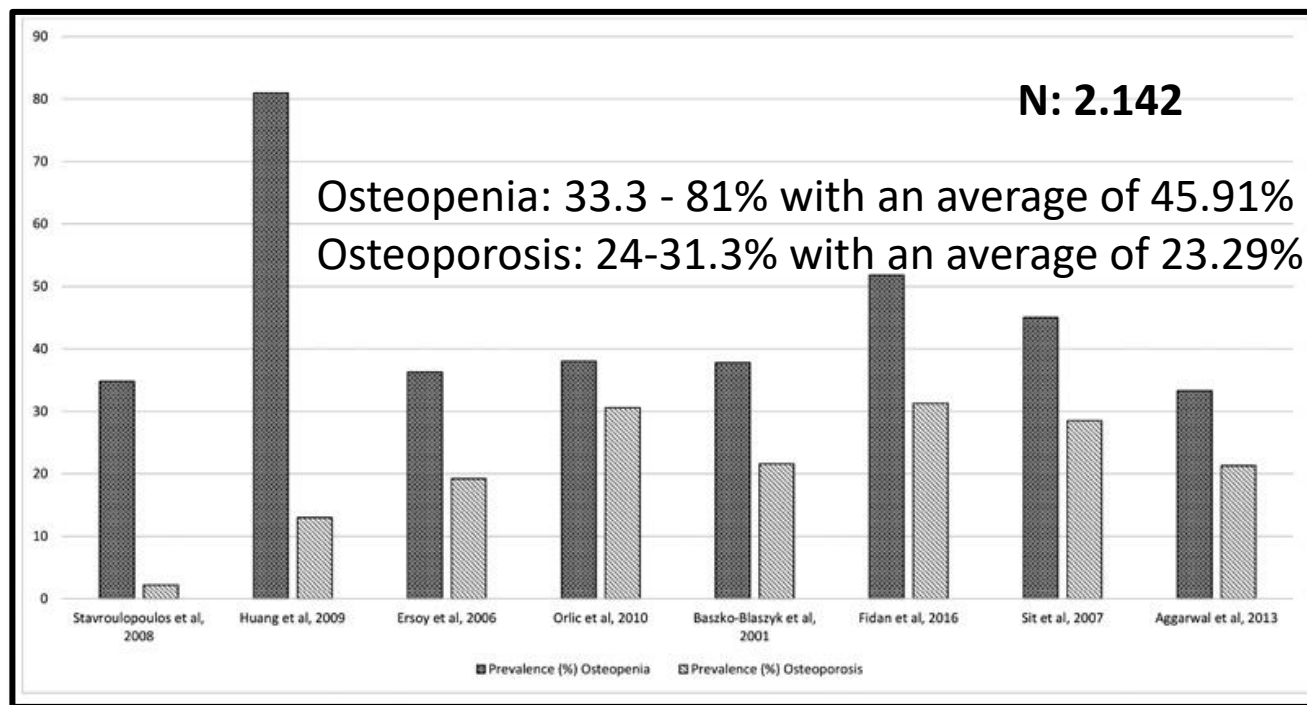
L'Osteoporosi nel paziente con IRC è dovuta al sommarsi dell'Osteodistrofia renale con l'Osteoporosi primitiva



E' necessario prevenire e curare entrambe le forme!



L'osteoporosi nell'IRC è spesso misconosciuta



Elevata variabilità nella prevalenza di osteopenia e Osteoporosi nei pazienti con IRC: Systematic Review (2020)





La diagnosi di osteoporosi e sottostimata utilizzando la DXA

Sovrastima della BMD

Calcificazioni aortiche

Artrosi e calcificazioni articolari

Deformità della colonna dovute

Alterazioni ossee qualitative e quantitative

Disposizione delle trabecole ossee

Densità di mineralizzazione non uniforme

Deposizione di cristalli ed altri metalli nella matrice ossea

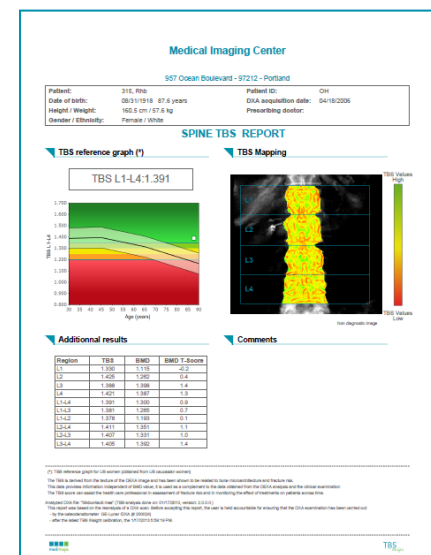
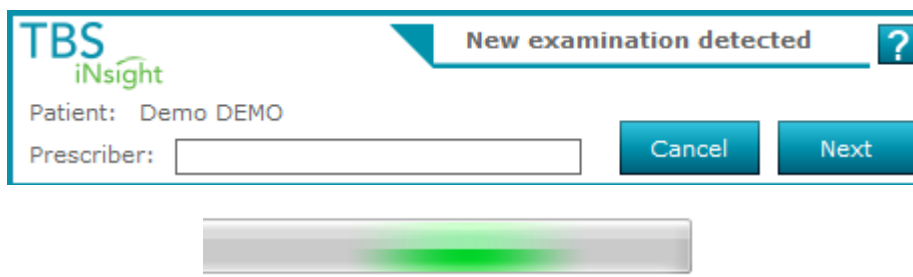
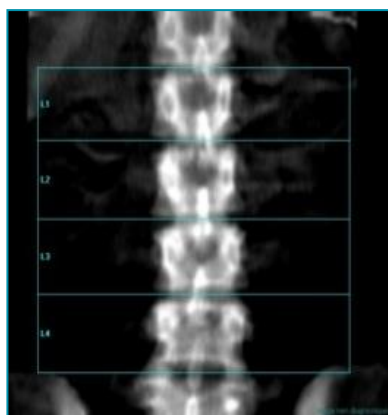


