Χρόνια Νεφρική Νόσος και Οστεοπόρωση
Chronic Kidney Disease and Osteoporosis

Ιωάννης Γ. Γριβέας, **MD,PhD**
Νεφρολόγος

athens-NEPHROLOGY

KDIGO 2017 Clinical Practice Guideline Update

Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD

2009 KDIGO

Controversies Conference 2013
"CKD-MBD: Back to the Future

2017 Update

- Work Group acknowledged the lack of high-quality evidence on which to base recommendations.
- Multiple randomized controlled trials (RCTs) and prospective cohort studies.
- KDIGO recognizes the need to reexamine the currency of its guidelines.

A total of 12 recommendations were identified for revision.

- 2017 Update3 followed a rigorous process of evidence review and appraisal, based on systematic reviews of results from clinical trials.
- GRADE

Where appropriate, the Work Group issued "not graded"recommendations, based on general advice, that were not part of a systematic evidence review.

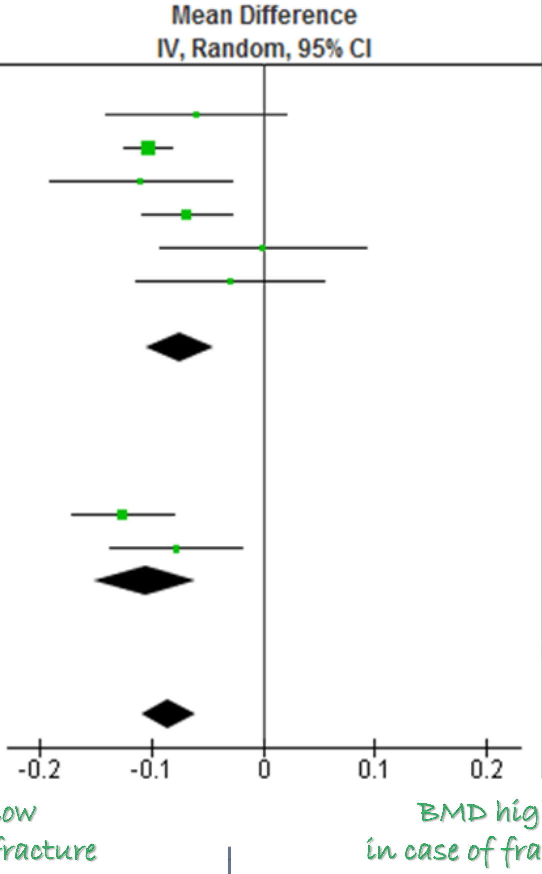
Table 1| Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
3.2.1. In patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (*2B*).	3.2.2. In patients with CKD G3a–G5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (*2B*).	Multiple new prospective studies have documented that lower DXA BMD predicts incident fractures in patients with CKD G3a–G5D. The order of these first 2 recommendations was changed because a DXA BMD result might impact the decision to perform a bone biopsy.
3.2.2. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).	3.2.1. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (*Not Graded*).	The primary motivation for this revision was the growing experience with osteoporosis medications in patients with CKD, low BMD, and a high risk of fracture. The inability to perform a bone biopsy may not justify withholding antiresorptive therapy from patients at high risk of fracture.

Meta-Analysis

DEXA-determined femoral BMD

Study or Subgroup	Fracture Group Mean	Fracture Group SD	Fracture Group Total	Non-Fracture Group Mean	Non-Fracture Group SD	Non-Fracture Group Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Dialysis Patients								
Ambrus 2011	0.66	0.18	21	0.72	0.14	109	7.0%	-0.06 [-0.14, 0.02]
Cejka 2011	0.573	0.048	24	0.6764	0.037	50	28.3%	-0.10 [-0.13, -0.08]
Fontaine 1999	0.62	0.13	11	0.73	0.12	77	7.0%	-0.11 [-0.19, -0.03]
Iimori 2012	0.567	0.133	46	0.636	0.141	416	17.9%	-0.07 [-0.11, -0.03]
Jamal 2002	1.3	0.23	54	1.3	0.25	50	5.7%	0.00 [-0.09, 0.09]
Jamal 2006	0.76	0.17	27	0.79	0.14	25	6.6%	-0.03 [-0.11, 0.05]
Urena 2003	0	0	21	0	0	49		Not estimable
Subtotal (95% CI)			**204**			**776**	**72.5%**	**-0.07 [-0.11, -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
1.2.2 Non-dialysis patients								
Nickolas 2010	0.621	0.0718	23	0.747	0.134	59	16.0%	-0.13 [-0.17, -0.08]
Nickolas 2011	0.677	0.127	32	0.755	0.154	59	11.4%	-0.08 [-0.14, -0.02]
Subtotal (95% CI)			**55**			**118**	**27.5%**	**-0.11 [-0.15, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 1 (P = 0.21); I² = 38%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Total (95% CI)			**259**			**894**	**100.**	**[-0.11, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 11.33, df = 7 (P = 0.12); I² = 38%								
Test for overall effect: Z = 6.91 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.5%								



Take home messages

- Prospective studies evaluating BMD testing in adults with CKD represent a substantial advance since the original guideline from 2009, making a reasonable case for BMD testing if the results will impact future treatment.
- It is important to emphasize the interdependency of serum calcium, phosphate, and PTH for clinical therapeutic decision-making.

Management of Osteoporosis in CKD

Pascale Khairallah and Thomas L. Nickolas

Clin J Am Soc Nephrol 13: 962–969, 2018. doi: https://doi.org/10.2215/CJN.11031017

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.

Unfortunately, data supporting that BMD testing is relevant in CKD has lagged behind that generated in the general population. In the 2003 Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, BMD testing was only recommended in post-transplant patients as there were no studies in patients with CKD demonstrating that a low BMD by DXA predicted subsequent fracture. In other words, its utility as a screening tool to identify those patients at risk was not yet proven.[16]. There was also concern that DXA may be artificially elevated in the setting of arterial calcification, especially at the lumbar spine[16]. In the 2009 KDIGO CKD-MBD guidelines there were studies demonstrating that low BMD predicted fractures in patients with all stages of CKD[17–21]. However, the consensus was that the risk of treating patients with the commonly used class of drugs, bisphosphonates, was high and the benefit uncertain despite secondary analyses of common anti-osteoporosis treatments in post-menopausal women. Unfortunately, these secondary analyses included generally normal creatinine and normal PTH levels and it was felt the results were not generalizable to more advanced CKD (See article by Paul Miller). Therefore the guideline did not recommend screening because there was no treatment[22]. In 2016 KDIGO guideline update (currently out for public comment www.kdigo.org), BMD is now recommended "if the results will change clinical management". The committee felt that although treatment options remain ill-defined and under-studied, in some patients, the treatment outweighs risk and clinicians must individualize treatments.

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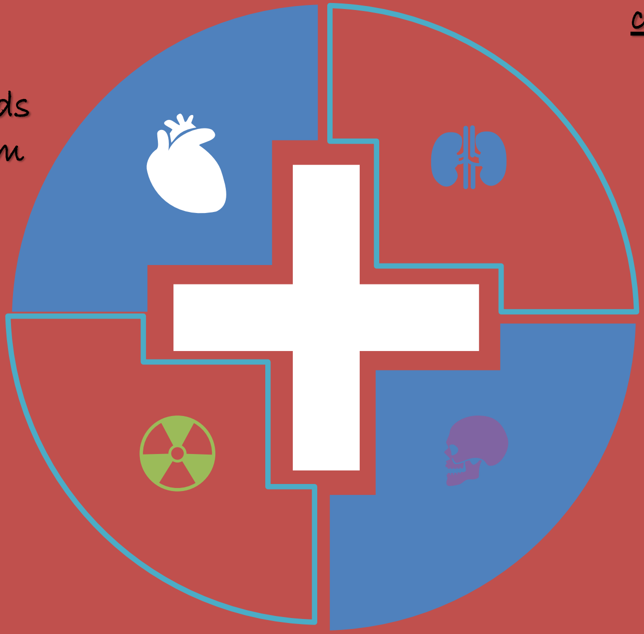
Renal Osteodystrophy or Kidney Induced Osteoporosis?

Sharon M. Moe, MD
Indiana University School of Medicine, Division of Nephrology, Indianapolis, Indiana and Department of Medicine, Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana

Secondary hyperparathyroidism (sHPT)

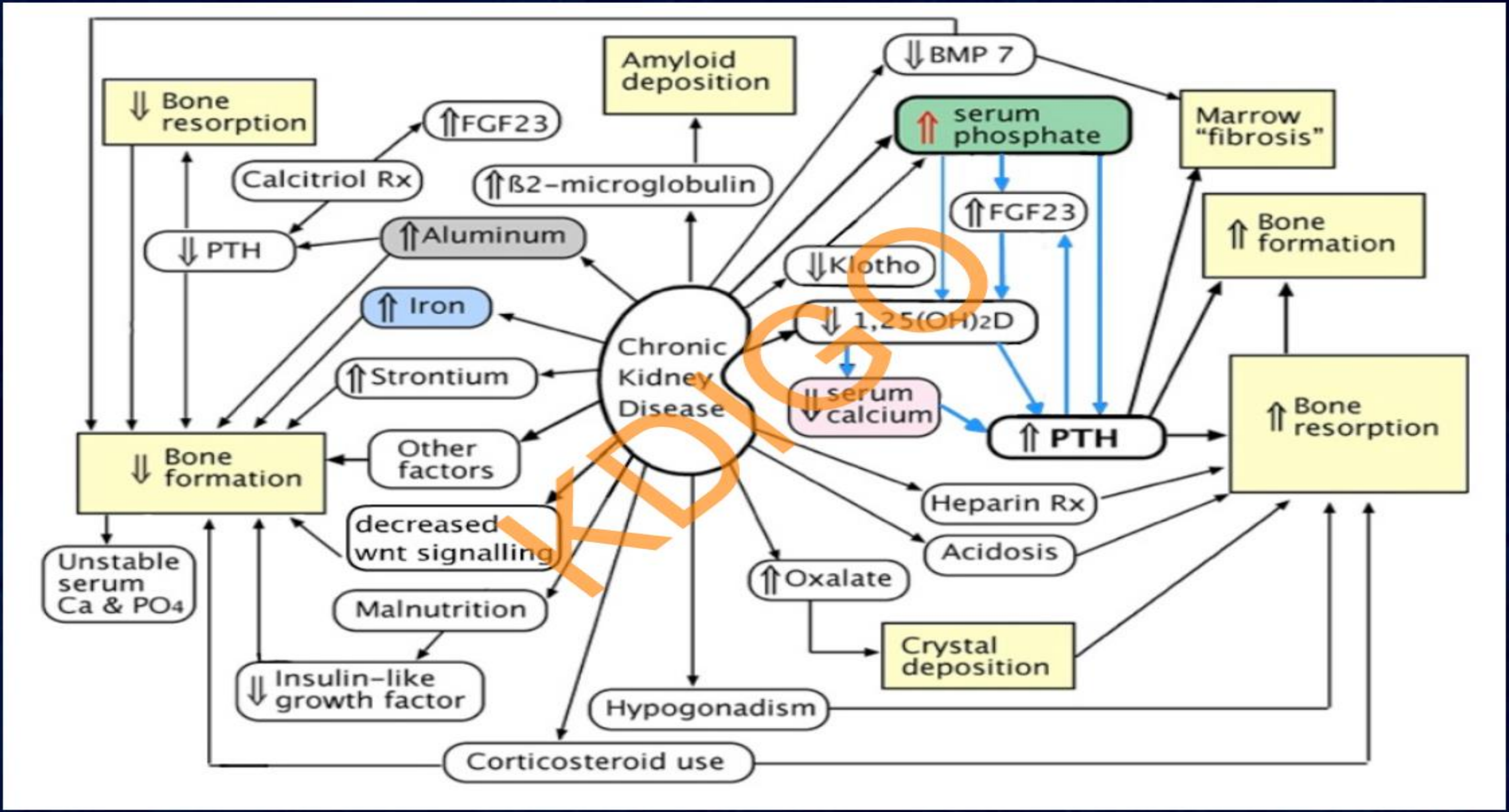
Attempt to control the disturbed calcium, phosphorus, and vitamin D metabolism. sHPT causes vascular and soft-tissue calcification and leads to disturbances of mineral metabolism CKD-related mineral and bone disorder (CKD-MBD).



The indication for sHPT treatment results from these clinical consequences

CKD-MBD abnormalities have also been implicated as risk factors for the very rare but devastating calcific and thrombotic arteriolopathy calciphylaxis and lead to reduced health-related quality of life (HRQoL).

sHPT-associated high FGF23 is independently associated with left ventricular hypertrophy, cardiovascular events and premature death.


Amyloid deposition
⇓ BMP 7
⇑ serum phosphate
Marrow "fibrosis"
⇓ Bone resorption
⇑FGF23
Calcitriol Rx
⇑ß2-microglobulin
⇑FGF23
⇑ Bone formation
⇓ PTH
⇑Aluminum
⇓Klotho
⇑ Iron
⇓ 1,25(OH)2D
Chronic Kidney Disease
⇑Strontium
⇓ serum calcium
⇑ PTH
⇑ Bone resorption
⇓ Bone formation
Other factors
Heparin Rx
decreased wnt signalling
Acidosis
Unstable serum Ca & PO4
⇑Oxalate
Malnutrition
Crystal deposition
⇓ Insulin-like growth factor
Hypogonadism
Corticosteroid use
KDIGO

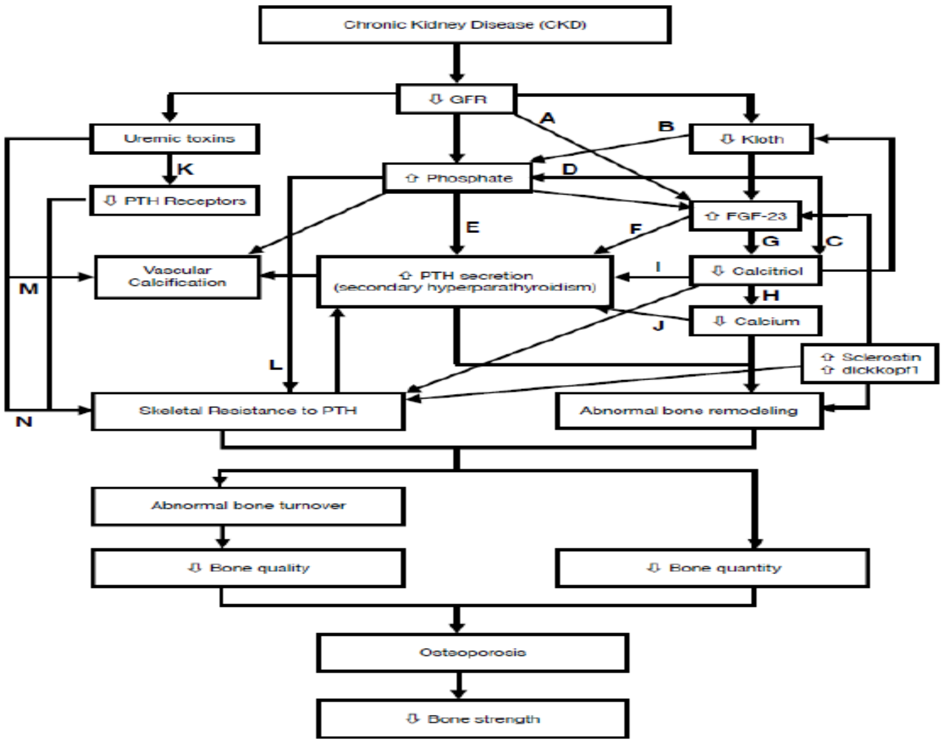


Figure 2. A summary of the mechanism underlying the effects of chronic kidney disease (CKD) on

International Journal of *Molecular Sciences*

MDPI

Review

Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review

Chia-Yu Hsu [1,2,†], Li-Ru Chen [3,4,†] and Kuo-Hu Chen [5,6,*]

1 Department of Rehabilitation Medicine, Ten-Chan General Hospital, Zhongli, Taoyuan 320, Taiwan; f927kimo@gmail.com
2 Department of Biomedical Engineering, Chung Yuan Christian University, Taoyuan 320, Taiwan
3 Department of Physical Medicine and Rehabilitation, Mackay Memorial Hospital, Taipei 104, Taiwan; gracealex168@gmail.com
4 Department of Mechanical Engineering, National Chiao-Tung University, Hsinchu 300, Taiwan
5 Department of Obstetrics and Gynecology, Taipei Tzu-Chi Hospital, The Buddhist Tzu-Chi Medical Foundation, Taipei 231, Taiwan
6 Department of Medicine, School of Medicine, Tzu-Chi University, Hualien 970, Taiwan
* Correspondence: alexgfctw@yahoo.com.tw; Tel.: +886-2662-89779
† These authors contributed equally to this work.

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check for updates

Table 1. Factors affecting bone strength in chronic kidney disease-mineral and bone disorder (CKD-MBD).