Diagnosi di OP in CKD-MBD

		PROS	CONS
PTH & bone turnover markers		<ul style="list-style-type: none"> • Noninvasive • Aids in prediction of bone turnover 	<ul style="list-style-type: none"> • Because of renal clearance, osteocalcin, P1NP and CTX has limited use in CKD
BMD- DEXA		<ul style="list-style-type: none"> • Widely available and noninvasive • Low radiation exposure & used in FRAX • Correlates with cortical porosity in CKD 	<ul style="list-style-type: none"> • Unable to assess type of ROD • Assess areal density only • Cannot distinguish cortical from trabecular bone
Trabecular bone score		<ul style="list-style-type: none"> • Noninvasive, Independent fracture predictor • Can be applied retrospectively to DEXA • No extra radiation, time and expense 	<ul style="list-style-type: none"> • Cannot detect type of ROD • Image noise degrades resolution • Variability among various software's
Quantitative ultrasound		<ul style="list-style-type: none"> • Non invasive with no radiation exposure • Portable • Correlates with BMD-DEXA 	<ul style="list-style-type: none"> • Only at distal extremity sites • Inter-observer variability • Lack of fracture predictability data in CKD
QCT		<ul style="list-style-type: none"> • 3D volumetric assessment of spine and femur • Not affected by extra skeletal calcification 	<ul style="list-style-type: none"> • High radiation exposure • Expensive and cannot detect type of ROD
HRpQCT		<ul style="list-style-type: none"> • Assesses microarchitecture noninvasively • Good cortical and trabecular differentiation • Correlates with bone histopathology 	<ul style="list-style-type: none"> • Expensive and not widely available • Investigational tool only • Only distal extremity site (tibia and radius)
HR-MRI		<ul style="list-style-type: none"> • Non-ionizing • Can image central bones (hip) 	<ul style="list-style-type: none"> • Expensive • Not widely available
Finite element analysis (FEA)		<ul style="list-style-type: none"> • Improves bone quality assessment by CT and MRI • Aids CT and MRI in evaluating mechanical properties & fracture prediction 	<ul style="list-style-type: none"> • Lack of standardization • Various loading conditions can affect the estimation of strength
Reference point indentation		<ul style="list-style-type: none"> • Good in-vivo measure of bone stiffness & quality • Correlates well with fracture risk • Correlates with BMD and TBS in CKD 	<ul style="list-style-type: none"> • Invasive and can cause local complications • Does not represent whole bone strength • Does not detect type of ROD
Bone biopsy		<ul style="list-style-type: none"> • Gold standard as it directly assesses bone turnover, mineralization and volume • Assess bone marrow, can detect heavy metals and micro-cracks 	<ul style="list-style-type: none"> • Invasive and cannot detect whole bone strength • Not widely available and needs expertise
FTIR & nano-indentation		<ul style="list-style-type: none"> • Provides data on bone material properties • Adds additional information about bone quality 	<ul style="list-style-type: none"> • Limited availability and needs bone tissue • Only provides relative measures of mineral/matrix etc



“TBS is derived from texture of the DXA image and has been shown to be related to microarchitecture and fracture risk”



1. DXA Scan



2. Software Processing 3s



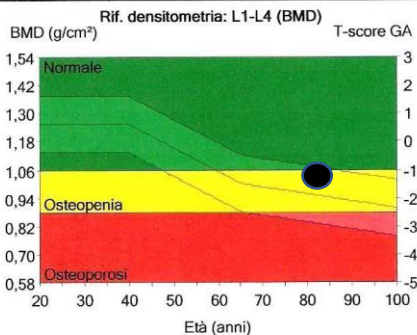
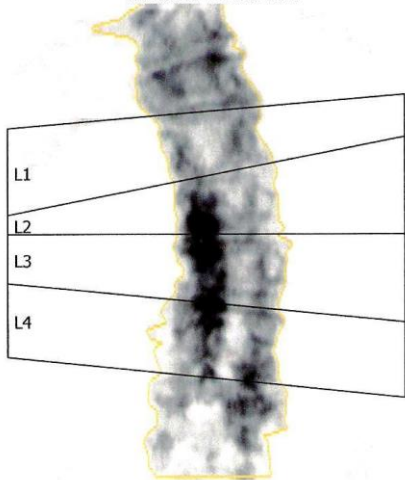
3. TBS Analysis & Report



Roma

Paziente:		ID ambulatorio:	
Data di nascita:	18/07/1929 82,6 anni	Medico referente:	
Altezza / Peso:	161,0 cm 78,0 kg	Misurato:	10/03/2012 9.38.19 (13,60)
Sesso / Etnia:	Femmina Bianco	Analizzato:	10/03/2012 9.39.11 (13,60)

Colonna AP Densità ossea

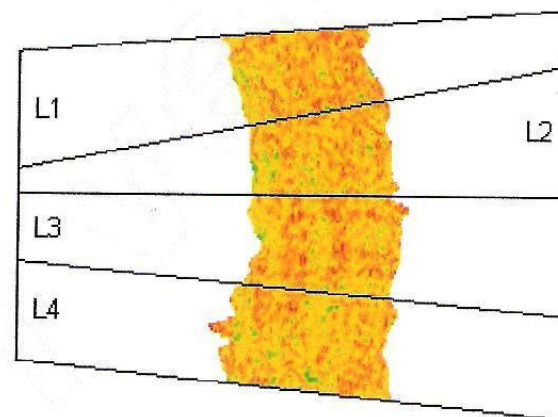
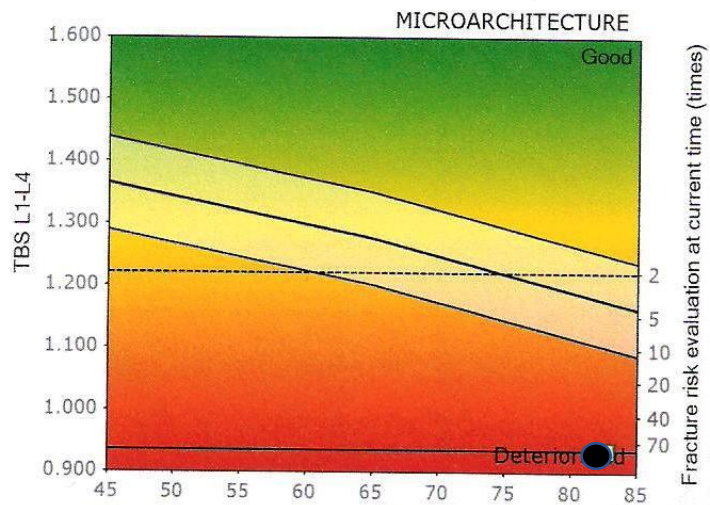


Regione	¹ BMD (g/cm ²)	² Giovane adulto T-score	³ Pari età Z-score
L1	0,845	-2,4	-0,5
L2	1,008	-1,6	0,3
L3	1,171	-0,2	1,7
L4	1,066	-1,1	0,8
L1-L4	1,033	-1,2	0,7

Paziente di 82 anni con osteoartrosi spinale

REPORT

TBS Cartography



High TBS
values





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Densitometria ossea con tecnologia R.E.M.S (Radiofrequency Ecografic Multi-Spectrometry)

L'unico densitometro osseo ecografico
Innovativa soluzione senza radiazioni per la valutazione dello stato osseo alle vertebre lombari e al collo del femore con una veloce scansione ecografica attraverso la tecnologia proprietaria R.E.M.S. Da oggi la prevenzione, la diagnosi precoce e il monitoraggio dell'osteoporosi è possibile direttamente in ambulatorio medico.