Factor	Main Effect	Category
↓ Kloth	↑ FGF-23 level [13]	Humoral
↑ FGF-23 [1]	↑ phosphate excretion [14] ↓ calcitriol synthesis [14,15]	Humoral
↑ Sclerostin	↓ bone formation [14,16] ↑ osteoclastogenesis [17]	Humoral
↑ dickkopf1	↓ bone formation [16,18]	Humoral
↑ phosphate	↑ SPTH [3] [19] ↓ calcitriol synthesis [20]	Mineral
↑ uremic toxins [2]	↓ PTH receptor [21] ↑ skeletal resistance to PTH [21]	Uremia
↓ $1{,}25(OH)_2$ D	↑ PTH secretion [20,22] ↓ calcium [23]	Humoral
↓ calcium	↑ SPTH [23] ↑ abnormal bone remodeling [23]	Mineral
↑Skeletal resistance to PTH	↑ SPTH [24]	Humoral

[1] FGF-23: fibroblast growth factor-23; [2] Uremic toxins refer to indoxyl sulfate and p-cresyl sulfate; [3] SPTH: secondary hyperparathyroidism; ↓: decrease, ↑: increase

Cureus

Open Access Review Article

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Osteoporosis, an Inevitable Circumstance of Chronic Kidney Disease: A Systematic Review

Nishat Tasnim [1] , Priyata Dutta [2] , Jannatun Nayeem [3] , Parisha Masud [4] , Afsana Ferdousi [5] , Ammy S. Ghosh [6] , Maksuda Hossain [7] , Sultana Rajia [8] , Khadija T. Kubra [9] , Md Sakibuzzaman [10, 11, 12, 13] , Asma T. Khan [14]

1. Internal Medicine, Sacramento Veterans Affairs Medical Center, Mather, USA 2. Internal Medicine, Mymensingh Medical College, Mymensingh, BGD 3. Internal Medicine, Cumilla Medical College and Hospital, Cumilla, BGD 4. Internal Medicine, Columbia University Medical Center, New York, USA 5. Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA 6. Internal Medicine, Institute of Applied Health Sciences, Chittagong, BGD 7. Biodesign Institute Center for Immunotherapy, Vaccines and Virotherapy, Arizona State University, Tempe, USA 8. Internal Medicine, Sher-E Bangla Medical College, Barishal, BGD 9. Internal Medicine, Bangladesh Medical College and Hospital, Dhaka, BGD 10. Internal Medicine, University of Mississippi Medical Center, Jackson, USA 11. Experimental Pathology (Cancer Biology), Mayo Clinic, Rochester, USA 12. Internal Medicine, Sir Salimullah Medical College, Dhaka, BGD 13. Neuroscience, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA 14. Division of Research & Academic Affairs, Larkin Community Hospital, South Miami, USA

Corresponding author: Jannatun Nayeem, jnayeemmoni@gmail.com

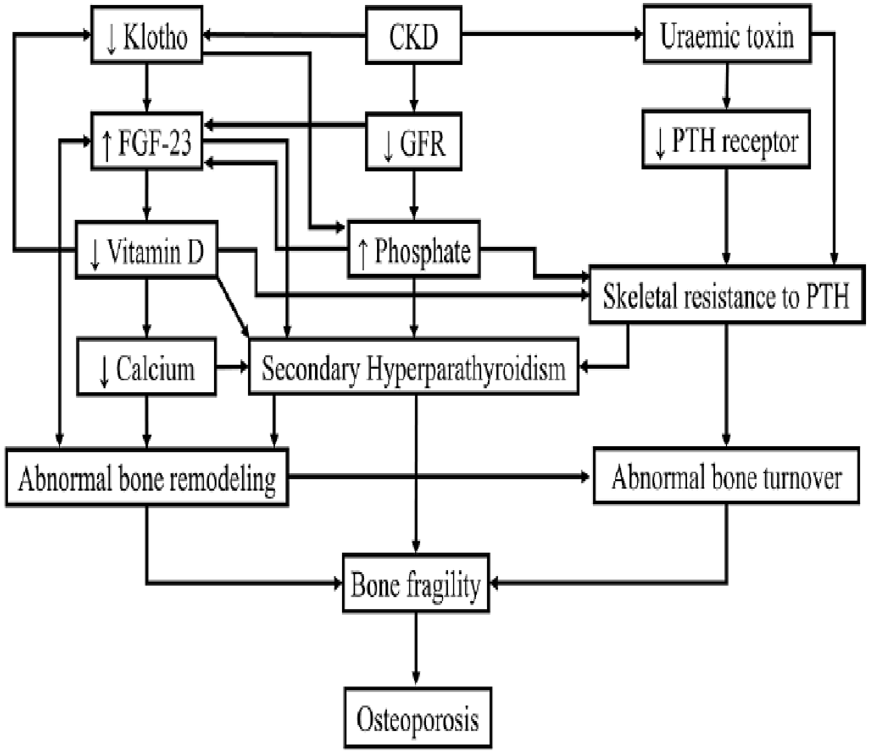


FIGURE 2: A summary of mechanisms showing the effects of CKD on osteoporosis.

CKD: chronic kidney disease; FGF-23: fibroblast growth factor-23; GFR: glomerular filtration rate; PTH: parathyroid hormone

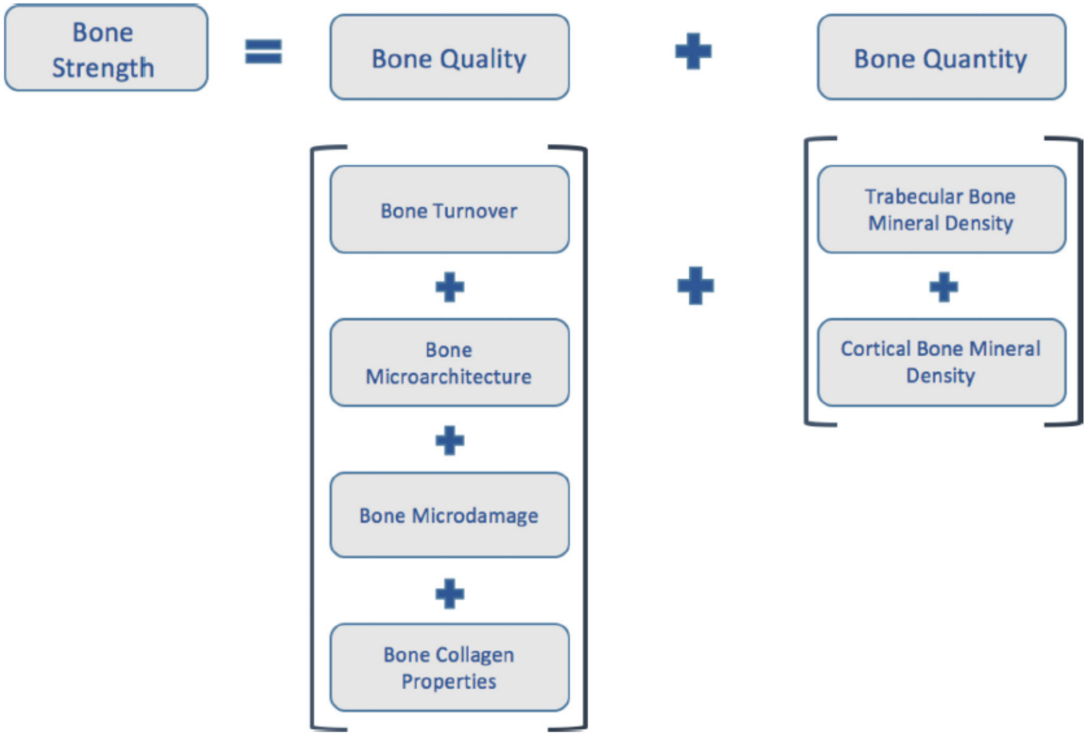
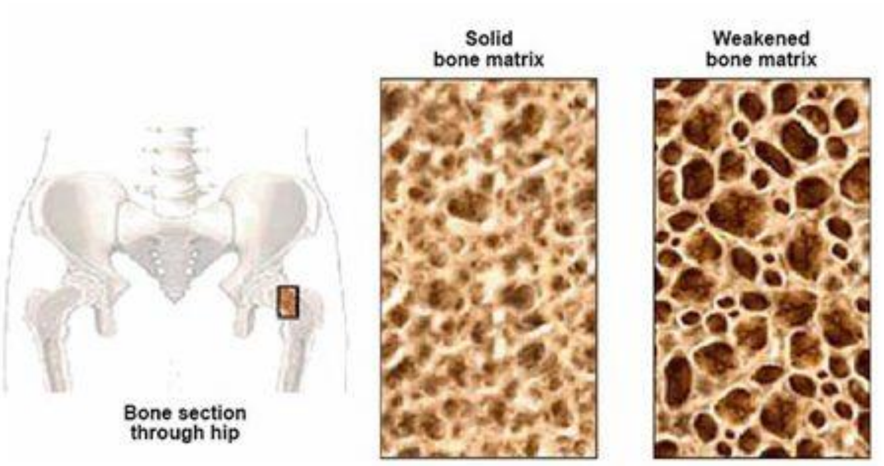


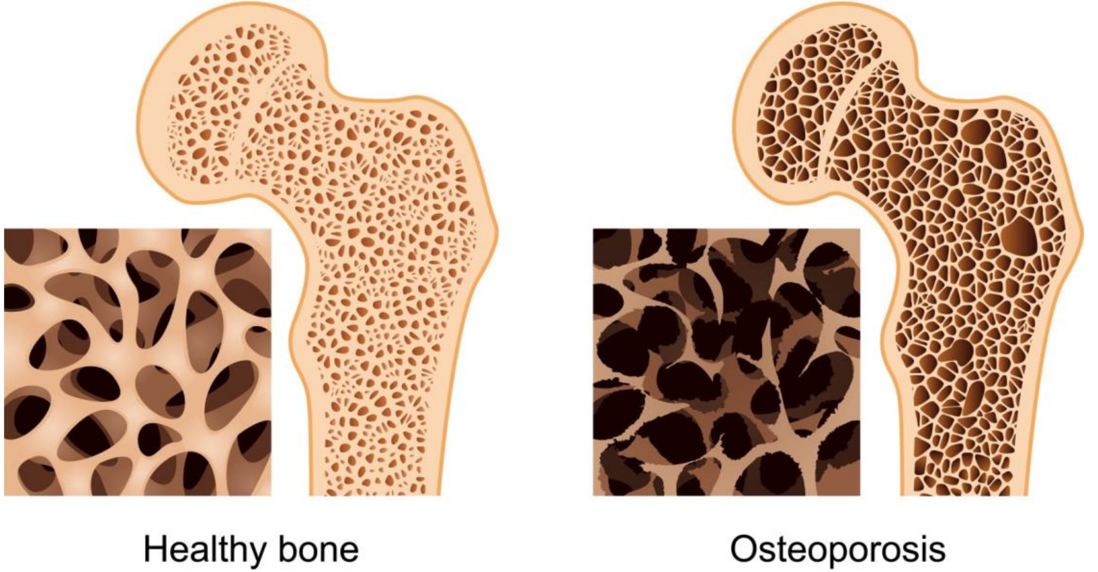
Figure 1. The Elements of Bone Strength

Bone strength is defined by bone quality and bone quantity. Bone quality pertains to bone material properties and includes bone turnover, microarchitecture, microdamange and collagen properties. Bone quantity pertains to the bone mineral density of trabecular and cortical bone.

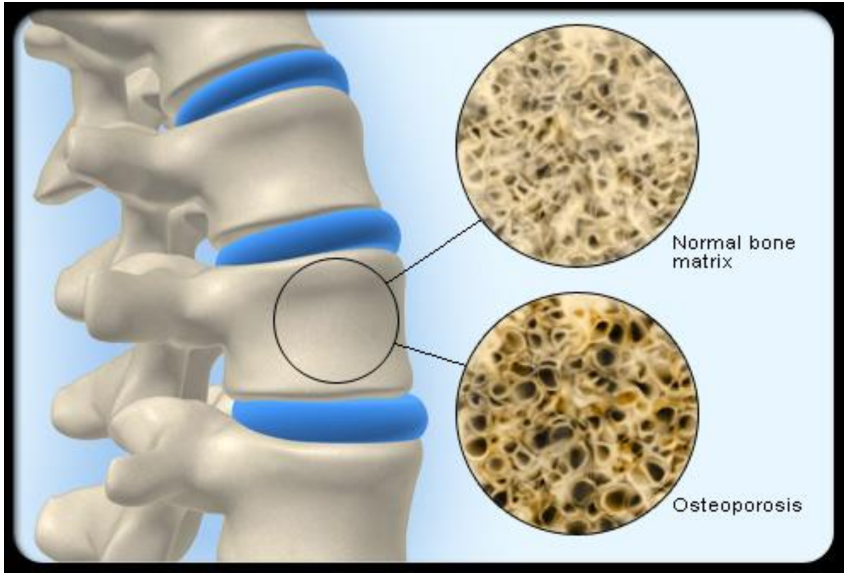


We all lose some bone mass as we age. Bones naturally become thinner (called osteopenia) as you grow older, because existing bone is broken down faster than new bone is made. As this occurs, our bones lose calcium and other minerals and become lighter, less dense, and more porous. This makes the bones weaker and increases the chance that they might break (fracture).

Osteoporosis

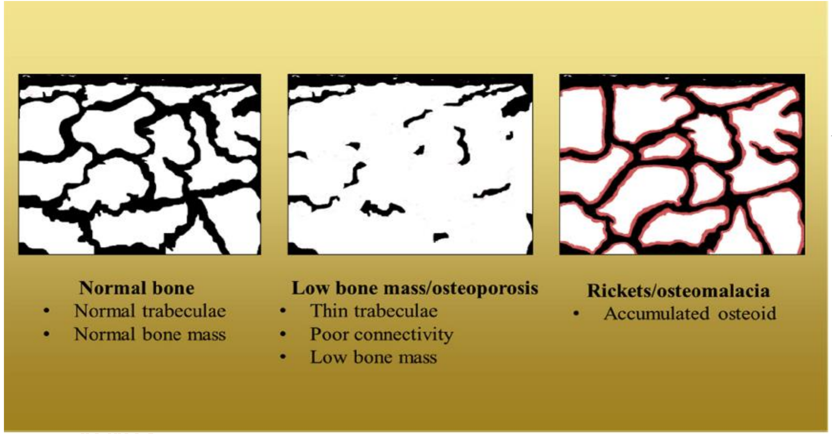


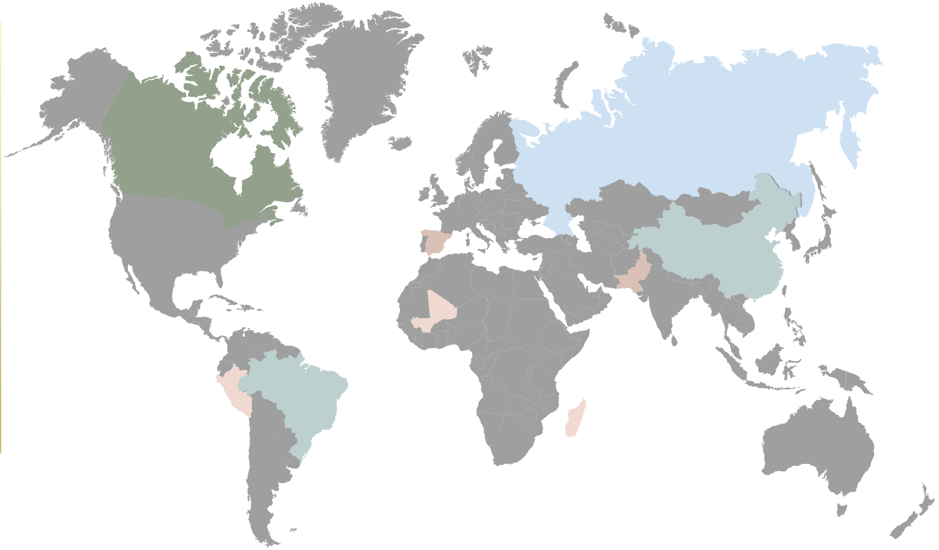
- Bone is living tissue, which is constantly being absorbed and replaced. Osteoporosis occurs when the creation of new bone doesn't keep up with the removal of old bone.
- White and Asian women — especially those who are past menopause — are at highest risk.



Low bone mass (medically termed osteopenia): A BMD defines osteopenia as a T-score between -1 and -2.5. This signifies an increased fracture risk but does not meet the criteria for osteoporosis.

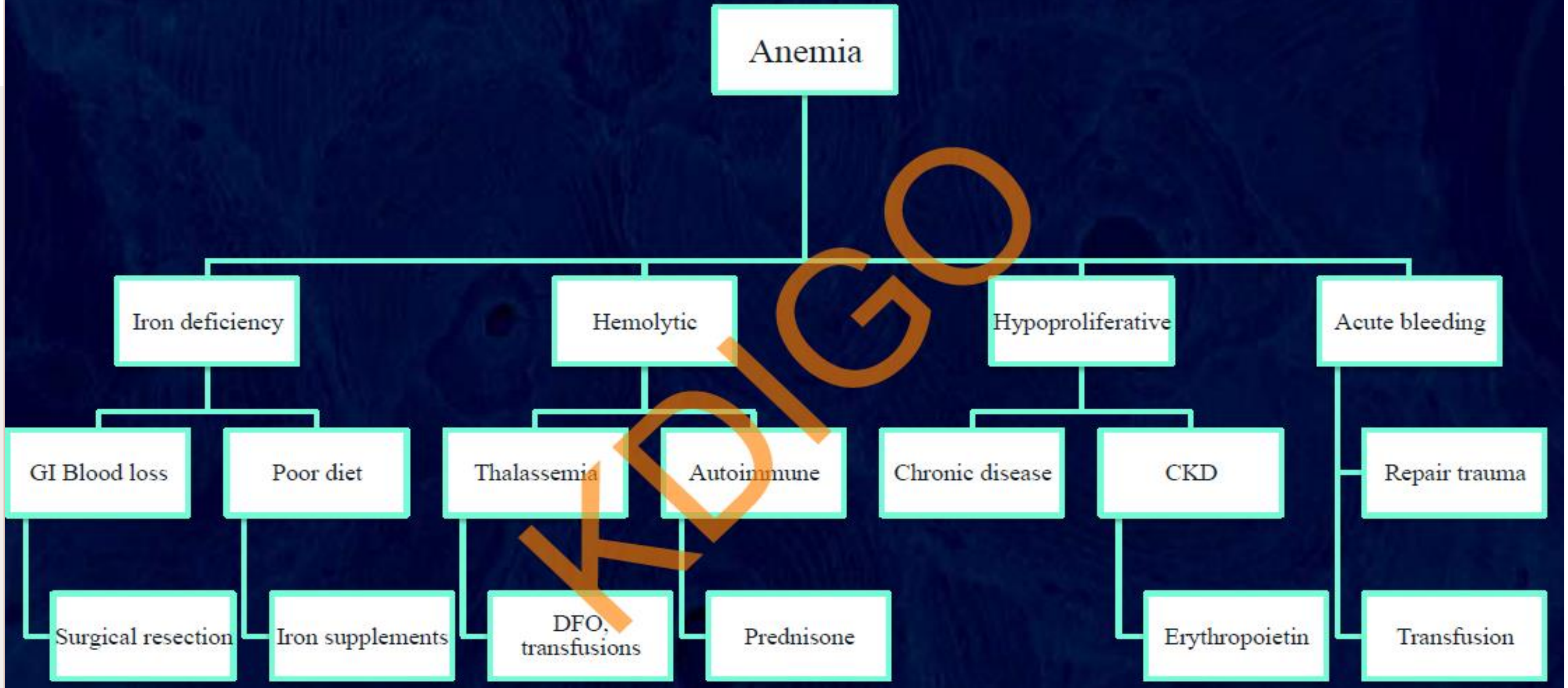
Osteoporosis: A BMD greater than 2.5 standard deviations from the normal (T score less than or equal to -2.5) defines osteoporosis.