Aging Clinical and Experimental Research (2023) 35:185–192

<https://doi.org/10.1007/s40520-022-02286-7>

ORIGINAL ARTICLE



Radiofrequency echographic multi-spectrometry and DXA for the evaluation of bone mineral density in a peritoneal dialysis setting

Angelo Fassio¹ · Stefano Andreola² · Davide Gatti¹ · Beatrice Bianco² · Matteo Gatti¹ · Giovanni Gambaro² · Maurizio Rossini¹ · Ombretta Viapiana¹ · Riccardo Negrelli³ · Giovanni Adami¹

Received: 22 August 2022 / Accepted: 16 October 2022 / Published online: 3 November 2022

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Abstract

Background The aim of this real-life cross-sectional explorative study was to compare radiofrequency echographic multi-

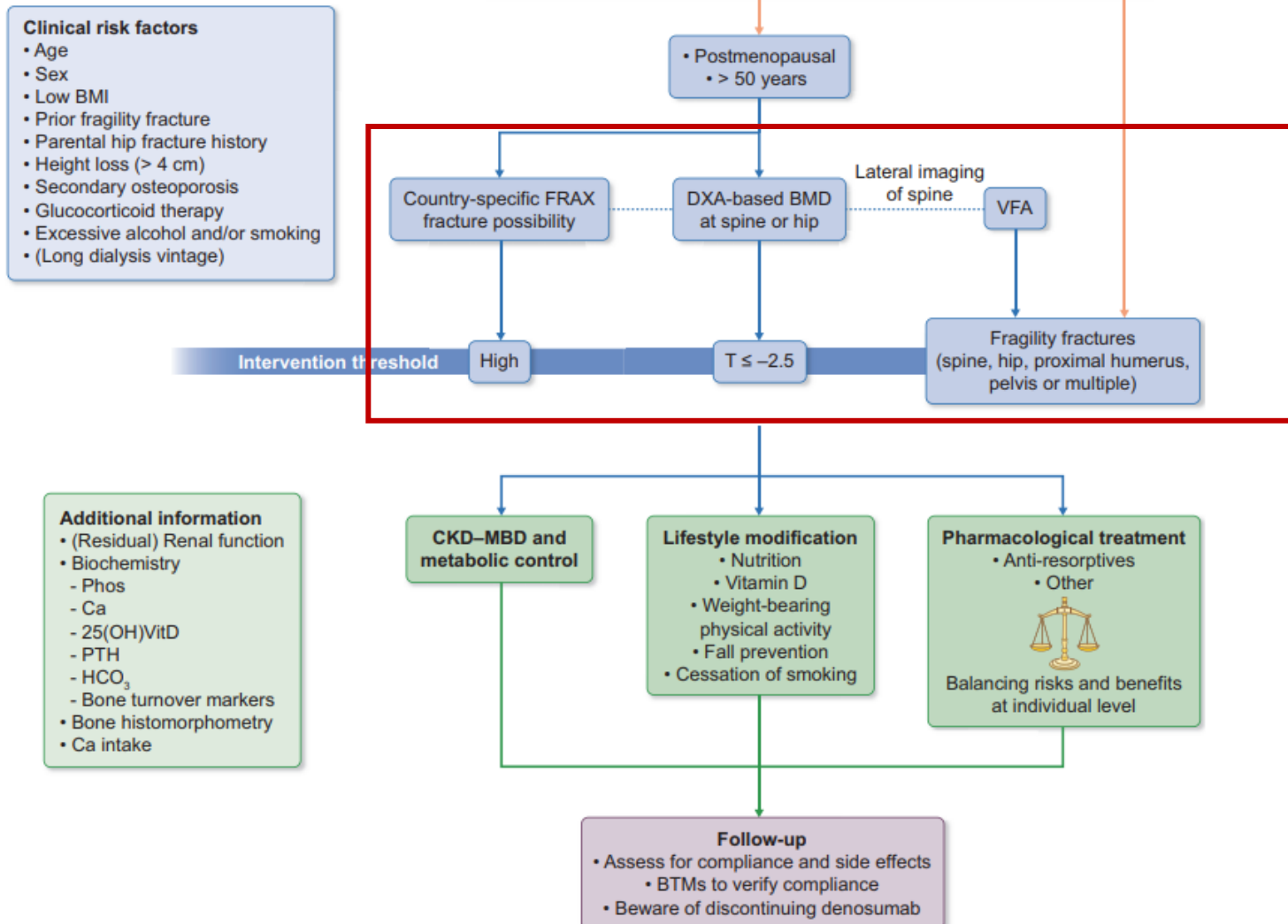
Conclusions Our data showed a promising agreement, in a real-life PD setting, between DXA and REMS BMD assessment and in the consequent fracture risk estimation and confirm the AOCs interference on the diagnostic accuracy of lumbar DXA.

Results 41 patients were enrolled. No significant differences were documented between the BMD *T*-scores measured through DXA or REMS at the femur. At the lumbar spine, the DXA anteroposterior mean *T*-score (-0.49 ± 1.98) was significantly higher than both the laterolateral DXA (-1.66 ± 0.99) and the REMS (-2.00 ± 1.94) measurements ($p < 0.01$ vs both). No significant differences were found between the DXA and REMS fracture risk estimates with both algorithms. The inter-technique Cohen's *k* coefficient (for the worst *T*-score, any site) was 0.421, $p < 0.001$. The discrepancy between the DXA laterolateral and anteroposterior lumbar *T*-score was positively associated with the AOCs extent and severity ($r = 0.402$, $p < 0.01$).

Conclusions Our data showed a promising agreement, in a real-life PD setting, between DXA and REMS BMD assessment and in the consequent fracture risk estimation and confirm the AOCs interference on the diagnostic accuracy of lumbar DXA.