Normal bone
Normal trabeculae
Normal bone mass
Low bone mass/osteoporosis
Thin trabeculae
Poor connectivity
Low bone mass
Rickets/osteomalacia
Accumulated osteoid

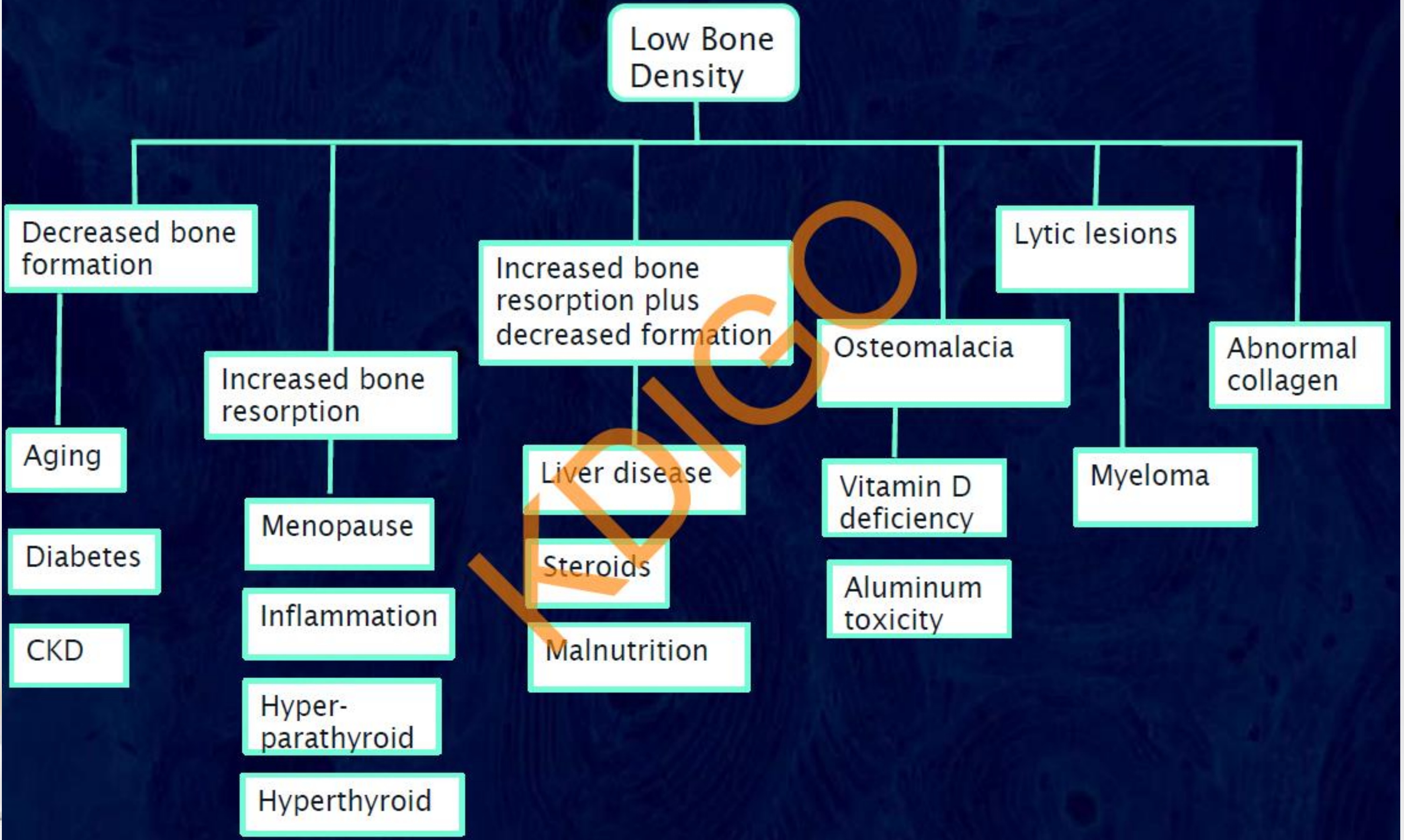


"Osteoporosis" is a
measurement on a bone density
and not a diagnosis.

Similar to anemia which
is a measurement on a blood sample
but not a diagnosis.



Anemia
Iron deficiency
Hemolytic
Hypoproliferative
Acute bleeding
GI Blood loss
Poor diet
Thalassemia
Autoimmune
Chronic disease
CKD
Repair trauma
Surgical resection
Iron supplements
DFO, transfusions
Prednisone
Erythropoietin
Transfusion
KDIGO



Low Bone Density
Decreased bone formation
Aging
Diabetes
CKD
Increased bone resorption
Menopause
Inflammation
Hyper-parathyroid
Hyperthyroid
Increased bone resorption plus decreased formation
Liver disease
Steroids
Malnutrition
Osteomalacia
Vitamin D deficiency
Aluminum toxicity
Lytic lesions
Myeloma
Abnormal collagen
KDIGO

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When low bone mineral density and fractures is not osteoporosis

Non-osteoporotic causes of low bone mineral density

1. Osteomalacia
- PTH-mediated disorders
- FGF23 mediated disorders
- Renal-mediated disorders

2. Osteogenesis imperfect and other connective tissue diseases
- Ehlers Danlos Syndrome
- Marfan Syndrome

3. Chronic kidney disease – mineral and bone disorder

4. Rare diseases
- Type 1 Neurofibromatosis
- Cystic Fibrosis
- Lowey Dietz Syndrome
- Fibrous Dysplasia
- Sickle Cell Disease
- Autosomal Dominant HyperIgE Recurrent Infection Syndrome
- Homocystinuria
- Gaucher`s disease

Mechanisms of osteomalacia

PTH-mediated Disorders		
Disease	**Mechanism**	**Genetic vs Acquired**
Vitamin D Deficiency	Decreased 25-OH_2-D by poor intake	Acquired
Renal Insufficiency	Decreased 1-alpha hydroxylase activity leads to decreased active 1,25-OH_2-D	Acquired
Hepatic Insufficiency	Decreased 25-hydroxylation of vitamin D in the liver leads to decreased active 1,25-OH_2-D	Acquired
FGF23-mediated Disorders		
Disease	**Mechanism**	**Genetic vs Acquired**
Tumor-induced osteomalacia	Mesenchymal tumor autonomously secretes FGF23	Acquired
X-linked hypophosphatemic rickets	Mutation in *PHEX*	Genetic
Autosomal Dominant Hypophosphatemic Rickets	Mutation in *FGF23* causes decreased cleavage and inactivation	Genetic
Autosomal Recessive Hypophosphatemic Rickets (Type 1 and 2)	Mutations in *DMP1* and *ENPP1*	Genetic
Renal-mediated Disorders		
Disease	**Mechanism**	**Genetic vs Acquired**
Fanconi Anemia	Renal proximal tubule damage	Genetic or Acquired
Hereditary Hypophosphatemic Rickets with Hypercalciuria	Mutation of SLC23A3 (renal phosphate channel)	Genetic

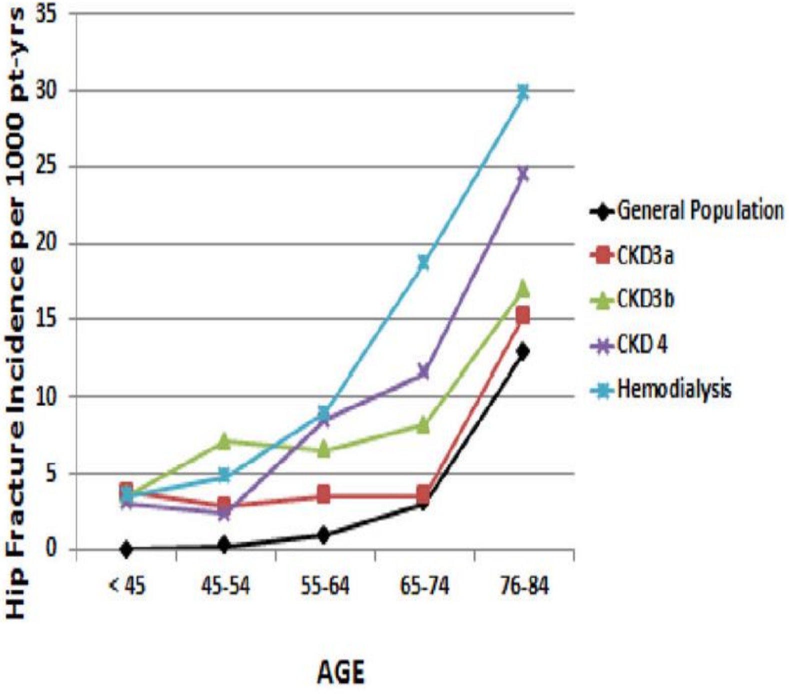

Figure 1. Hip Fracture Incidence Increases with Progressive CKD

As patients age in the general population there is an increased incidence of hip fracture. This incidence increases with progression of CKD. Data from Alem et al for dialysis patients and the general population from Olmstead Minnesota[28], Naylor et al for CKD stages 3–4[29] courtesy of the Canadian Institute for Clinical Evaluative Sciences (ICES). Pt-yrs = patient years. From: Moe SM, Nickolas TL. Fractures in patients with CKD: Time for Action. Clin J Am Soc Nephrol. 2016 Nov 7;11(11):1929–1931. Epub 2016 Oct 24. Used with permission from the American Society of Nephrology.

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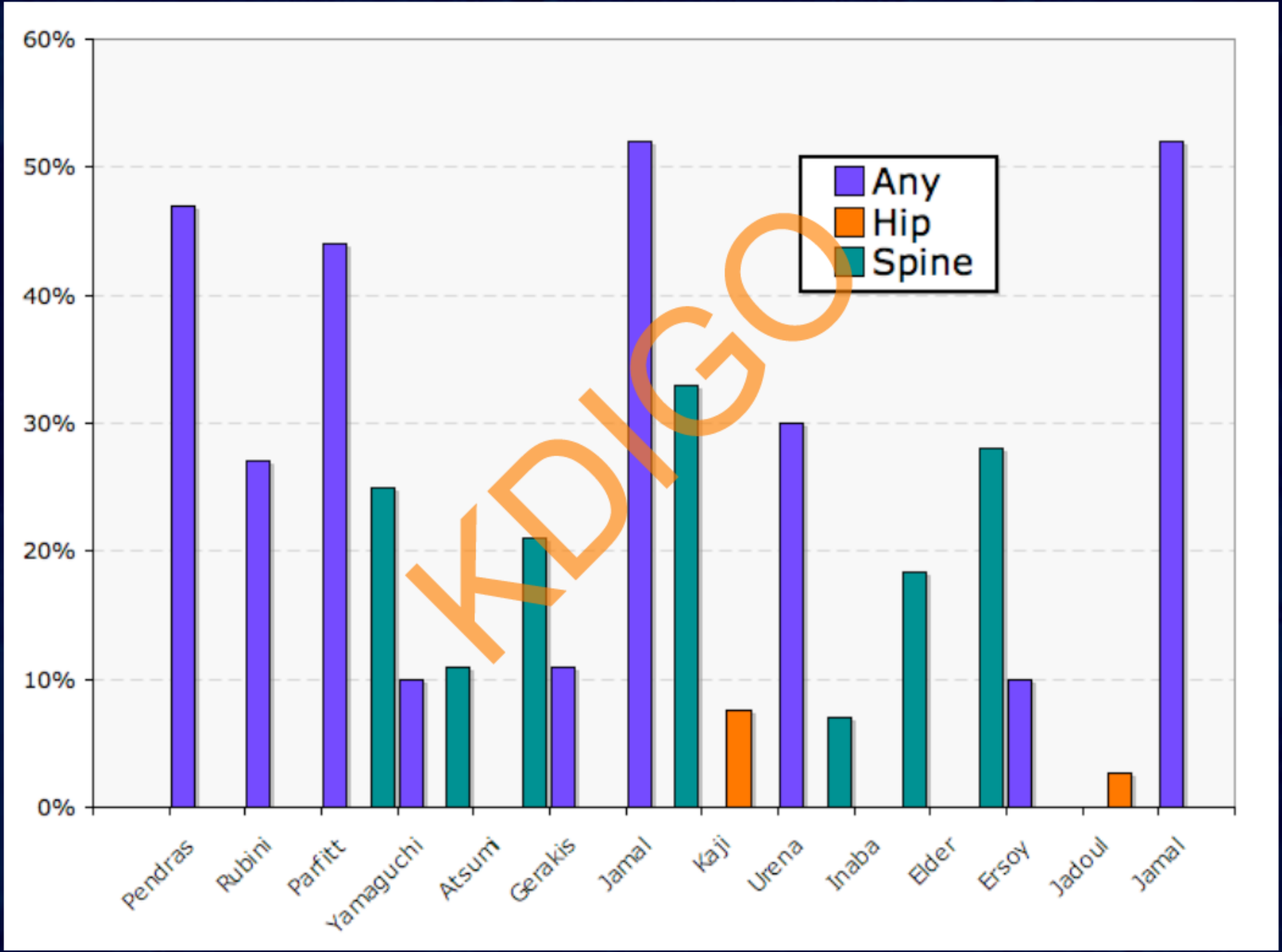
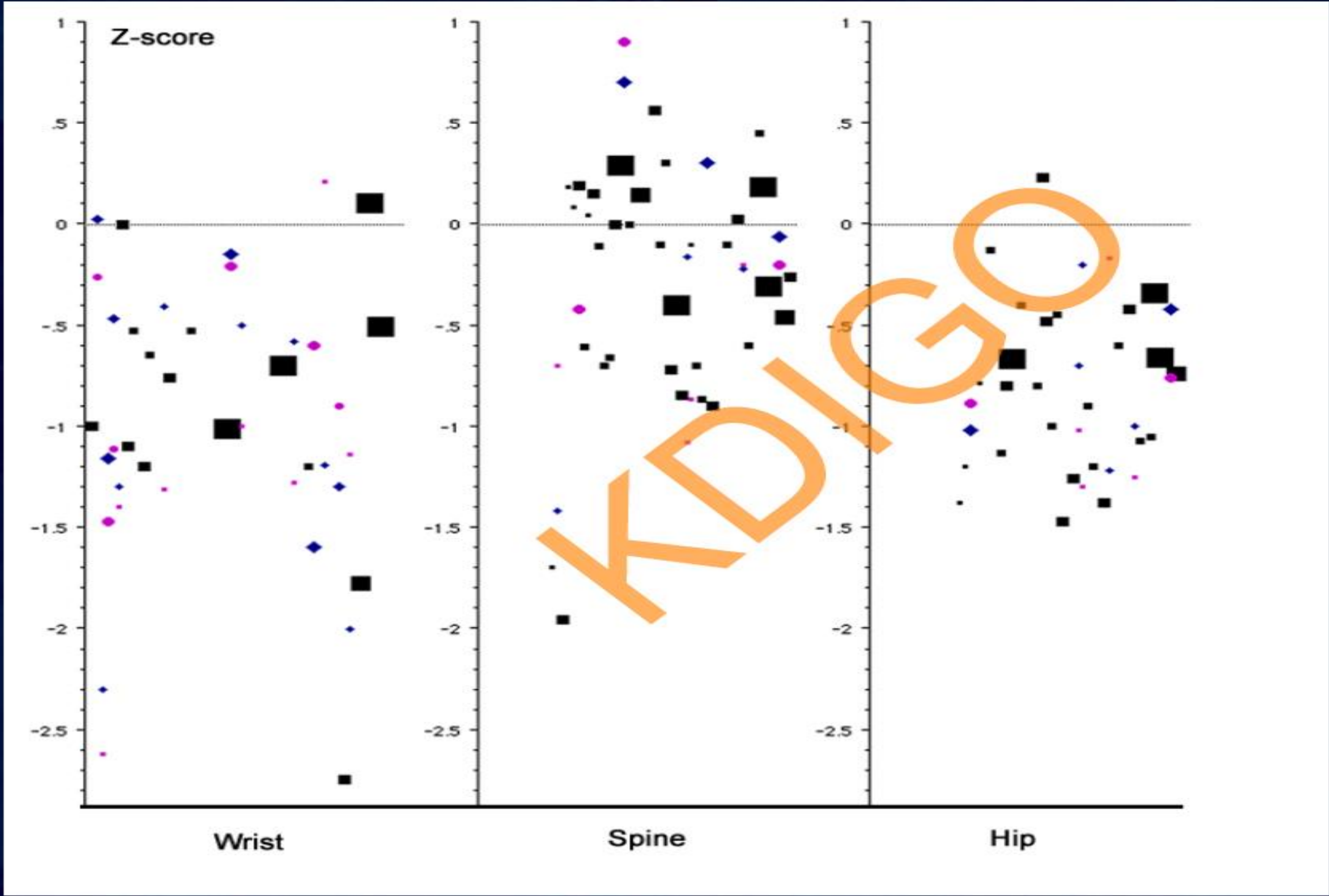
Renal Osteodystrophy or Kidney Induced Osteoporosis?

Sharon M. Moe, MD
Indiana University School of Medicine, Division of Nephrology, Indianapolis, Indiana and Department of Medicine, Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana

Fracture Prevalence in CKD 5D

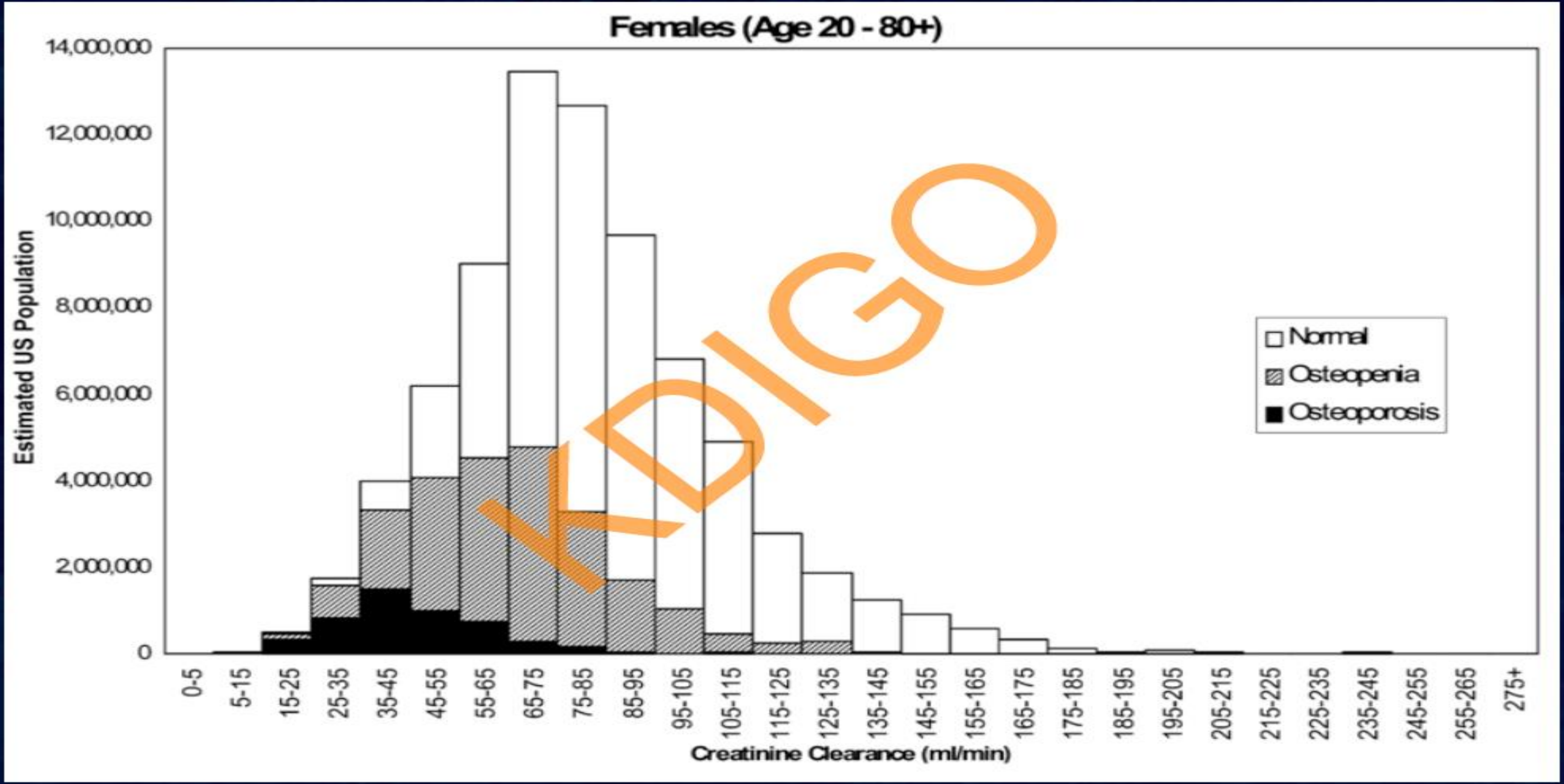


Bone density in Dialysis Patients



Ott, Nephrology, 2009

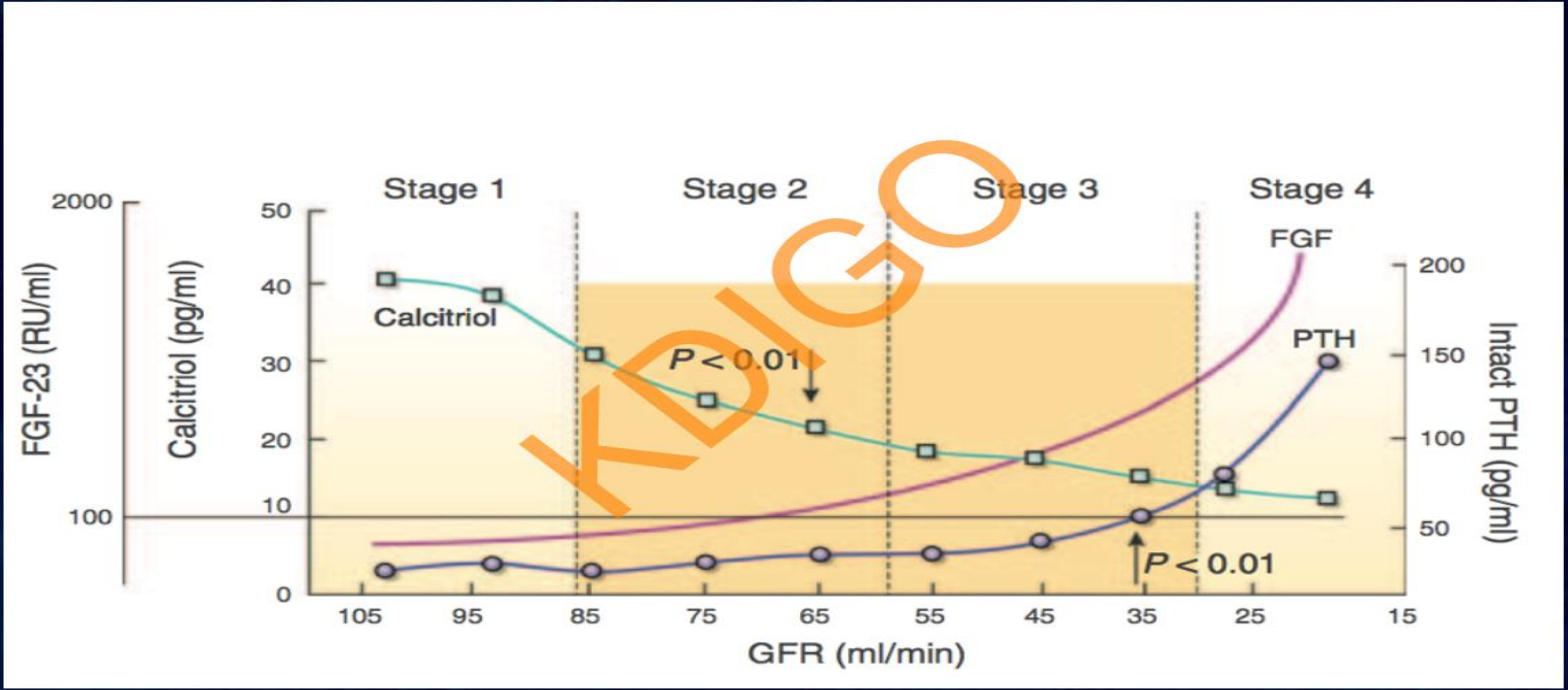
Bone density by eGFR



data from NHANES

Klawansky, Osteo Int, 2003

Progressive abnormalities in CKD



Gal-Moscovici, KI 2010

NEFROLOGIA. 2018;38(5):476–490

Revista de la Sociedad Española de Nefrología

www.revistanefrologia.com

Review

Osteoporosis, bone mineral density and CKD–MBD complex (I): Diagnostic considerations☆

Jordi Bover[a,], Pablo Ureña-Torres[b], Josep-Vicent Torregrosa[c], Minerva Rodríguez-García[d], Cristina Castro-Alonso[e], José Luis Górriz[f], Ana María Laiz Alonso[g], Secundino Cigarrán[h], Silvia Benito[a], Víctor López-Báez[a], María Jesús Lloret Cora[a], Iara daSilva[a], Jorge Cannata-Andía[i]*

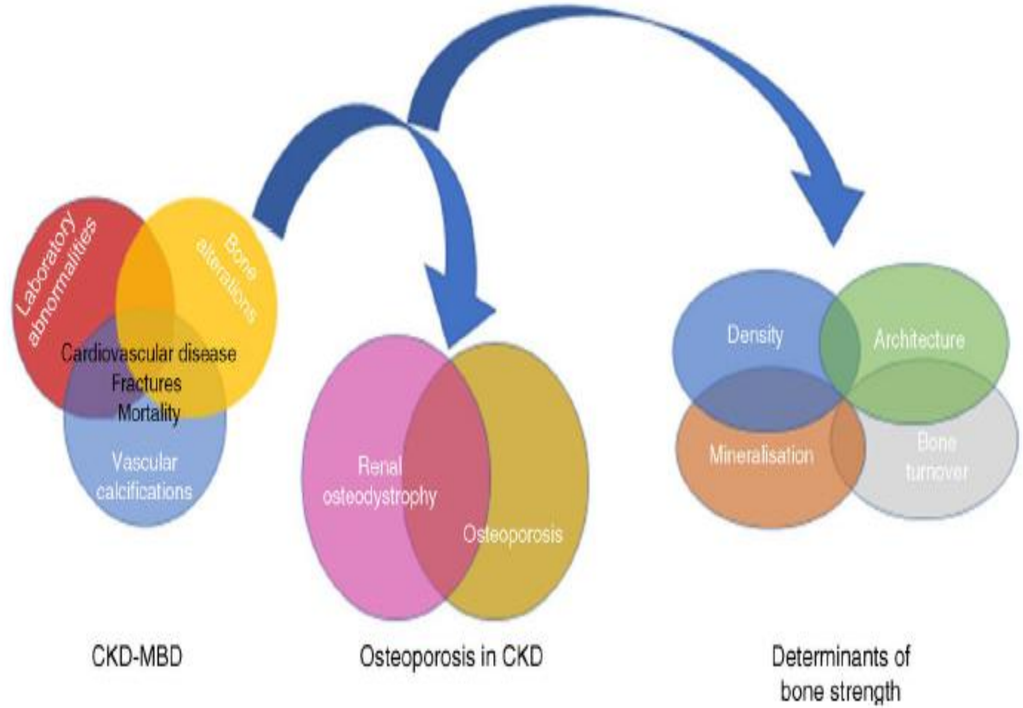


Fig. 1 – Relationship between Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD), renal osteodystrophy (bone changes secondary to chronic kidney disease [CKD]) and OP (associated with uraemia or age and gender of patients, among other factors). Bone strength is determined not only by bone mineral *density*, but also by bone *quality*, expressed by its determinants.[94,151] Although some authors use the term “uraemic” OP,[17] it is important to remember the existence of non-terminal CKD, which could be integrated within the CKD–MBD complex due to its capacity to worsen the condition. Adapted from Moe[151] and West et al.[94]

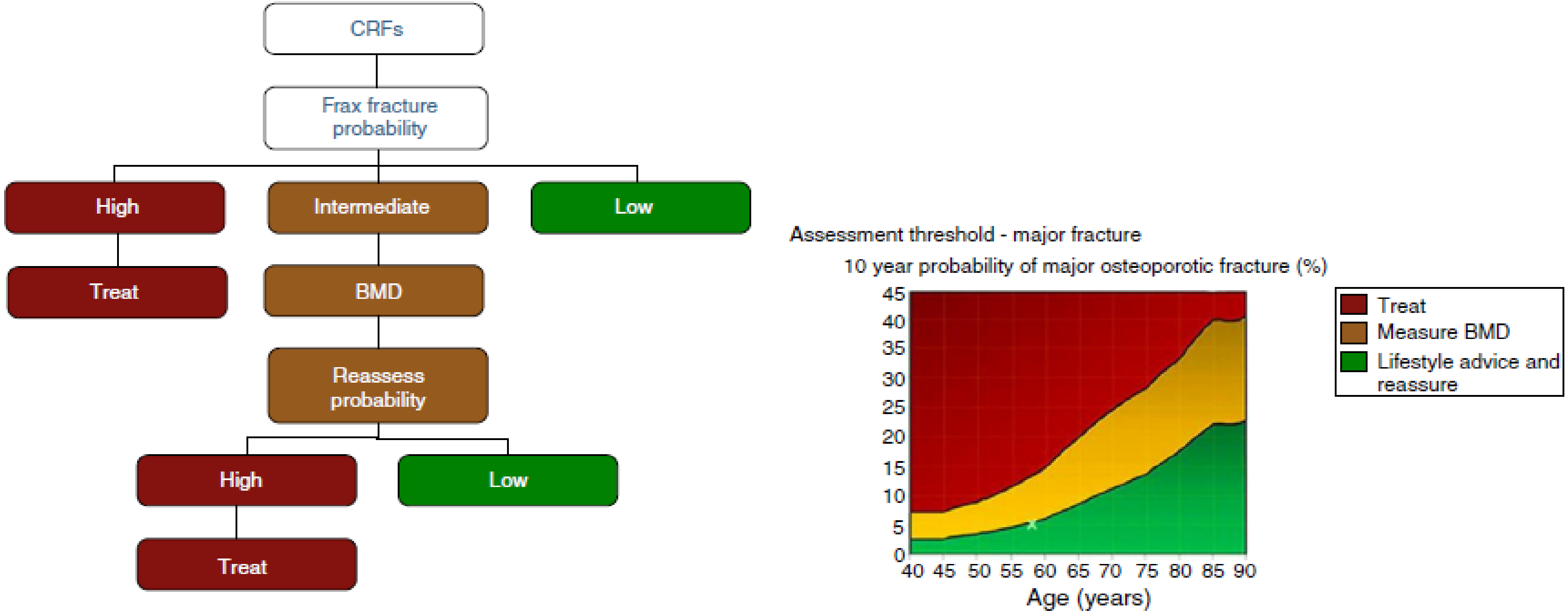


Fig. 3 – Estimation of fracture probability using FRAX® (fracture probability according to risk factors [CRF]). High, intermediate, and low risk levels vary according to guidelines and countries. In the United States and the United Kingdom, ≥20% 10-year probability of major osteoporotic fracture or ≥3% probability of hip fracture is considered high, 10–20% is considered an intermediate probability (densitometry [BMD, bone mineral density] and recalculation is recommended), and <10% is considered a low probability (figures based on cost-effectiveness). Some guidelines (see Fig. 4) recommend recalculating FRAX (reassess probability) using BMD for both intermediate- and high-risk patients before treating (BMD can also be used to evaluate response to treatment).[26].

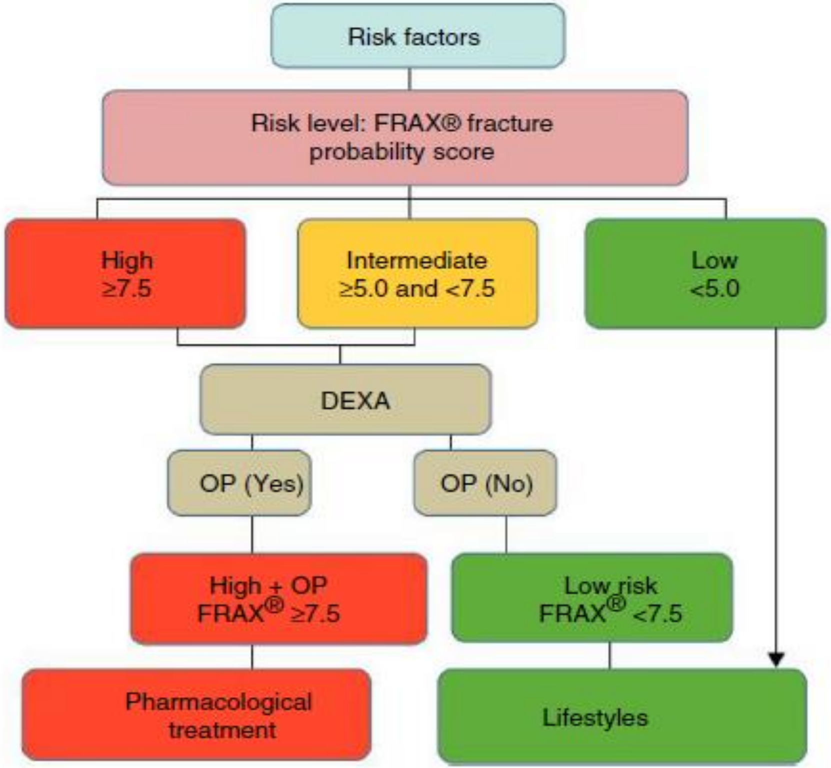


Fig. 4 – Decision tree based on the most cost-effective option in the Spanish FRIDEX cohort of Spanish women (general population) who did not receive treatment during the 10 years of follow-up.[47] DXA or DEXA: Dual-Energy X-ray absorptiometry; OP: osteoporosis.