Osteoporosis diagnosis and management in patients with CKD G4–G5D

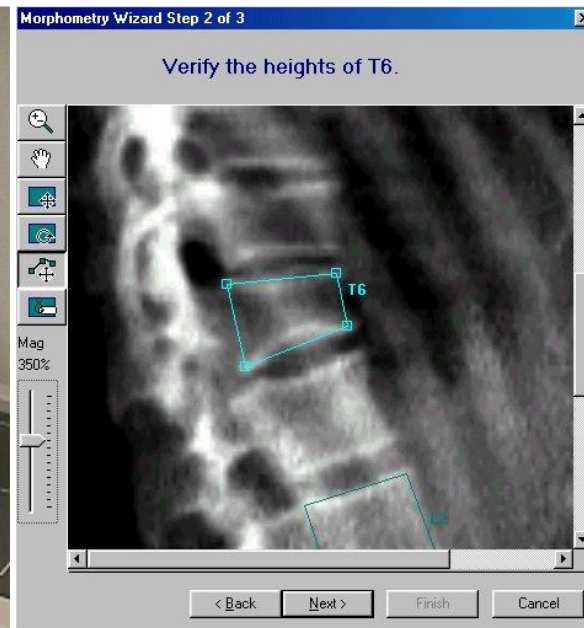
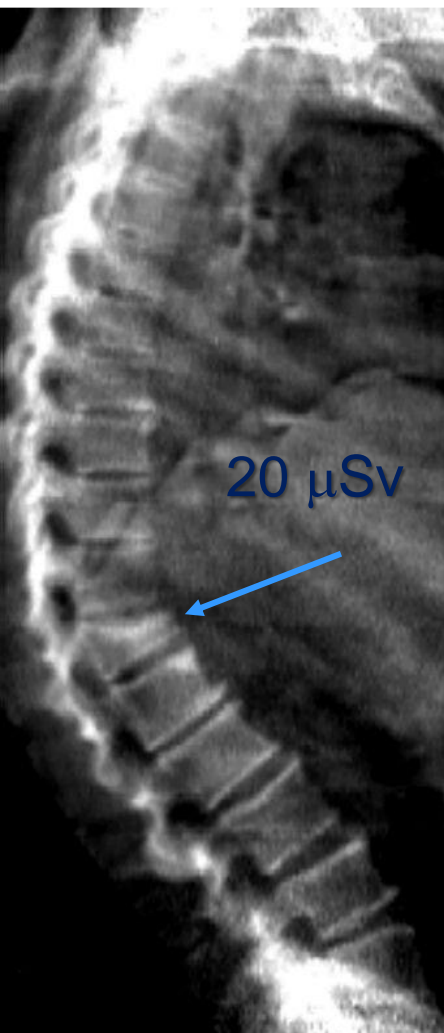




Special report on the 2007 adult and pediatric Position Development Conferences of the International Society for Clinical Densitometry

Vertebral Fracture Assessment (VFA)

is the correct term to denote densitometric spine imaging by Dual-X-Ray Absorptiometry (DXA) technique performed for the purpose of detecting vertebral fractures





Strategie terapeutiche preventive: ridurre i fattori di rischio per fratture da fragilità nella CKD G4-G5D

Table 1. Clinical risk factors used for assessment of fracture probability

General risk factors
Older age
Gender (female)
Low BMI
Previous fragility fracture, particularly of the hip, wrist and spine, including morphometric vertebral fracture in adult life
Parental history of hip fracture
Glucocorticoid treatment (>5 mg prednisolone daily or equivalent for ≥3 months)
Current smoking
Alcohol intake ≥3 units daily
Causes of secondary osteoporosis
Rheumatoid arthritis
Untreated hypogonadism in men and women
Inflammatory bowel disease
Prolonged immobility
Organ transplantation
Type 1 and type 2 diabetes
Thyroid disorders, e.g. untreated hyperthyroidism, thyroid hormone suppressive therapy
Chronic obstructive pulmonary disease
HIV infection
CKD-related risk factor
Dialysis vintage

European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4–G5D





Strategie terapeutiche preventive: ridurre i fattori di rischio per fratture da fragilità nella CKD G4-G5D

Cause di osteoporosi secondaria

Da Farmaci

Glucocorticoidi

L-Tiroxina a dosi soppressive

Eparina e anticoagulanti orali (AVK)

Anticonvulsivanti

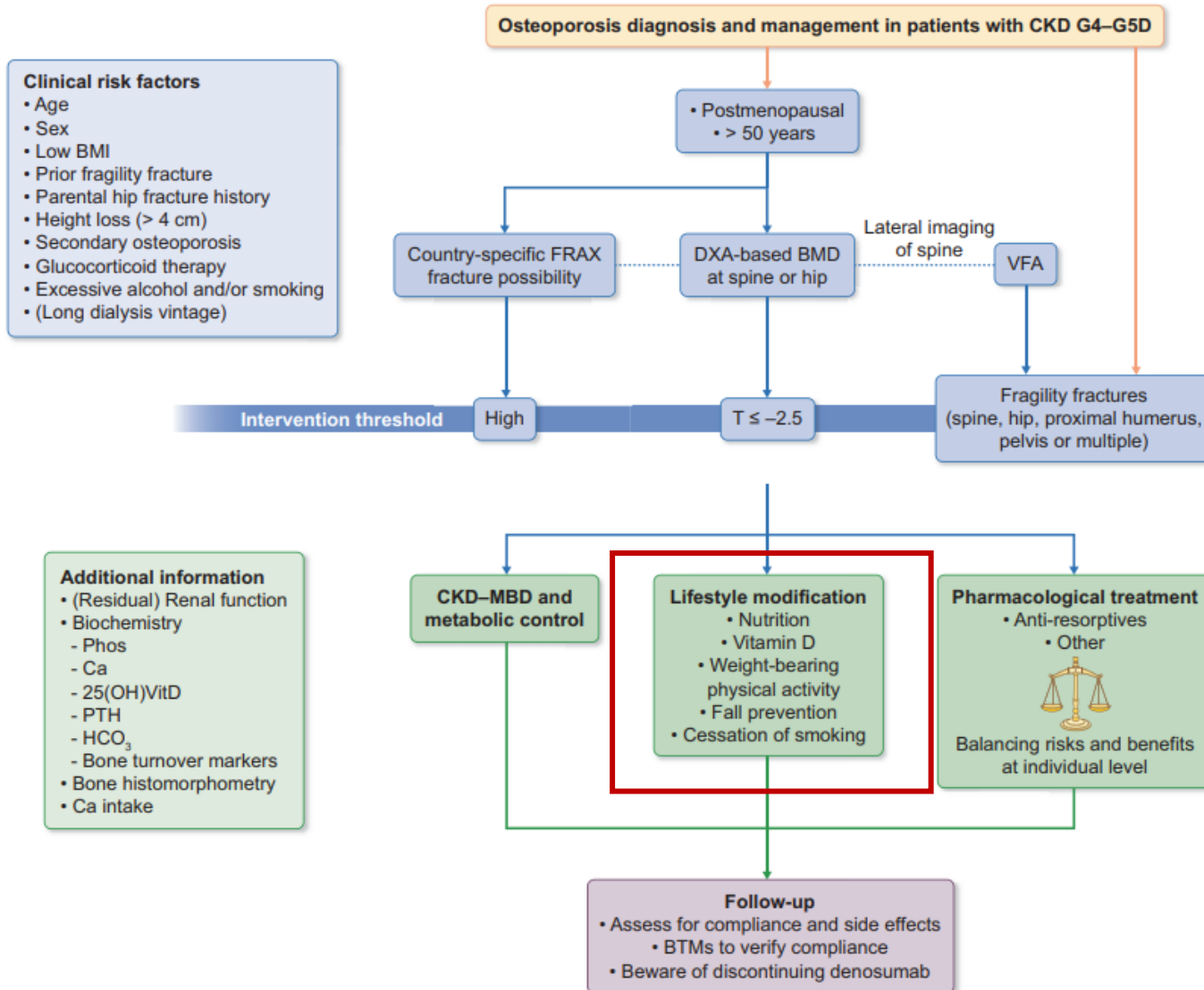
Inibitori dell'Aromatasi

Antiandrogeni

Antagonisti del GnRH

Immunosoppressori Antiretrovirali Tiazolinedioni Inibitori di

Pompa Protonica (PPI) Inibitori selettivi della ricaptazione
della serotonina (SSRI)