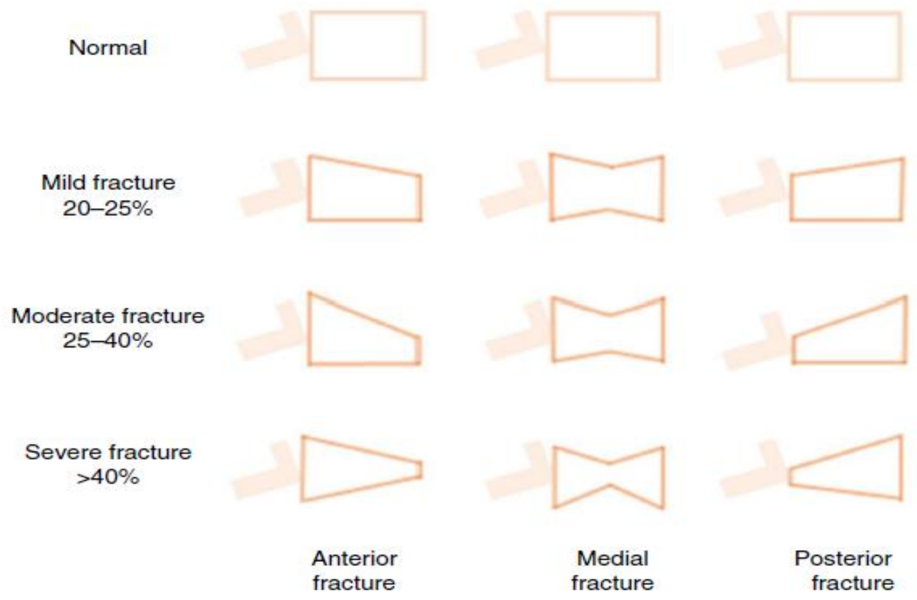


Fig. 5 – Schematic representation of Genant's semi-quantitative approach to the visual measurement of vertebral deformities. Normal = 0; mild = 1; moderate = 2; severe = 3; doubtful = 0.5. Vertebral fractures are often diagnosed fortuitously (morphometric fracture), although diagnosis can also be made on the basis of symptoms. It is based on more than 20% loss of vertebral body height in any of the vertebral segments. The following formula is used: ([posterior height of the vertebral body – lowest height]/posterior height) x 100.[115,152]

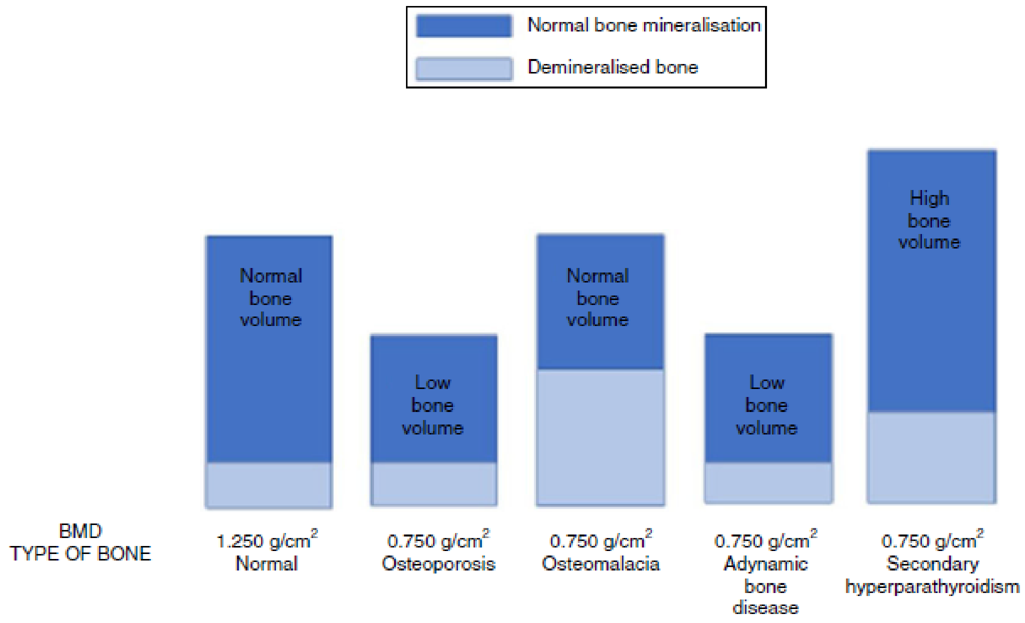


Fig. 6 – The image shows how different pathologies (senile osteoporosis or osteoporosis secondary to hypogonadism, osteomalacia, adynamic bone disease and secondary hyperparathyroidism) can show the same low bone mineral density (in this example, BMD = 0.750 g/cm^2) although they are caused by a completely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

CKD-MBD	Ordinary osteoporosis
Increased PTH and alkaline phosphatase	Normal PTH and alkaline phosphatase
Bone density weakly related to fractures	Bone density predicts fractures
Bone loss mostly in cortical bone	Bone loss in trabecular and cortical bone
High prevalence of adynamic bone or very high bone formation	Bone formation generally normal to slightly high
Associated with vascular calcifications	Weakly associated with vascular calcifications
Abnormal calcium, phosphate, FGF23, BMP7, Klotho, 1,25-vitamin D, iron, bicarbonate, sclerostin, and cytokines	Normal or mildly abnormal

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Renal Osteodystrophy or Kidney Induced Osteoporosis?

Sharon M. Moe, MD
Indiana University School of Medicine, Division of Nephrology, Indianapolis, Indiana and Department of Medicine, Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana

Abstract

Purpose of Review—Chronic Kidney Disease (CKD) affects nearly 10% of the population. The incidence of fractures in population studies demonstrate an increase with worsening stages of kidney disease suggesting specific CKD related causes of fracture.

Recent Findings—The increase in fractures with CKD most likely represents disordered bone quality due to the abnormal bone remodeling from renal osteodystrophy. There is also an increase in fractures with age in patients with CKD, suggesting that patients with CKD also have many fracture risk factors common to patients without known CKD. Osteoporosis is defined by the National Institutes of Health as “A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone quantity and bone quality”.

Summary—Thus, CKD related fractures can be considered a type of osteoporosis- where the bone quality is additionally impaired above that of age/hormonal related osteoporosis. Perhaps using the term CKD induced osteoporosis, similar to steroid induced osteoporosis, will allow patients with CKD to be studied in trials investigating therapeutic agents. In this series we will examine how CKD induced osteoporosis may be diagnosed and treated.

Fracture risk is excessively high in patients with CKD.[13–15] For example, patients on hemodialysis show a fracture risk of the hip that is 4-fold higher than the risk observed in age- and sex-matched non-CKD counterparts.[16] After kidney transplantation, the risk further increases, at least transiently.[17] Compared with patients without fractures, those with CKD and fractures furthermore have a multifold increased risk of mortality.[18] Fragility fractures inflate the already impressive economic and societal burden of advanced CKD.


review www.kidney-international.org

Differentiating the causes of adynamic bone in advanced chronic kidney disease informs osteoporosis treatment

see commentary on page 502
OPEN

Mathias Haarhaus[1,2] and Pieter Evenepoel[3]; on behalf of the European Renal Osteodystrophy (EUROD) workgroup, an initiative of the Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) working group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA)

[1]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Diaverum Sweden AB, Malmö, Sweden; and [3]Division of Nephrology, University Hospitals Leuven, Leuven, Belgium

Patients with chronic kidney disease (CKD) have an increased fracture risk because of impaired bone quality and quantity. Low bone mineral density predicts fracture risk in all CKD stages, including advanced CKD (CKD G4-5D). efficacy of anti-osteoporosis pharmacotherapy in advanced CKD.

Kidney International (2021) 100, 546–558; https://doi.org/10.1016/j.kint.2021.04.043

During the last 2 decades, knowledge of the pathophysiology of bone fragility in the setting of CKD has increased, and the ability to predict patients with CKD at risk has improved through the validation of fracture prediction tools and an increasing understanding of imaging modalities. Alongside, the armamentarium to tackle osteoporosis has been continuously expanding. Against this background, the existence of a huge treatment gap between those at risk of fracture and those receiving treatment for the prevention of fragility fractures is remarkable. The reluctance toward pharmacological fracture prevention in general, and, more specifically, toward the use of antiresorptive agents, in patients with advanced CKD is largely driven by the lack of adequately powered randomized controlled trials in this population and the fear to induce or worsen adynamic bone. Adynamic bone, overall, is perceived as being problematic and referred to as a disease.

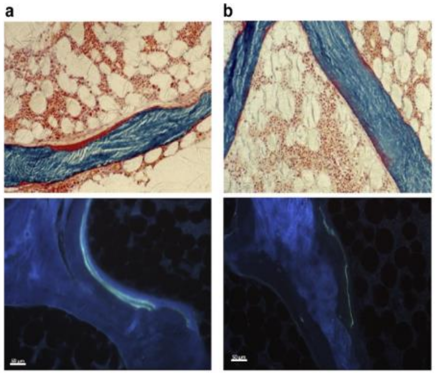

Figure 1 | Histomorphometry slides showing (a) normal and (b) low bone turnover. Compared to normal bone, conventional light microscopy of Goldner-stained sections shows the almost complete absence of osteoblasts, osteoclasts, and osteoid deposition as well as the absence of tetracycline labels as visualized by fluorescence microscopy. Courtesy Patrick D'Haese and Geert Behets.

Differentiating the causes of adynamic bone in advanced chronic kidney disease informs osteoporosis treatment

Check for updates

see commentary on page 502

OPEN

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Patients with chronic kidney disease (CKD) have an increased fracture risk because of impaired bone quality and quantity. Low bone mineral density predicts fracture risk in all CKD stages, including advanced CKD (CKD G4-5D). efficacy of anti-osteoporosis pharmacotherapy in advanced CKD.

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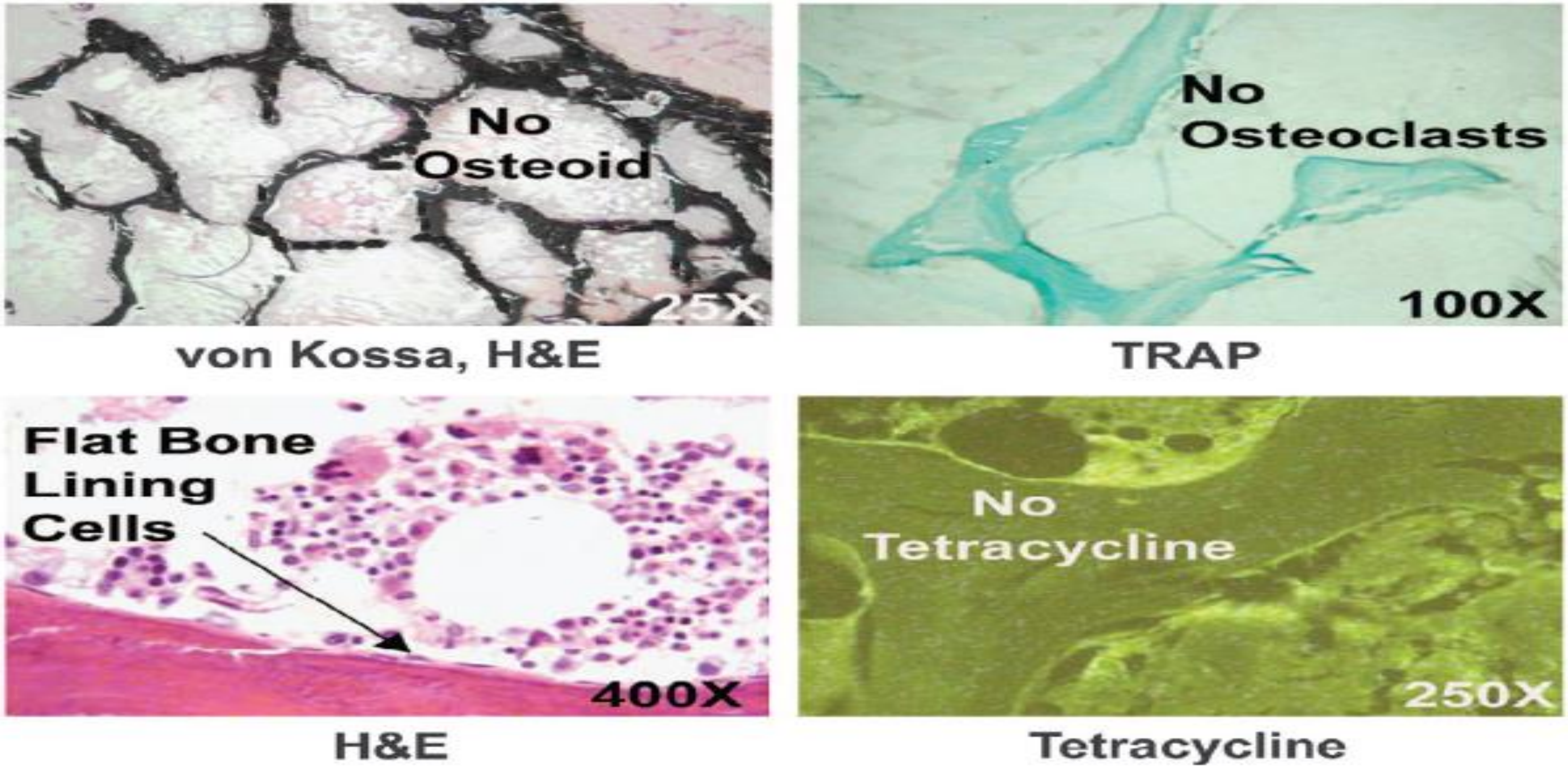

Figure 3 Renal adynamic bone disease.[21] TRAP, tartrate-resistant acid phosphatase.

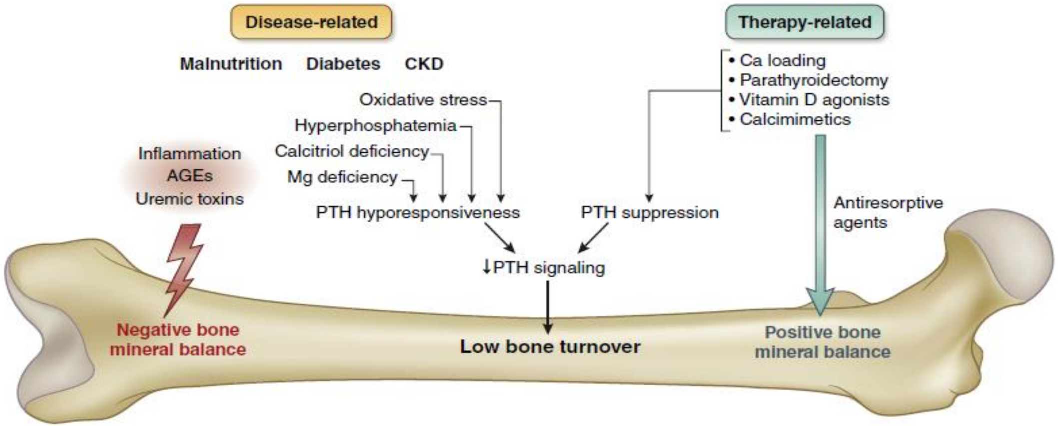

Figure 2 | Causes of low bone turnover: diseases and therapies may affect bone metabolism both indirectly by modifying parathyroidism (PTH) signaling and directly. Diseases go along with PTH hyporesponsiveness and a negative bone mineral balance (resorption > formation). Therapies, overall, can mediate a positive bone mineral balance, either directly or through PTH suppression. AGE, advanced glycation end-products; CKD, chronic kidney disease.

Nephrol Dial Transplant (2021) 36: 42–59
doi: 10.1093/ndt/gfaa192
Advance Access publication 24 October 2020

ndt
Nephrology Dialysis Transplantation

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

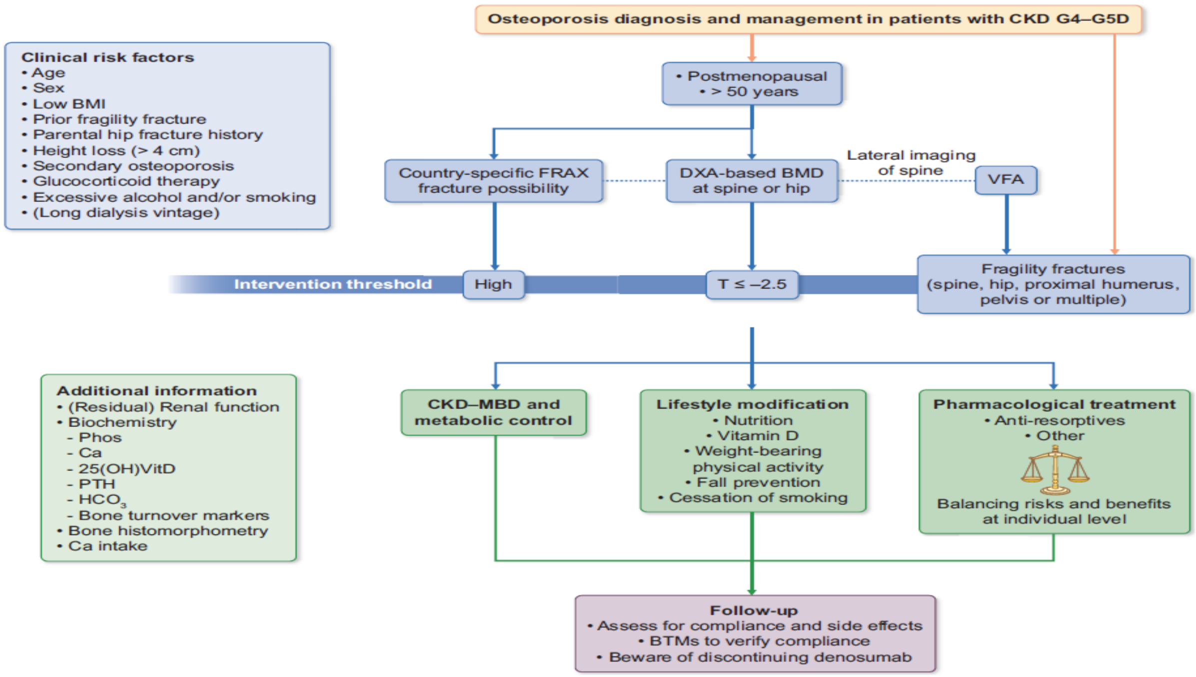

FIGURE 1: Pragmatic approach to patients with CKD G4–G5D and osteoporosis.

Nephrol Dial Transplant (2021) 36: 42–59
doi: 10.1093/ndt/gfaa192
Advance Access publication 24 October 2020

ndt
Nephrology Dialysis Transplantation

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

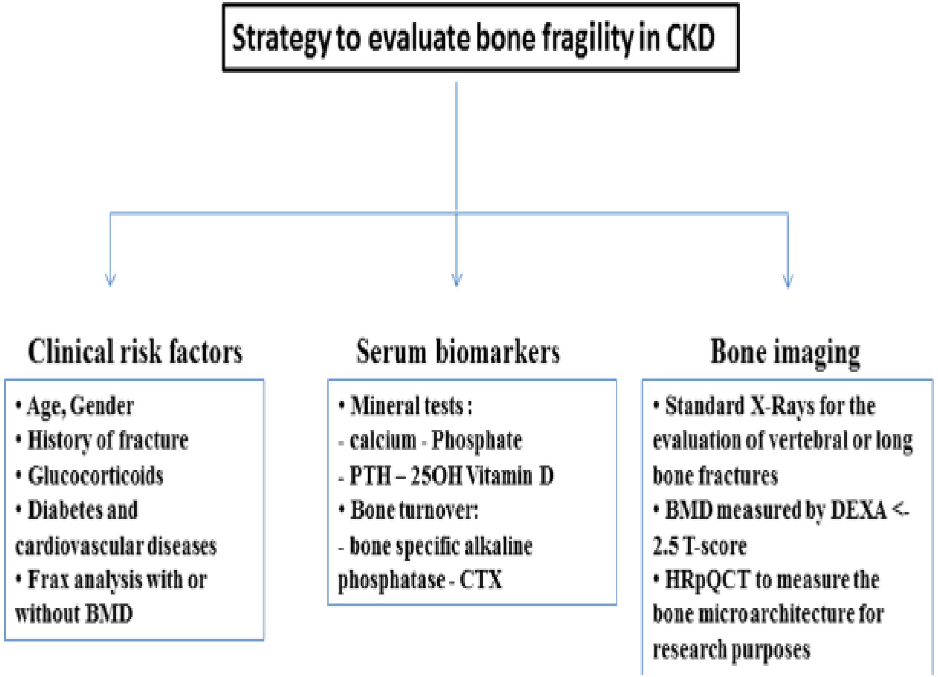

Figure 1

Tools available to assess bone fragility. A combination of clinical factors, bone and mineral biomarkers as well as imaging are required to characterize the profile of fragility and help to guide treatment decisions.