Strategie terapeutiche preventive: migliorare la qualità dell'osso

Treatment modalities

Lifestyle

Smoking cessation

Limiting alcohol

Role in bone metabolism

Smoking induces bone resorption and mineralization defect

Smoking increases phosphorus levels in predialysis CKD patients

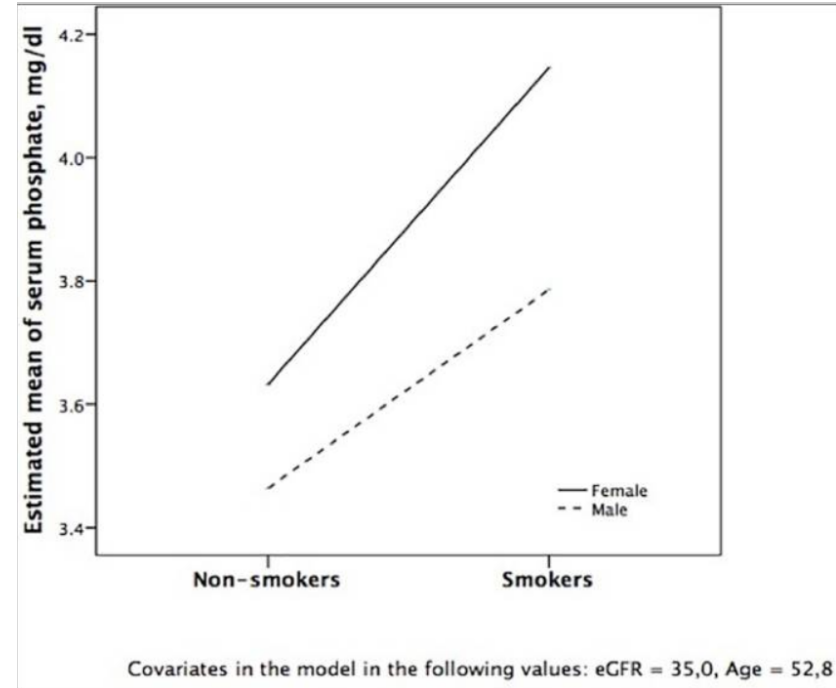
Reduces osteoblast and increases osteoclast
Systemic alterations



Chronic kidney disease patients who smoke have higher serum phosphorus

J Bras Nefrol.2019

Smoking negatively affects bone health by inducing more bone resorption and mineralization defect



L'esposizione al fumo di sigaretta altera la composizione della matrice ossea e peggiora la mineralizzazione ossea, portando alla fragilità ossea aumentando la sintesi e la deposizione del collagene V e compromettendo la formazione e l'assemblaggio delle fibrille di collagene tipo I. E questi effetti deleteri hanno contribuito al peggioramento della guarigione delle fratture nei topi dopo l'osteotomia della tibia.



Treatment modalities

Lifestyle

Exercise as tolerated

Diet (micronutrients, vitamins, antioxidants, plant-based food, fibers, polyunsaturated fatty acids, and Mediterranean)

Role in bone metabolism

Anabolic effects: prevents muscle wasting, improves BMI and BMD

Reduces inflammation

Improves Ca and PO₄ homeostasis

Experimentally improves bone microarchitecture in CKD rats

Downregulates sclerostin production

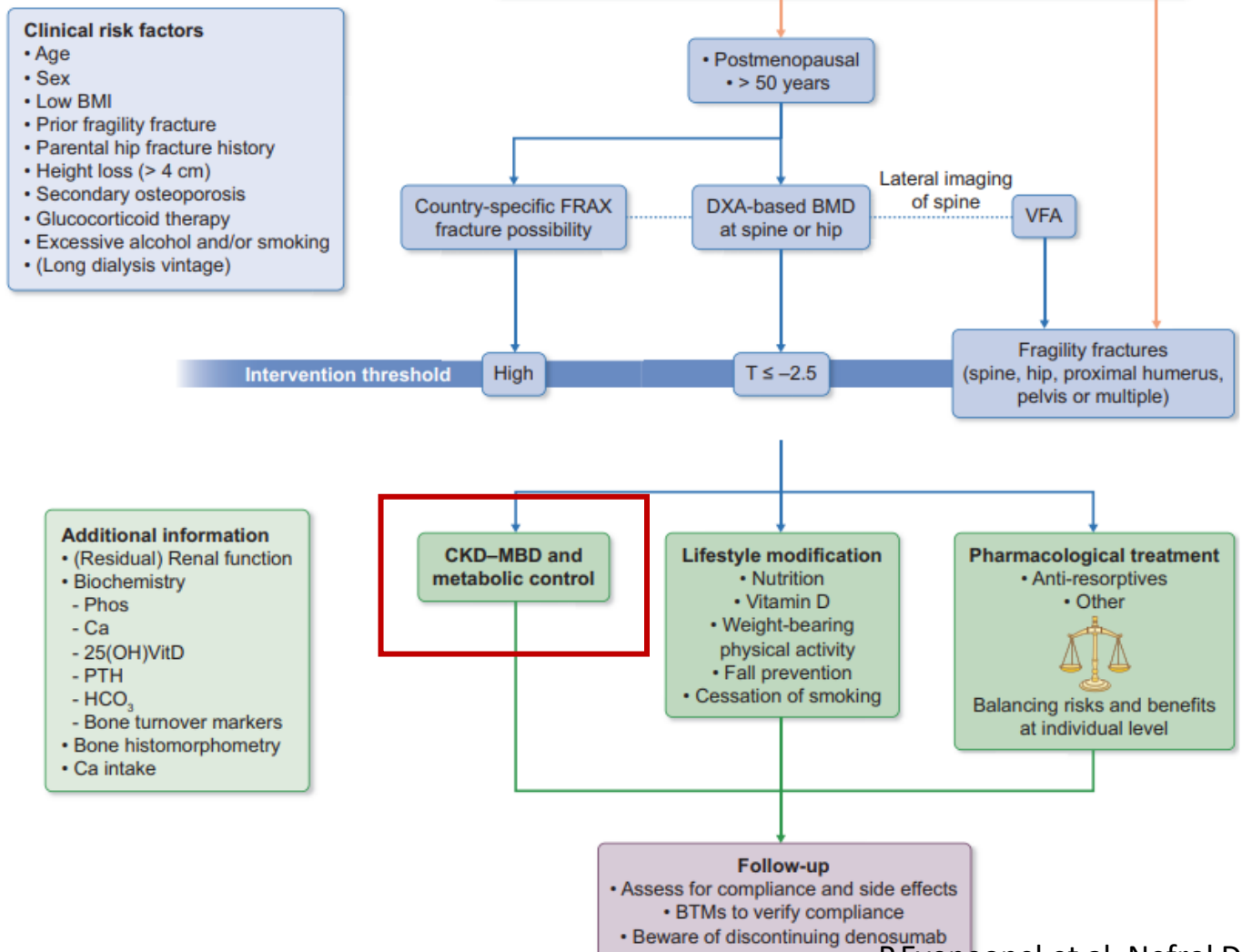
Pro-inflammatory diet (high-calorie nutrients) is associated with lower BMD and higher fracture risk

Plant sources of proteins can help bone collagen without inducing acid load

Low-protein diet with ketoanalogues may help CKD parameters



Osteoporosis diagnosis and management in patients with CKD G4–G5D





Livelli di Fosforo

Stage	Target PO ₄
3	<p>KDIGO: Maintain Normal</p> <p>KDOQI: 2.7-4.6 mg/dL</p>
4-5	<p>KDIGO: Maintain Normal</p> <p>KDOQI: 2.7-4.6 mg/dL</p>
5D	<p>KDIGO: Towards Normal</p> <p>KDOQI: 3.5-5.5 mg/dL</p>

mantenere P nell'intervallo di normalità

- limitare assunzione di P (evitare latticini)
- limitare l'assorbimento di P (chelanti del fosforo non contenenti alluminio)

Decidere sull'andamento dei dati di laboratorio piuttosto che sul singolo dato

Livelli di PTH

Treatment Initiation Ranges

Stage	Treatment Initiation Range iPTH
3	KDIGO: > Upper limit of Normal 4.2.2 (2C) KDOQI: 35-70 pg/mL
4	KDIGO: > Upper limit of Normal 4.2.2 (2C) KDOQI: 70-110 pg/mL
5	KDIGO: > Upper limit of Normal 4.2.2 (2C) KDOQI: 150-300 pg/mL
5D	KDIGO: 2 to 9x upper limit of Normal 4.2.3 (2C) KDOQI: 150-300 pg/mL

CKD3–5D Se PTH aumenta e non è controllabile: Vit. D (Calcitriolo o analogo di Vit. D: Paracalcitolo o associazione)

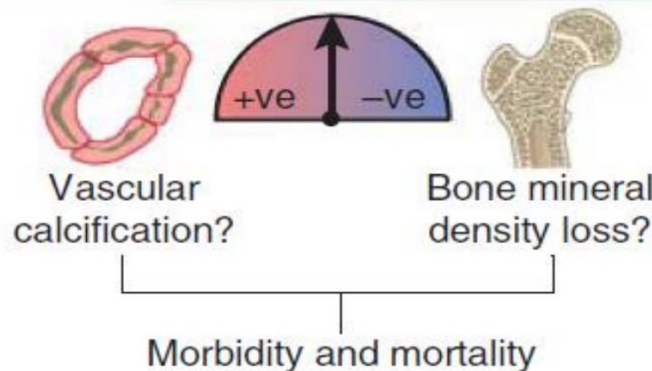
CK5D: Se PTH aumenta e non è controllabile: calciomimetico (cinacalcet e etelcalcetide) +Vit D
Valutare paratiroidectomia nei non responder

Decidere sull'andamento dei dati di laboratorio piuttosto che sul singolo dato



Livelli di calcio

Stage	Target Ca
3	<p>KDIGO: Maintain Normal</p> <p>KDOQI: Normal for Lab</p>
4-5	<p>KDIGO: Maintain Normal</p> <p>KDOQI: Normal for Lab</p>
5D	<p>KDIGO: Maintain Normal</p> <p>KDOQI: 8.4-9.5 mg/dL</p>



- Cercare di mantenersi neutrali nell'equilibrio del calcio durante le fasi della malattia renale cronica
- Equilibrio neutro del calcio consumando 800-1000 mg/giorno
- Per i pazienti che scendono al di sotto di 800-1000 mg/giorno, fonti alimentari ricche di calcio, integratori di calcio, chelanti del fosfato a base di calcio

Decidere sull'andamento dei dati di laboratorio piuttosto che sul singolo dato



Supplementazione con Vitamina D

- Terapia di prima linea nella malattia renale cronica con Iperparatiroidismo secondario (SHPT) e carenza di vitamina D
- Rischio più elevato di ipercalcemia e iperfosfatemia con Calcitriolo rispetto alla vitamina D
- Mantenere la vitamina D a un livello equilibrato, anche la combinazione di vitamina D e calcitriolo è utile per SHPT e i marcatori ossei
- VDRA possono indurre Low Turnover Bone Disease



Forme di vitamina D nell'IRC

Vitamin D Term	Sterol	Type of Vitamin D
Vitamin D	<u>Cholecalciferol</u>	D ₃
	Ergocalciferol	D ₂
25-Hydroxyvitamin D	<u>Calcidiol (25(OH)D₃)</u>	D ₃
	Ercalcidiol (25(OH)D ₂)	D ₂
Vitamin D receptor agonist prohormone ^a	<u>Alfacalcidol (1(OH)D₃)</u>	D ₃ ; Synthetic prohormone
	Doxercalciferol (1(OH)D ₂)	D ₂ ; Synthetic prohormone
Vitamin D receptor agonist	Calcitriol (1,25(OH) ₂ D ₃)	D ₃ ; Natural analog
	Paricalcitol (19nor,1,25(OH) ₂ D ₂)	D ₂ ; Synthetic analog
	Maxacalcitol (22oxa,1,25(OH) ₂ D ₃)	D ₃ ; Synthetic analog