Endocrine CONNECTIONS | M Cohen-Solal *et al.* | Bone fragility in chronic kidney diseases | 9:4 | **R93**–R101

REVIEW

Bone fragility in patients with chronic kidney disease

Martine Cohen-Solal[1], **Thomas Funck-Brentano**[1] and **Pablo Ureña Torres**[2,3]

[1]Department of Skeletal Diseases, INSERM U1132 & Université de Paris, Hôpital Lariboisière, Paris, France
[2]AURA Nord, Saint Ouen, France
[3]Department of Renal Physiology, Necker Hospital, Université de Paris, Paris, France

Correspondence should be addressed to M Cohen-Solal: martine.cohen-solal@inserm.fr

Abstract

Mineral and bone diseases (MBD) are predominant in patients with chronic kidney disease (CKD) and lead to several bone manifestations, from pain to skeletal fractures. Cumulative traditional clinical risk factors, such as age and gender, in addition to those related to CKD, enhance the risk of comorbidity and mortality related to fractures. Despite great advances in understanding MBD in CKD, clinical and biological targets are lacking, which leads to under-management of fractures. Optimal PTH control results in a net improvement in defining the levels of bone remodeling. In addition, circulating biomarkers such as bone-specific alkaline phosphatase and cross-linked collagen type I peptide will also provide additional information about remodeling rate, bone mineralization and the evaluation of fracture risk. Imaging techniques identify patients at risk by measurement of bone mineral density by DEXA or by high peripheral QCT, which allow the discrimination of trabecular and cortical bone. Here, we have reviewed the literature related to epidemiology and the pathophysiological role of mineral and biochemical factors involved in CKD-MBD with a special focus on fracture risk. We also provide an algorithm that could be used for the management of bone diseases and to guide treatment decisions. Finally, the combined expertise of clinicians from various disciplines is crucial for the best prevention of fractures.

Key Words

- bone
- skeleton
- fracture
- bone mineral density
- CKD-MBD
- phosphate
- calcium
- parathyroid hormone
- vitamin D

Endocrine Connections (2020) **9**, R93–R101

NEFROLOGIA. 2018;38(5):476–490

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Review

Osteoporosis, bone mineral density and CKD–MBD complex (I): Diagnostic considerations☆

Jordi Bover[a,], Pablo Ureña-Torres[b], Josep-Vicent Torregrosa[c], Minerva Rodríguez-García[d], Cristina Castro-Alonso[e], José Luis Górriz[f], Ana María Laiz Alonso[g], Secundino Cigarrán[h], Silvia Benito[a], Víctor López-Báez[a], María Jesús Lloret Cora[a], Iara daSilva[a], Jorge Cannata-Andía[i]*

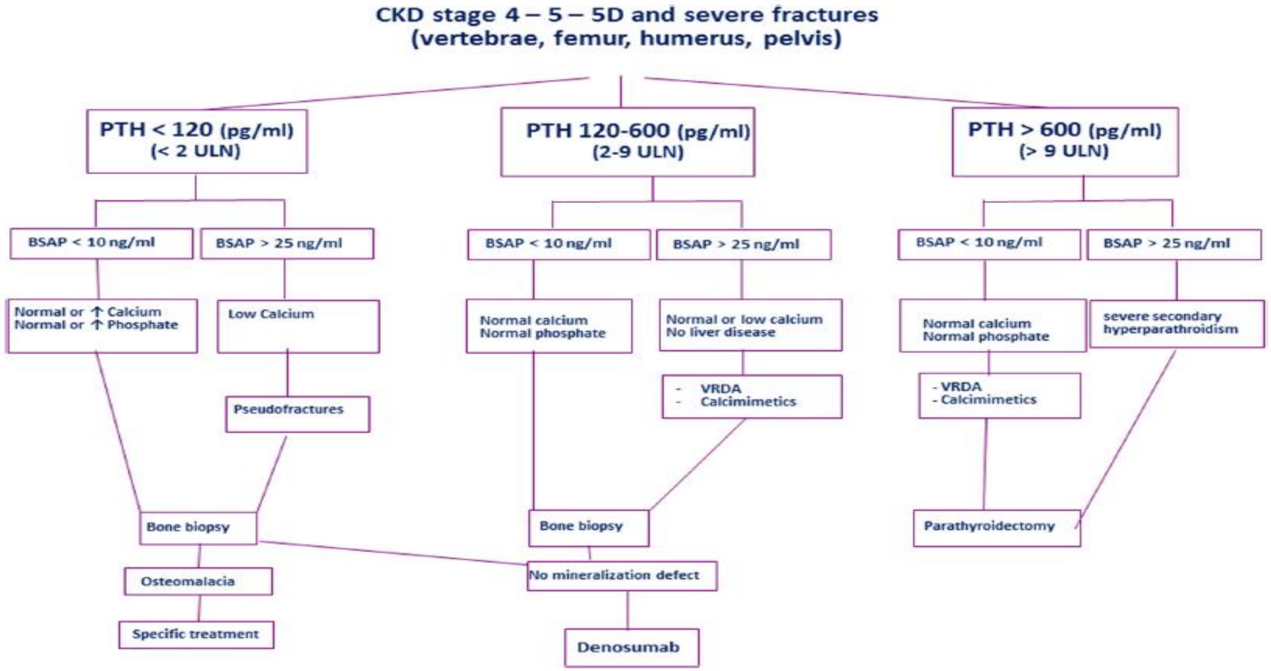


Figure 2

Proposed algorithm for treatment decision in patients with CKD and fracture. Treatment decisions are dependent of the levels of parathyroid hormone (PTH) and bone specific alkaline phosphatase (BSAP) levels. The different conditions are shown, to guide treatment decisions appropriately.

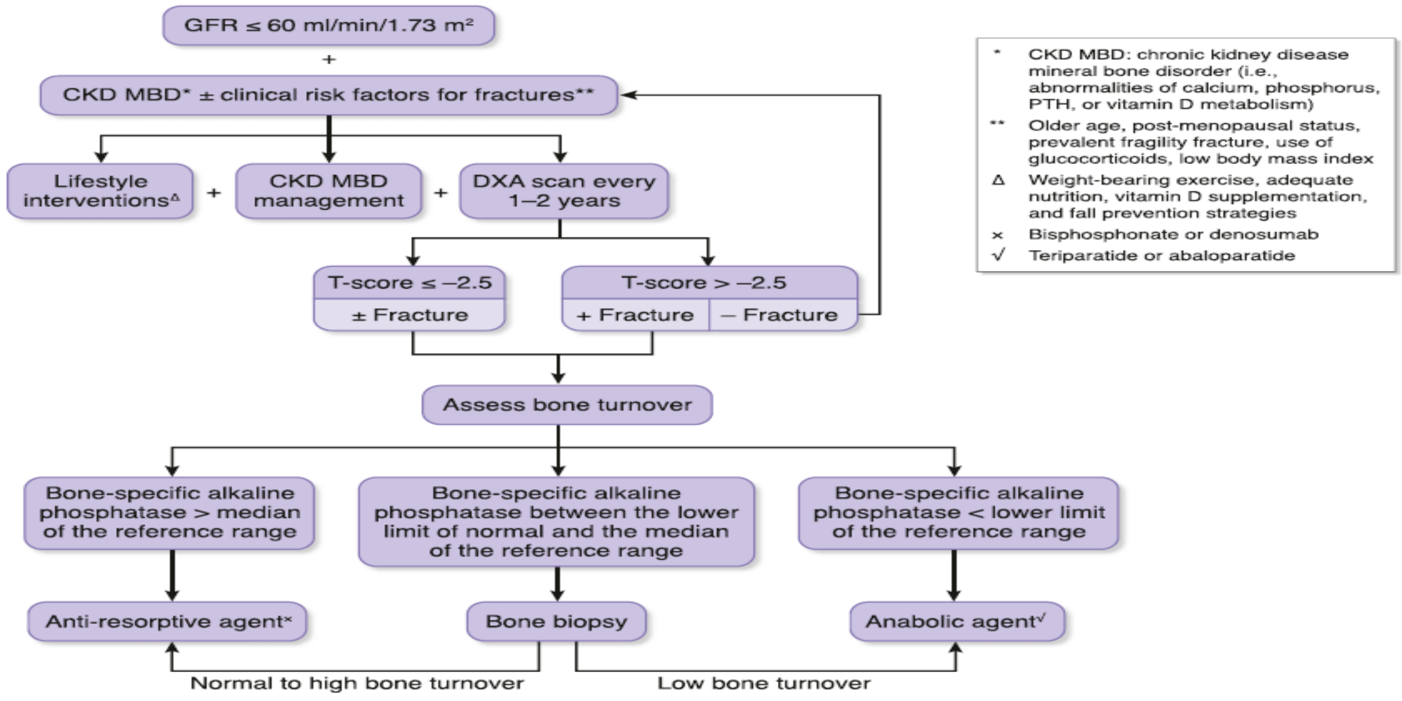


Figure 1. | An algorithm for fracture risk screening and initiation of anti-fracture strategies in patients with CKD. CKD-MBD, CKD mineral and bone disease; DXA, dual energy x-ray absorptiometry; PTH, parathyroid hormone.

Management of Osteoporosis in CKD

Pascale Khairallah and Thomas L. Nickolas
Clin J Am Soc Nephrol 13: 962–969, 2018. doi: https://doi.org/10.2215/CJN.11031017

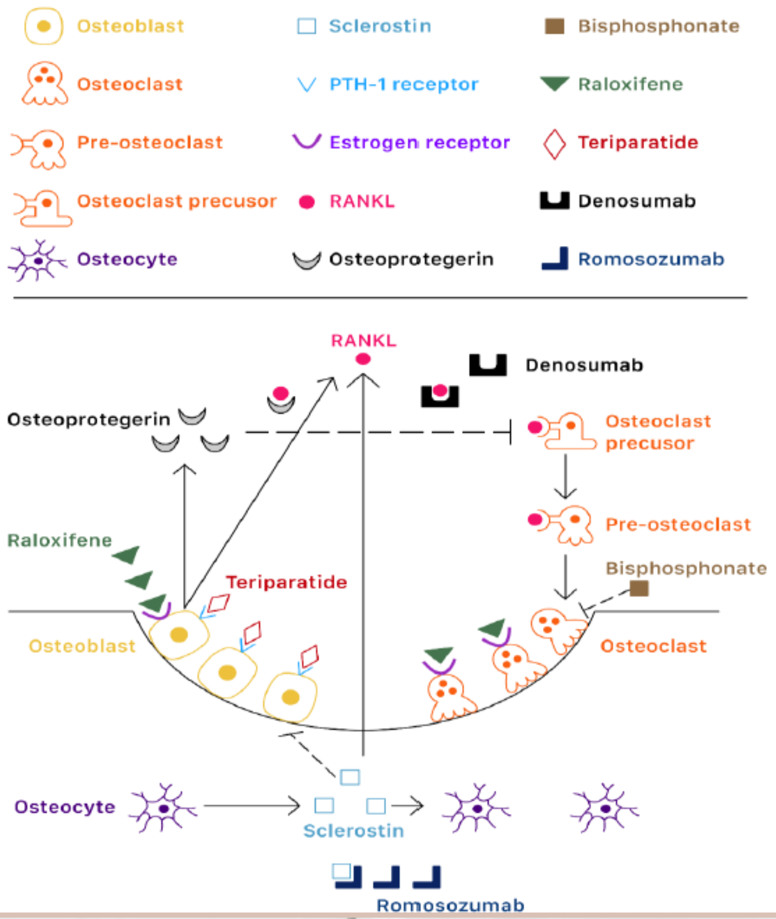
Table 2. Overview of available therapies for kidney-associated osteoporosis

Drugs	Dosage	FDA-Approved eGFR Cutoffs	Effect on Mineral Metabolism
Alendronate	70 mg PO once weekly	eGFR≥35 ml/min	Hypocalcemia, hypophosphatemia
Ibandronate	150 mg PO once monthly or 3 mg iv every 3 mo	eGFR>30 ml/min	—
Risendronate	5 mg PO daily or 35 mg PO weekly	eGFR>30 ml/min	Hypocalcemia, hypophosphatemia, increased PTH levels
Abaloparatide	80 μg Subcutaneously once daily	Any eGFR, not studied in ESKD	Hypercalcemia, hypercalciuria
Teriparatide	20–40 μg Subcutaneous daily	eGFR>30 ml/min	Hypercalcemia, hypocalcemia, hypercalciuria
Denosumab	60 mg Subcutaneous every 6 mo	Any eGFR	Hypocalcemia, hypophosphatemia
Romosozumab	210 mg Subcutaneous monthly	Not studied in CKD	—

FDA, Food and Drug Administration; PO, per oral; iv, intravenous; —, unknown PTH, parathyroid hormone.

Pharmacokinetics of bisphosphonates

- Cleared only by kidney
- Very poor oral absorption
- About 50% of dose deposited in the skeleton
- Deposits in calcified tissues
- Remains in skeleton for longer than 10 years
- Pamidronate clearance 69 ml/min



Osteoblast
Sclerostin
Bisphosphonate
Osteoclast
PTH-1 receptor
Raloxifene
Pre-osteoclast
Estrogen receptor
Teriparatide
Osteoclast precusor
RANKL
Denosumab
Osteocyte
Osteoprotegerin
Romosozumab
RANKL
Denosumab
Osteoprotegerin
Osteoclast precusor
Pre-osteoclast
Raloxifene
Teriparatide
Bisphosphonate
Osteoblast
Osteoclast
Osteocyte
Sclerostin
Romosozumab

Table 1 | Studies on antiresorptive agents in advanced CKD

Study	Population	Specific inclusion criteria	Specific exclusion criteria	Intervention	Outcome
Kunizawa *et al.*,[122] prospective, observational, safety and efficacy study	HD: 102 CKD 1–2: 144 CKD 3a: 44 CKD 3b: 35 CKD 4–5: 20	Any denosumab-treated patient with CKD and osteoporosis	Peritoneal dialysis, kidney transplantation, history of parathyroidectomy, hypo- or hypercalcemia (Ca <8.5 or >15 mg/dl)	Denosumab 60 mg s.c. every 6 mo, follow-up unclear	Annual ΔBMD HD: FN 4.3%, LS 6.7% Annual ΔBMD CKD: FN 3.1%, LS 7.5% Hypocalcemia: HD 35.6%, CKD 5.4% (risk factors: high TRAP5b, steroid Tx, no $CaCO_3$ pretreatment)
Chen *et al.*,[108] non-randomized safety and efficacy study	Dialysis: 42 (21 Dmab, 21 control)	PTH >800 pg/ml, low BMD, ongoing treatment with Ca and calcitriol	Parathyroidectomy with parathyromatosis, aluminum levels >20 µg/l	Single-dose denosumab 60 mg s.c. + $CaCO_3$ 3 g/d + calcitriol 1 µg/d + dialysate Ca 1.75 mmol/l for 2 wk, dialysate Ca and $CaCO_3$ tapered after 1 wk	CAC score unchanged in Dmab, increased in controls ($P = 0.004$) ΔBMD: FN 15.2%, LS 13.4% Hypocalcemia: 38%
Iseri *et al.*,[79] randomized, prospective, safety and efficacy study	HD: 46 (22 denosumab, 24 alendronate)	Osteoporosis, age >20 yr, hemodialysis for >6 mo, iPTH ≥60 and ≤240 pg/ml	Bisphosphonate or denosumab in the preceding 6 mo, corr Ca <8.4 mg/dl, poor oral condition	Denosumab 60 mg s.c. every 6 mo or alendronate 900 µg i.v. every 4 wk for 1 yr. All received calcitriol 0.25 µg/d and calcium lactate 1.5 g/d during 2 wk after study drug administration	ΔBMD: Dmab: FN 1.5%, LS 5.6%, alendronate: FN <0%, LS 5.4% CAC, CA-IMT, ABI, baPWV, and FMD: no change from baseline
Takami *et al.*,[123] retrospective case-control study, efficacy study	HD: 37 male patients (Dmab 17, control 20)	Male patients with low BMD (<70% of the young adult mean)	Conditions that influence bone metabolism, treated with bisphosphonates, parathyroid hormone, steroids, or selective estrogen receptor modulators, parathyroidectomy	Denosumab 60 mg every 6 mo for 1 yr, control: no treatment	ΔBMD distal radius: control: –4.5%, Dmab: 2.6% Hypocalcemia (<8.0 mg/dl): 29.4%
Cheng and Chen,[119] retrospective efficacy study	CKD 1–5: 109	Any denosumab-treated patient with CKD 1–5	No specific exclusion criteria	Any denosumab treatment during 1 yr	Best BMD effect in young patients and patients with advanced CKD
Huynh *et al.*,[28] retrospective safety study	CKD 1–3: 136 CKD 4–5: 19	Any denosumab-treated patient at a single center	No specific exclusion criteria	Any denosumab treatment	Hypocalcemia: CKD 3–4, 37%, CKD 1–3, 11%
Festuccia *et al.*,[120] retrospective efficacy study	HD: 12	Any denosumab-treated patient at a single center?	No specific exclusion criteria	Denosumab 60 mg every 6 mo for 24 mo	ΔBMD (QUS of fingers): 10%, N.S. Symptomatic hypocalcemia: 25%
Hiramatsu *et al.*,[121] prospective, single-arm, open-label, efficacy study	HD: 13	BMD < –2.5 SDs, well-controlled mineral metabolism	History of Ptx, anti-osteoporotic drugs	Denosumab 60 mg 1 single dose	ΔBMD: FN 4%, LS 37%
Chen *et al.*,[125] prospective, single-arm, open-label, efficacy study	HD/PD: 24	iPTH >800 pg/ml, DXA: forearm or FN or LS < –2.5 SDs	Total Ptx, s-Al >50 g/l	Denosumab 60 mg 1 single dose, $CaCO_3$ 3 g/d, calcitriol 2 µg/d, dialysate Ca 1.75 mmol/l	ΔBMD: FN: Sev HPT 27%, Mod HPT 9%
Chen *et al.*,[118] prospective, single-arm, open-label, efficacy study	HD/PD: 12	Dialysis treatment for >3 yr, iPTH >1000 pg/ml Ca and vitamin D supplement according to KDOQI, DXA: FN or LS T-score < –1 SD, stable laboratory results for 6 mo	No bone-specific exclusion criteria	Denosumab 60 mg 1 single dose, follow-up at 24 wk	ΔBMD: FN 23%, LS 17%

Table 2 | Bisphosphonates vs. denosumab in advanced CKD (pros and cons)

	Bisphosphonates	Denosumab
Pros	Improves BMD in all CKD stages	Improves BMD in all CKD stages
	Oral or i.v. dose (can be administered during dialysis)	Subcutaneous dosing every 6 mo
	Low risk of severe hypocalcemia	Continued effectiveness for at least 10 yr (in patients without CKD)
	Can be stopped after limited treatment time	
Cons	Risk of kidney damage in CKD 4–5	Risk of severe hypocalcemia
	Wear out after several years	Risk of fractures if stopped
	Osteonecrosis of the jaw	Osteonecrosis of the jaw
	Atypical femoral fractures	Atypical femoral fractures
	Acute phase reaction (i.v. bisphosphonates only)	Risk of infections
	Esophagitis	
	Uveitis	
	Atrial fibrillation	

BMD, bone mineral density; CKD, chronic kideny disease.

CKD stage 3

Post-hoc analysis of studies of osteoporosis medications (bisphosphonates, raloxifene, teriparatide and denosumab) that included subjects with age-related CKD stage 3 found fracture benefit, similar to patients with normal eGFR

These studies excluded sick patients. The subjects had normal calcium, PTH, and alkaline phosphatase.

Citation: BoneKEy Reports **3**, Article number: 542 (2014) | doi:10.1038/bonekey.2014.37

www.nature.com/bonekey

REVIEW

Chronic kidney disease and osteoporosis: evaluation and management

Paul D Miller

University of Colorado Health Sciences Center, Colorado Center for Bone Research, Lakewood, CO, USA.

Management of Fractures in Stages 4 and 5/5D CKD

DXA underestimates the fracture risk in stages 4 and 5 CKD. The abnormalities in bone turnover and mineralization and bone microarchitecture are so deranged by these more advanced stages of CKD that DXA measurements of BMD cannot alone capture these additional bone quality abnormalities that add to reduced bone strength in stages 4 and 5 CKD.[43] High-resolution peripheral quantitative computerized tomography (HRpQCT) of the forearm or tibia has been shown to be a better predictor of fracture risk in stages 4 and 5 CKD than DXA.[44,45] Until HRpQCT

The management of patients with fragility fractures across the spectrum of CKD should not differ between persons without reductions in eGFR as compared with persons with stages 1 and 3 CKD. This suggestion is predicated on the absence of information that could suggest the presence of CKD-MBD. In patients with stages 4 and 5 CKD and who have fragility fractures, the first management step is making the correct diagnosis. Diagnosis of osteoporosis in stages 4 and 5 CKD is an exclusionary one. Exclusion is best made by quantitative histomorphometry. Biochemical markers of bone turnover, in particular serum PTH and tissue-specific alkaline phosphatase, may provide differentiation between biopsy-proven adynamic, hyperparathyroid and/or osteomalacia. The exclusion, in

hyperparathyroid and/or osteomalacia. The exclusion, in particular, of renal adynamic bone disease is important as even off-label use of antiresorptive agents may not, in theory, be beneficial in persons with no bone turnover to begin with. There is a great need to gain knowledge and evidence for a beneficial or non-beneficial effect of registered therapies for post-menopausal, male or steroid-induced osteoporosis in very high-risk stage 4 and 5 CKD subjects who have sustained a low trauma fracture. In addition, the treatment of idiopathic adynamic renal bone disease may be facilitated by better understanding of the regulation of osteoblast activity, including sclerostin and FGF-23

Key learnings

- Fracture risk is increased in CKD, most probably as a consequence of increased fall risk, low bone mass and impaired bone quality
- Bone densitometry and fracture scores inform on fracture risk in CKD as in the general population
- The utility of bone biomarkers for prognostication remains unclear
- A bone biopsy, though being the gold standard to evaluate bone health, is unlikely to become routine clinical practice due to procedural complexity, vanishing pathological expertise and high cost
- Osteoporosis in CKD is a composite of primary, secondary and drug-induced osteoporosis, all requiring a specific therapeutic approach
- Therapy of osteoporosis in CKD is multi-faceted. Lacking evidence from randomised controlled trials, a pragmatic approach should be favoured above current ‘renalism’
- There is a pressing need for biomarkers for prognostication and therapy guidance in patients with advanced CKD presenting with osteoporosis

Key learnings

- Fracture burden is excessively high in CKD
- Osteoporosis in CKD is a composite of primary, secondary and drug-induced osteoporosis. As CKD is a state of premature ageing, the contribution of primary osteoporosis should not be underestimated
- Evidence-guided treatment of osteoporosis in CKD is almost non-existent. It is unlikely that this gap of knowledge will be filled soon
- Integration of biomarkers, imaging techniques and, eventually, bone biopsy data may help identify patients who will benefit most from intervention. DEXA screening should be considered in patients with advanced CKD, if postmenopausal or aged ≥50 years, accounting for comorbidities
- Bone biomarkers may inform on therapeutic response. A lack of response may question the indication if non-adherence is excluded

Key learnings

- In CKD patients, low BMD does not (automatically) equal osteoporosis, which does not (automatically) equal bisphosphonate treatment
- If a clear diagnosis/obvious history of CKD-MBD is present, CKD-MBD should be treated first (and not "osteoporosis")
- In CKD patients, the use of antiresorptive agents (bisphosphonates, denosumab) should be restricted to individuals with verified high-turnover osteoporosis (with few exceptions)
- To better assess the efficacy of calcimimetics and/or vitamin D analogues in clinical routine, studies should first systematically evaluate their effects on bone mineralisation (by DEXA)
- Antiresorptive agents are effective (at increasing BMD) in the first year after kidney transplantation, but steroid-sparing regimens may abolish the need for this therapeutic approach

Key learnings

- 64-year-old retired teacher
- CKD (cause uncertain, small kidneys) with hypertension
- Traumatic hip fracture 4 years ago
- Amlodipine, ramipril, bendroflumethiazide, atorvastatin
- eGFR 25 ml/min/1.73m2
- Calcium 2.3 mmol/L (2.2–2.6 mmol/L) [9.2 mg/dL; 8.8–10.4]
- Phosphate 1.8 mmol/L (0.4–1.4 mmol/L) [5.6 mg/dL; 1.2–4.3]

- 24-year-old shop assistant
- CKD secondary to juvenile nephronophthisis
- Haemodialysis 2004–2011 and restarted 2013
- Kidney transplant 2011–2013 (recurrent humoral rejection)
- Sevelamer hydrochloride 800 mg tds with food
- Calcium 2.34 mmol/L [9.36 mg/dL]
- Phosphate 3.94 mmol/L [12.20 mg/dL]
- iPTH 414 pg/ml [43.9 pmol/L]

CONCLUSION

Conclusions

As nephrologists, we must take action to tackle the longstanding and complex disorder of bone disease in patients with CKD so that we can improve our patients' short- and long-term clinical outcomes. Although treatment strategies for patients who meet the inclusion criteria for the pivotal fracture trials can be easily chosen, the majority of patients seen by nephrologists will require a personalized approach to determine the underlying renal osteodystrophy type and appropriateness of administering one of the current antiosteoporosis agents that has FDA approval for use in the general population. The future of the field must be patient-centric. We need to show that the battery of agents used in the general population has skeletal and nonskeletal safety and antifracture efficacy in patients with CKD-MBD, and we must push for the development of agents that are specific to the treatment of CKD-associated osteoporosis.

THANKS!

Does anyone have any questions?

giannisgriv@hotmail.com
www.athens-nephrology.gr

back-up slides

Management of Osteoporosis in CKD

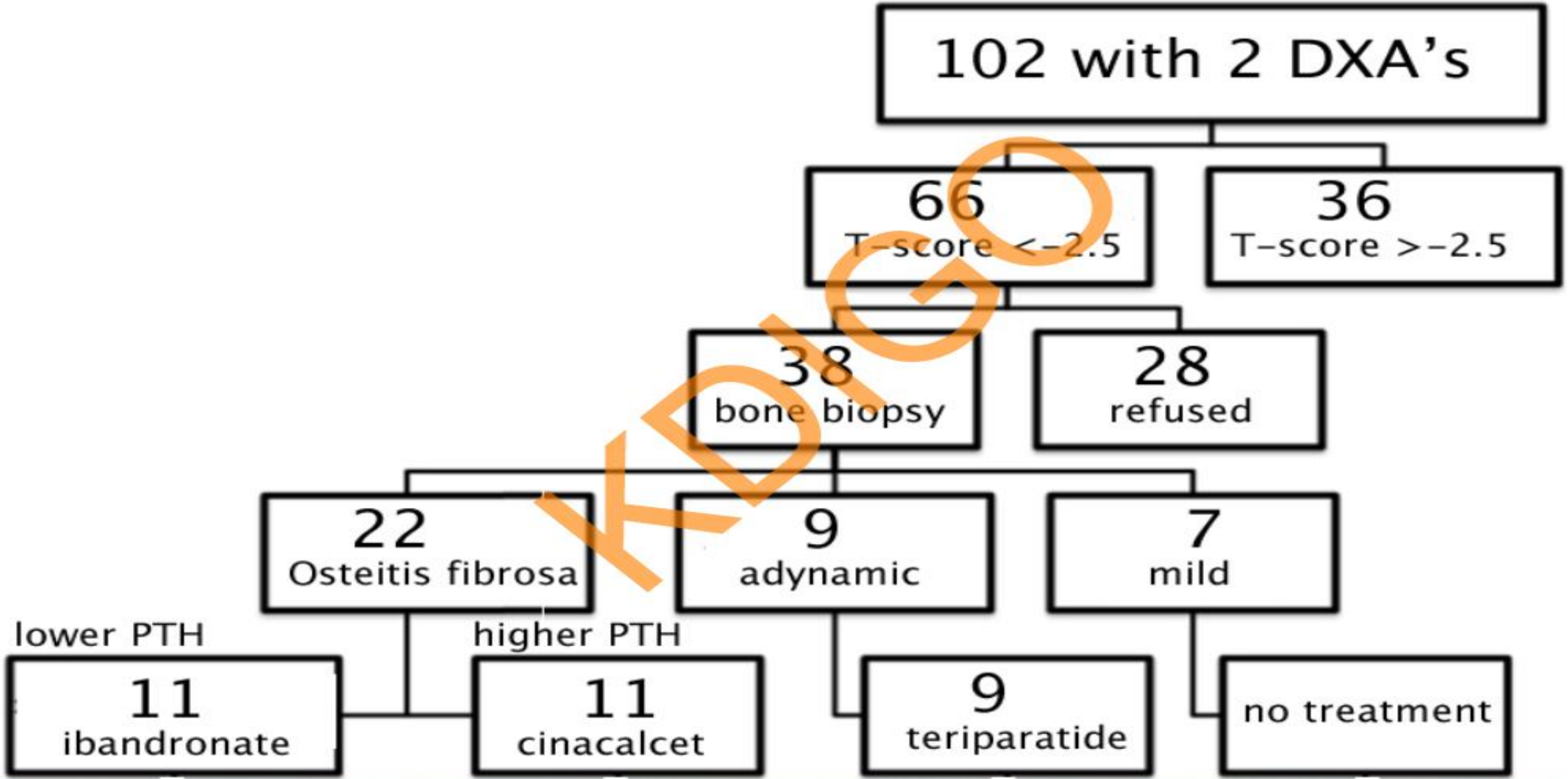
Pascale Khairallah and Thomas L. Nickolas

Clin J Am Soc Nephrol 13: 962–969, 2018. doi: https://doi.org/10.2215/CJN.11031017

Conclusions

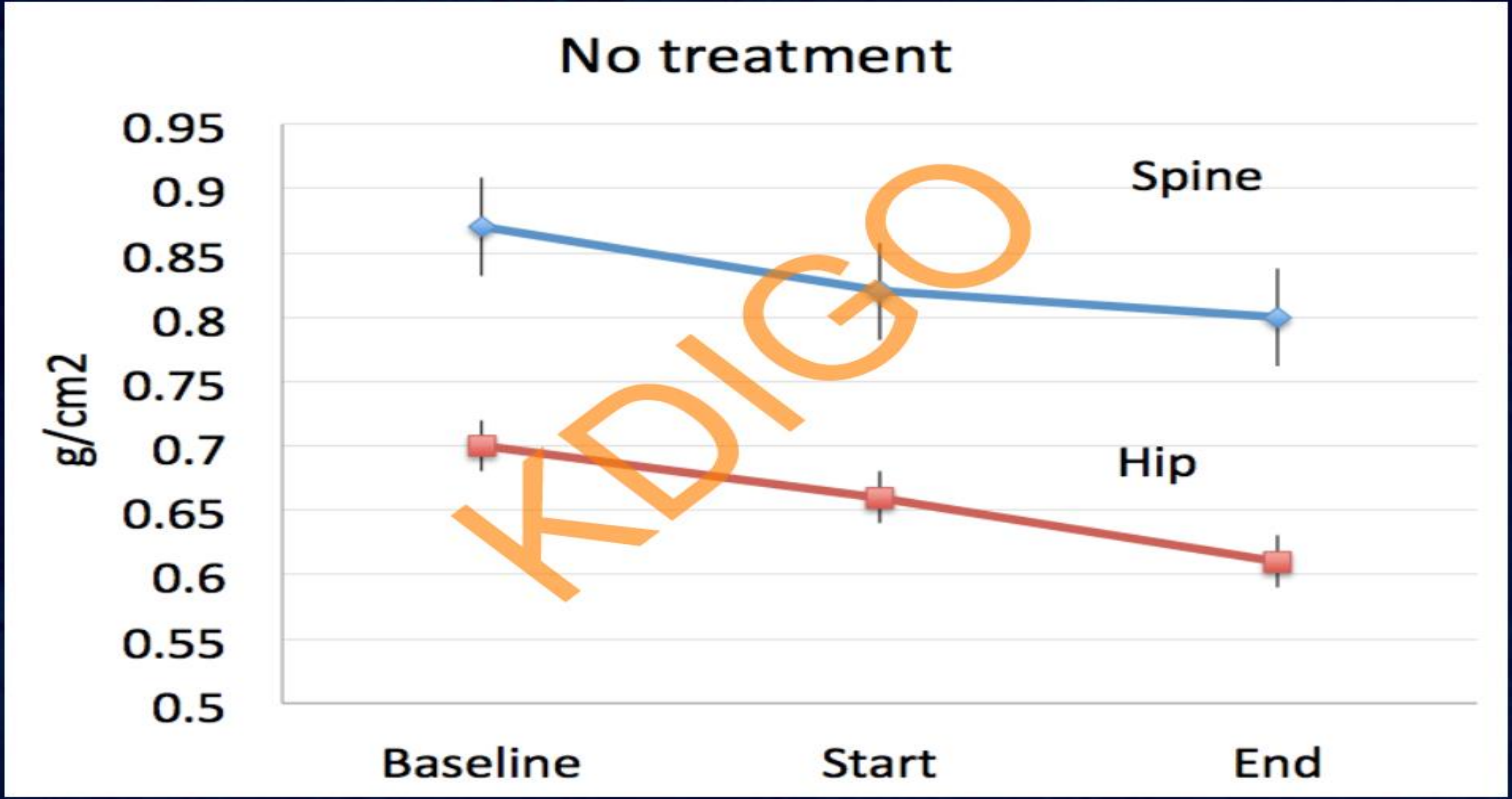
As nephrologists, we must take action to tackle the longstanding and complex disorder of bone disease in patients with CKD so that we can improve our patients' short- and long-term clinical outcomes. Although treatment strategies for patients who meet the inclusion criteria for the pivotal fracture trials can be easily chosen, the majority of patients seen by nephrologists will require a personalized approach to determine the underlying renal osteodystrophy type and appropriateness of administering one of the current antiosteoporosis agents that has FDA approval for use in the general population. The future of the field must be patient-centric. We need to show that the battery of agents used in the general population has skeletal and nonskeletal safety and antifracture efficacy in patients with CKD-MBD, and we must push for the development of agents that are specific to the treatment of CKD-associated osteoporosis.