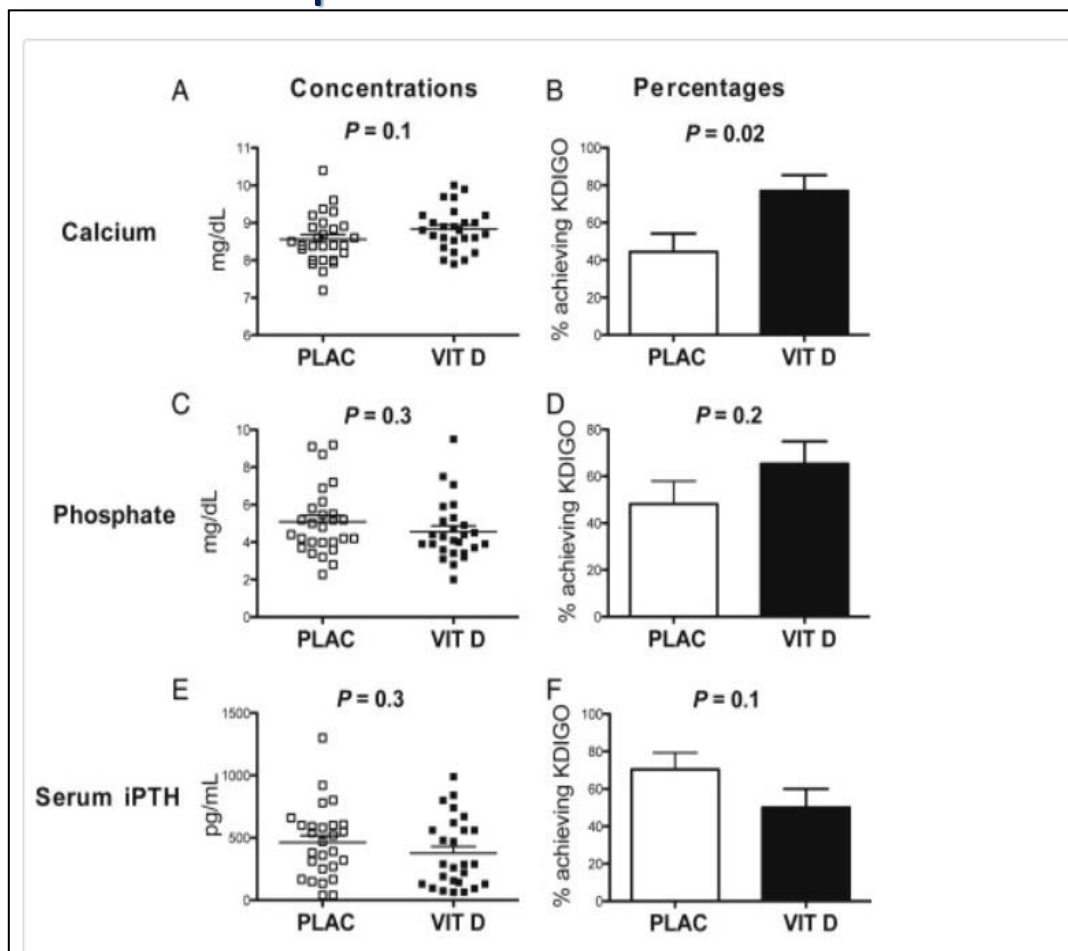
^aRequires 25-hydroxylation by the liver to become an active analog.

Non solo calcitriolo!

Sprague SM, Coyne D. Clinical journal of the American Society of Nephrology (CJASN) 2010



La somministrazione di colecalciferolo è efficace nel correggere il metabolismo osseo nei pazienti con IRC severa



Massart A, et al. American journal of kidney diseases : the official journal of the National Kidney Foundation, 2014.

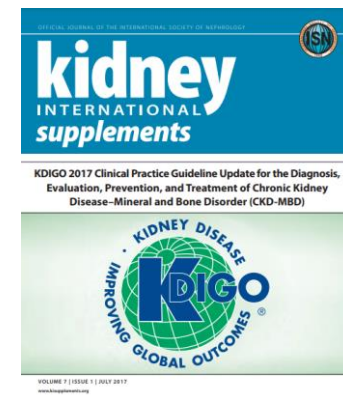


CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on cause, GFR category (G1–G5), and albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

				Persistent Albuminuria Categories		
				Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR Categories (mL/min/1.73 m ²)	Description and Range			Stesso trattamento della popolazione generale		
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
G5	Kidney failure	<15				





Review

Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)

Table 6. Suggestions and recommendations concerning vitamin D supplementation in subjects with hypovitaminosis D or candidates to receive anti-fracture drugs.

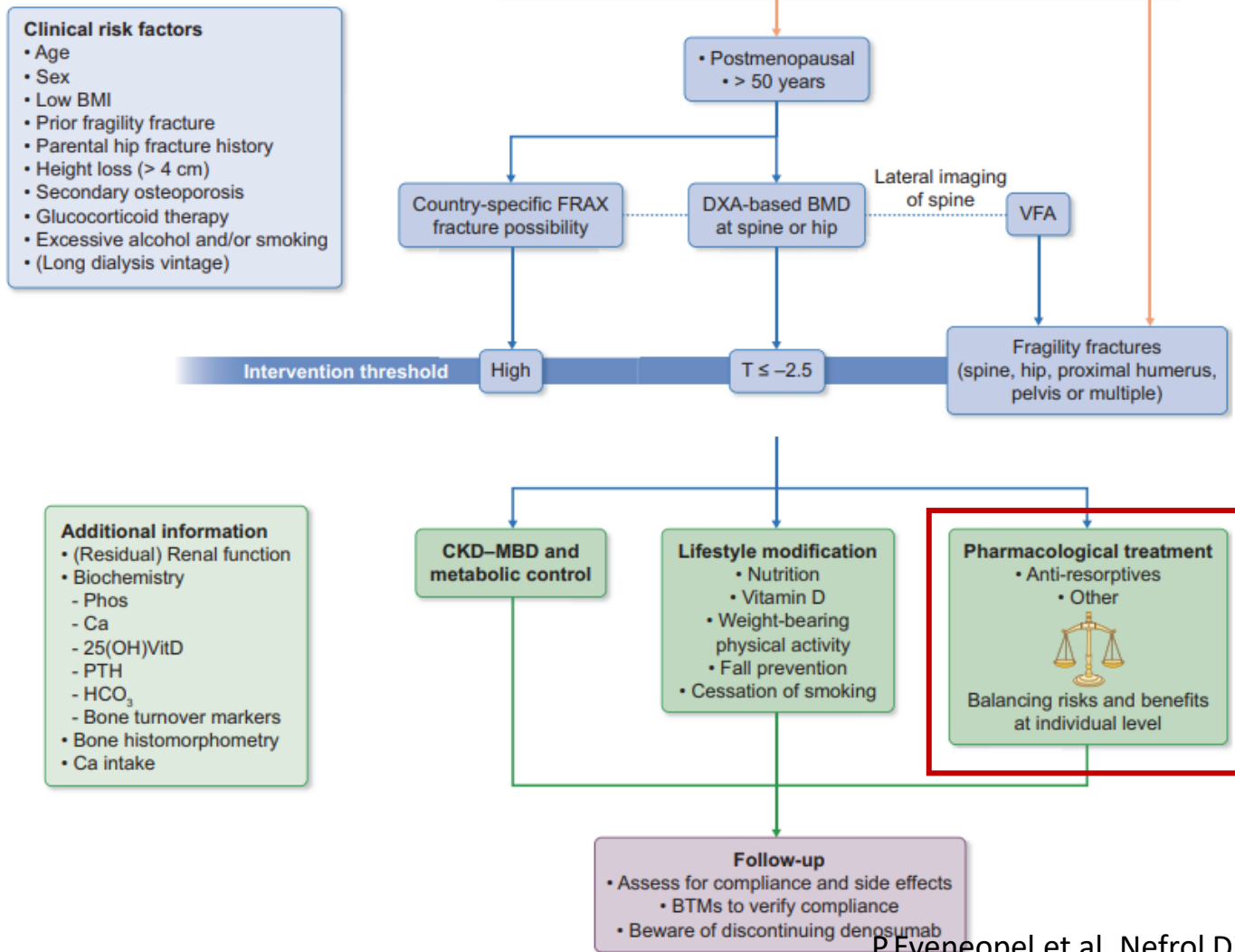
In Subjects with Hypovitaminosis D, or Candidates for Bone Active Agents for Osteoporosis:	Evidence Levels
We suggest a dose of cholecalciferol supplementation between 800 IU/day and 2000 IU/day. There is no single, fixed dose for all subjects that needs to be supplemented.	⊕
We suggest a daily, weekly, monthly schedule based on the dose administered. In these settings, the maximum single daily dose to be administered should not exceed 100,000 IU. An adequate calcium intake (800–1000 mg/day) must always be ensured.	⊕
We recommend the use of an initial loading dose, followed by the maintenance dose in patients with symptomatic osteomalacia and/or serum 25(OH)D < 10 ng/mL, or in patients starting bone anti-resorptive therapy with intravenous bisphosphonates or denosumab with serum 25(OH)D < 20 ng/mL.	⊕⊕⊕
We recommend , as loading dose, cholecalciferol 3000–10,000 IU/day (average 5000 IU/day) for 1–2 months, or cholecalciferol in a single dose of 60,000 to 150,000 IU followed by the maintenance dose (2000 IU/day). Alternatively, we suggested calcifediol 20–40 mcg/day (4–8 gtt/day) for 20–30 days, before switching to maintenance dose *.	⊕⊕⊕

* With a limited recommendation

Raccomandato l'uso di colecalciferolo o calcifediolo

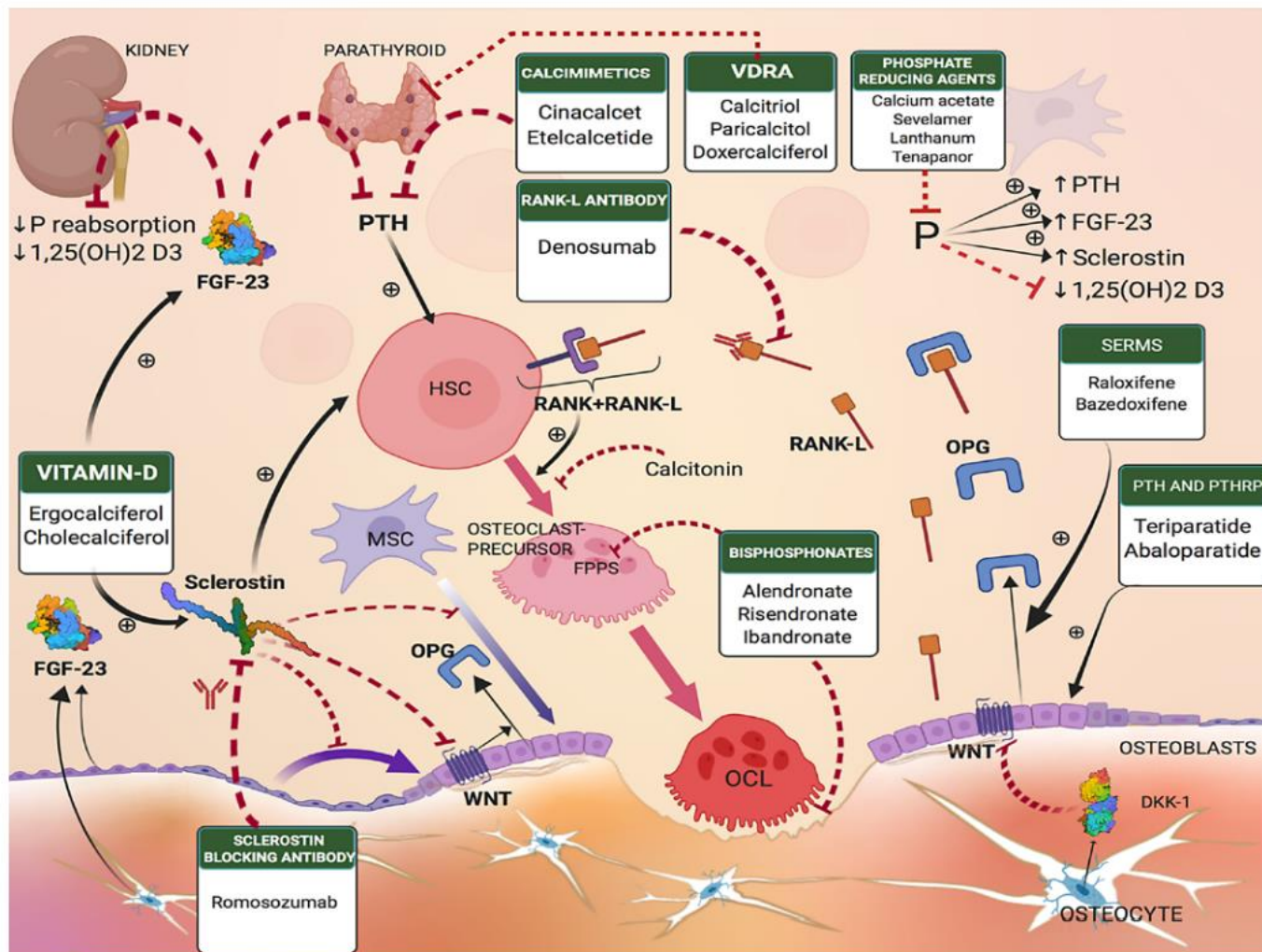


Osteoporosis diagnosis and management in patients with CKD G4–G5D





Trattamento Farmacologico: sintesi





Conclusioni

L'osteoporosi nel paziente anziano con IRC è:

- Più grave: peggiore qualità dell'osso (ROD+OP)
- Più difficile da diagnosticare: si nasconde dietro le calcificazioni
- Può essere trattata fino allo stadio di pre-dialisi come l'osteoporosi senile
- Importante è la supplementazione di Vitamina D nativa ed un buon apporto di calcio con la dieta per mantenere un buon metabolismo fosfo-calcico

Se con queste strategie riusciamo ad evitare l'iperparatiroidismo possiamo migliorare la salute dell'osso ed evitare le fratture nel paziente anziano con IRC!