Osteoporosis medicines in CKD-MBD



Mitsopoulos AJN 2012

Osteoporosis medicines in CKD-MBD



N = 5; PTH = 267

Mitsopoulos AJN 2012

Table 1 | Studies on antiresorptive agents in advanced CKD

Study	Population	Specific inclusion criteria	Specific exclusion criteria	Intervention	Outcome
Kunizawa *et al.*,[122] prospective, observational, safety and efficacy study	HD: 102 CKD 1–2: 144 CKD 3a: 44 CKD 3b: 35 CKD 4–5: 20	Any denosumab-treated patient with CKD and osteoporosis	Peritoneal dialysis, kidney transplantation, history of parathyroidectomy, hypo- or hypercalcemia (Ca <8.5 or >15 mg/dl)	Denosumab 60 mg s.c. every 6 mo, follow-up unclear	Annual ΔBMD HD: FN 4.3%, LS 6.7% Annual ΔBMD CKD: FN 3.1%, LS 7.5% Hypocalcemia: HD 35.6%, CKD 5.4% (risk factors: high TRAP5b, steroid Tx, no $CaCO_3$ pretreatment)
Chen *et al.*,[108] non-randomized safety and efficacy study	Dialysis: 42 (21 Dmab, 21 control)	PTH >800 pg/ml, low BMD, ongoing treatment with Ca and calcitriol	Parathyroidectomy with parathyromatosis, aluminum levels >20 μg/l	Single-dose denosumab 60 mg s.c. + $CaCO_3$ 3 g/d + calcitriol 1 μg/d + dialysate Ca 1.75 mmol/l for 2 wk, dialysate Ca and $CaCO_3$ tapered after 1 wk	CAC score unchanged in Dmab, increased in controls ($P = 0.004$) ΔBMD: FN 15.2%, LS 13.4% Hypocalcemia: 38%
Iseri *et al.*,[79] randomized, prospective, safety and efficacy study	HD: 46 (22 denosumab, 24 alendronate)	Osteoporosis, age >20 yr, hemodialysis for >6 mo, iPTH ≥60 and ≤240 pg/ml	Bisphosphonate or denosumab in the preceding 6 mo, corr Ca <8.4 mg/dl, poor oral condition	Denosumab 60 mg s.c. every 6 mo or alendronate 900 μg i.v. every 4 wk for 1 yr. All received calcitriol 0.25 μg/d and calcium lactate 1.5 g/d during 2 wk after study drug administration	ΔBMD: Dmab: FN 1.5%, LS 5.6%, alendronate: FN <0%, LS 5.4% CAC, CA-IMT, ABI, baPWV, and FMD: no change from baseline
Takami *et al.*,[123] retrospective case-control study, efficacy study	HD: 37 male patients (Dmab 17, control 20)	Male patients with low BMD (<70% of the young adult mean)	Conditions that influence bone metabolism, treated with bisphosphonates, parathyroid hormone, steroids, or selective estrogen receptor modulators, parathyroidectomy	Denosumab 60 mg every 6 mo for 1 yr, control: no treatment	ΔBMD distal radius: control: −4.5%, Dmab: 2.6% Hypocalcemia (<8.0 mg/dl): 29.4%
Cheng and Chen,[119] retrospective efficacy study	CKD 1–5: 109	Any denosumab-treated patient with CKD 1–5	No specific exclusion criteria	Any denosumab treatment during 1 yr	Best BMD effect in young patients and patients with advanced CKD
Huynh *et al.*,[28] retrospective safety study	CKD 1–3: 136 CKD 4–5: 19	Any denosumab-treated patient at a single center	No specific exclusion criteria	Any denosumab treatment	Hypocalcemia: CKD 3–4, 37%, CKD 1–3, 11%
Festuccia *et al.*,[120] retrospective efficacy study	HD: 12	Any denosumab-treated patient at a single center?	No specific exclusion criteria	Denosumab 60 mg every 6 mo for 24 mo	ΔBMD (QUS of fingers): 10%, N.S. Symptomatic hypocalcemia: 25%
Hiramatsu *et al.*,[121] prospective, single-arm, open-label, efficacy study	HD: 13	BMD < −2.5 SDs, well-controlled mineral metabolism	History of Ptx, anti-osteoporotic drugs	Denosumab 60 mg 1 single dose	ΔBMD: FN 4%, LS 37%
Chen *et al.*,[125] prospective, single-arm, open-label, efficacy study	HD/PD: 24	iPTH >800 pg/ml, DXA: forearm or FN or LS < −2.5 SDs	Total Ptx, s-Al >50 g/l	Denosumab 60 mg 1 single dose, $CaCO_3$ 3 g/d, calcitriol 2 μg/d, dialysate Ca 1.75 mmol/l	ΔBMD: FN: Sev HPT 27%, Mod HPT 9%
Chen *et al.*,[118] prospective, single-arm, open-label, efficacy study	HD/PD: 12	Dialysis treatment for >3 yr, iPTH >1000 pg/ml Ca and vitamin D supplement according to KDOQI, DXA: FN or LS T-score < −1 SD, stable laboratory results for 6 mo	No bone-specific exclusion criteria	Denosumab 60 mg 1 single dose, follow-up at 24 wk	ΔBMD: FN 23%, LS 17%

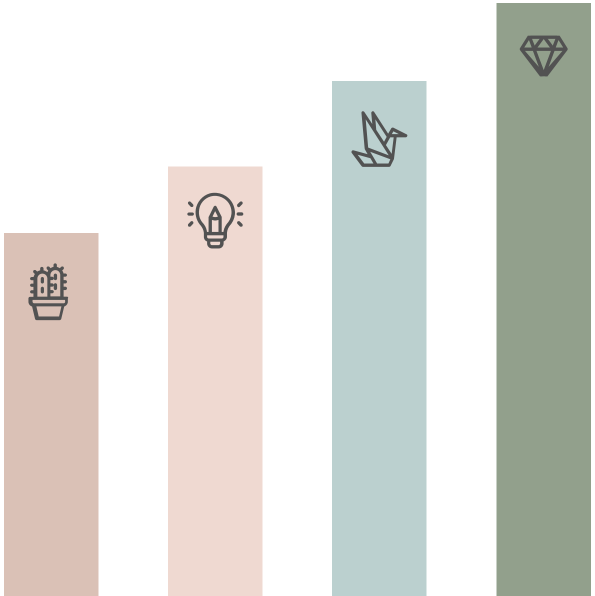
REINFORCE THE CONCEPT USING INFOGRAPHICS!

JUPITER
It’s a gas giant and the biggest planet in our Solar System

MARS
Despite being red, Mars is a cold place, not hot. It’s full of iron oxide dust

MERCURY
Mercury is the closest planet to the Sun and is only a bit larger than our Moon

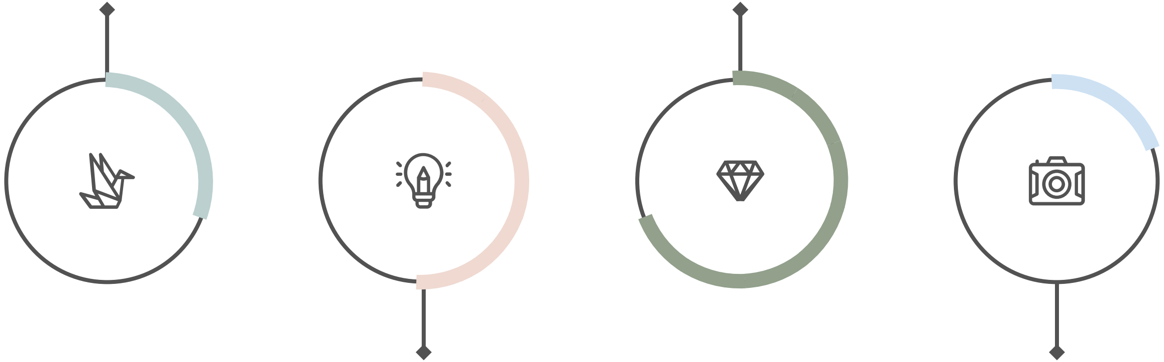
VENUS
Venus has a beautiful name, but it’s terribly hot, even hotter than Mercury



INFOGRAPHICS MAKE YOUR IDEA UNDERSTANDABLE…

MERCURY
It’s the closest planet to the Sun and is only a bit larger than our Moon

MARS
Despite being red, Mars is a cold place, not hot



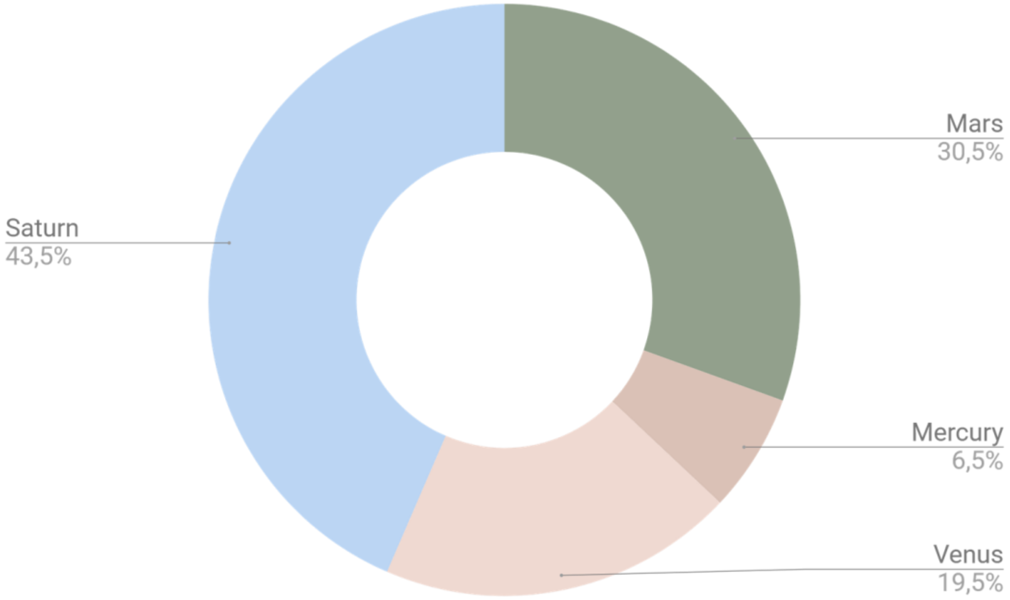
VENUS
Venus has a beautiful name, but it’s terribly hot, even hotter than Mercury

JUPITER
It’s a gas giant and the biggest planet in our Solar System

... AND THE SAME GOES FOR TABLES

	MASS (earths)	DIAMETER (earths)	SURFACE GRAVITY (earths)
MERCURY	0,06	0,38	0,38
MARS	0,11	0,53	0,38
SATURN	95,2	9,4	1,16

IF YOU WANT TO MODIFY THIS GRAPH, CLICK ON IT, FOLLOW THE LINK, CHANGE THE DATA AND REPLACE IT



A TIMELINE ALWAYS WORKS FINE

DAY 1

Mercury is the closest planet to the Sun and is only a bit larger than our Moon

DAY 2

Despite being red, Mars is a cold place, not hot. The planet is full of iron oxide dust

DAY 3

The Sun is the star at the center of the Solar System

DAY 4

Venus has a beautiful name, but it’s terribly hot

DAY 5

Jupiter is the biggest planet in our Solar System

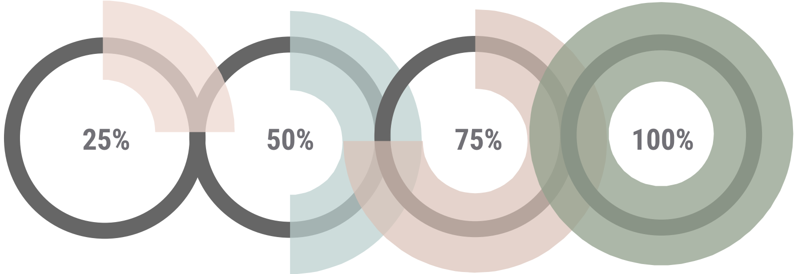
HOW ABOUT THE PERCENTAGES?

VENUS

Venus has a beautiful name, but it's terribly hot, even hotter than Mercury

MERCURY

Mercury is the smallest planet in our Solar System



JUPITER

It's a gas giant and the biggest planet in our Solar System

MARS

Despite being red, Mars is a cold place, not hot

SOMETIMES, REVIEWING CONCEPTS IS A GOOD IDEA

VENUS

Venus has a beautiful name and is the second planet from the Sun. It’s terribly hot

MARS

Despite being red, Mars is a cold place, not hot. It’s full of iron oxide dust, which gives the planet its reddish cast

SATURN

Yes, this is the ringed one. It’s a gas giant, composed mostly of hydrogen and helium

MERCURY

Mercury is the smallest planet in our Solar System—it’s only a bit larger than our Moon

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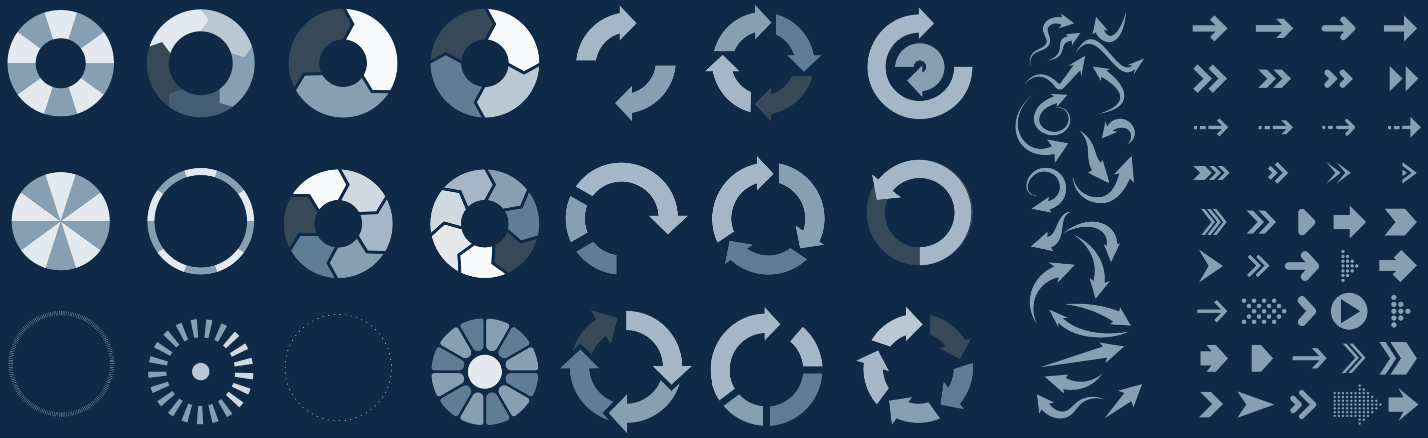

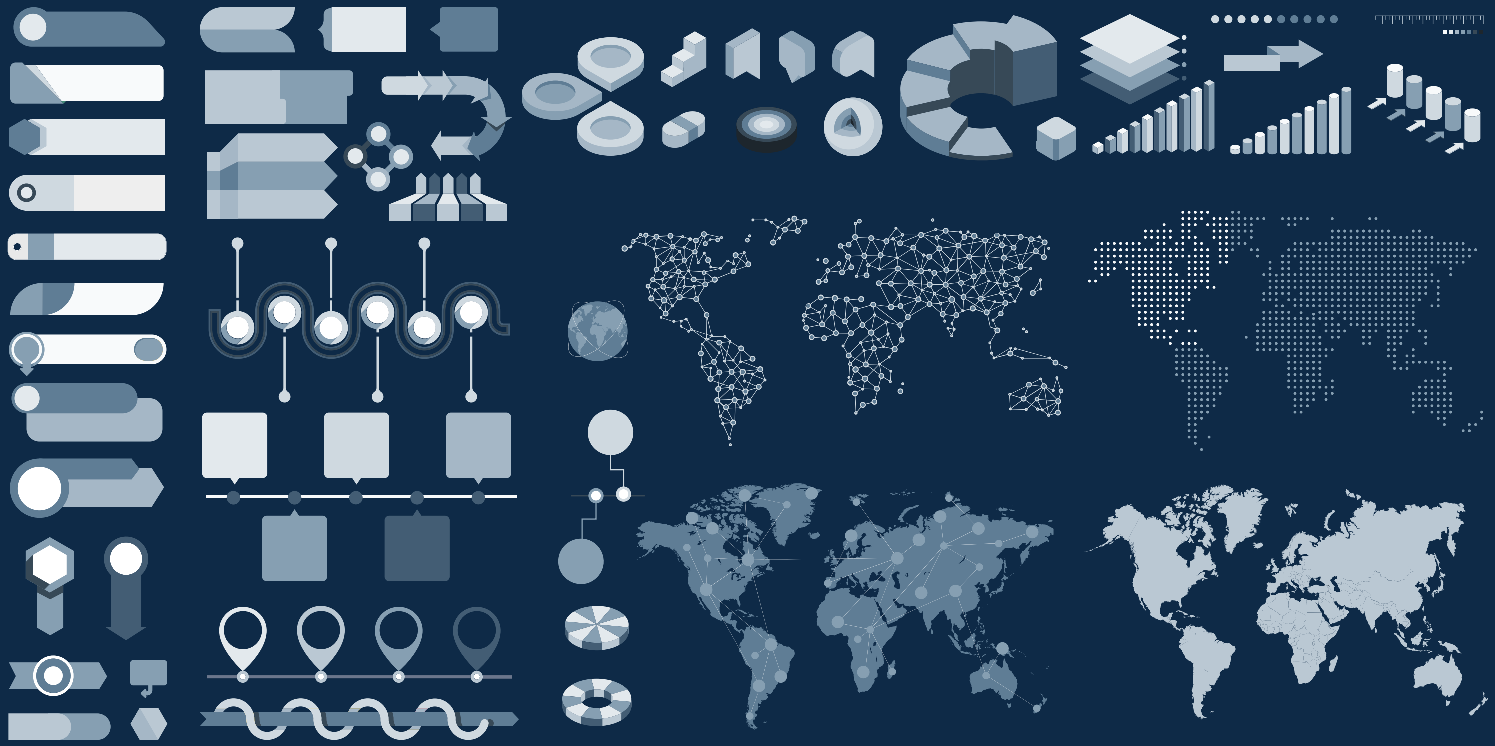

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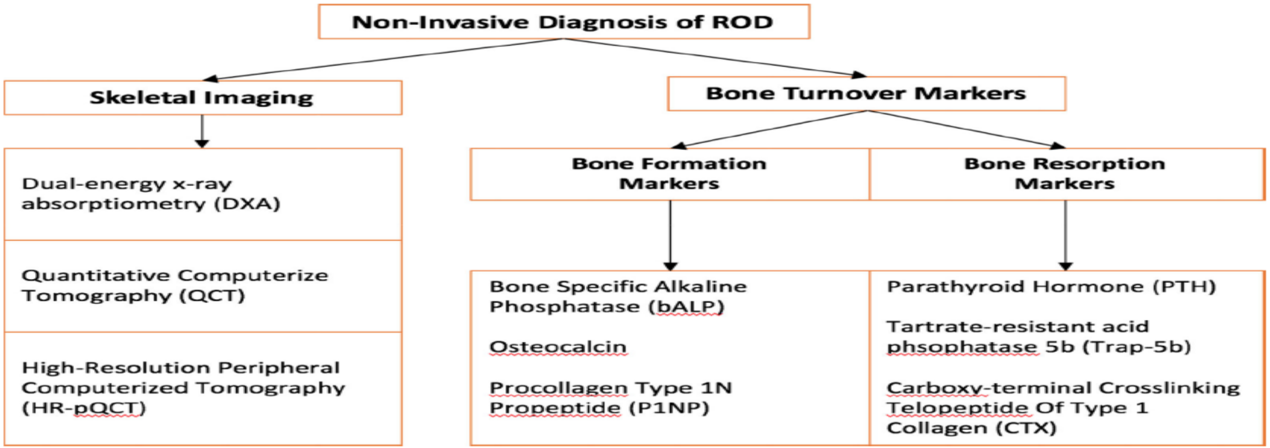

Figure 2. Non-Invasive Diagnosis of ROD

Non-invasive skeletal imaging can be used to assess the presence of skeletal abnor-malities and to classify fracture risk. Measurement of bone mineral density can be done by dual energy X-ray absorptiometry (DXA). Microarchitecture and mineral density of trabecular and cortical bone can be assessed by quantitative computerized tomography (QCT) and by high-resolution peripheral computerized tomography (HR-pQCT).

Alternatively, assessment of turnover type can also be based on bone turnover markers. Bone formation markers, which are markers of osteoblast function, include bone specific alkaline phosphatase (BALP), osteocalcin, and procollagen type-1 N-terminal propeptide (P1NP). Bone resorption markers, which are markers of osteoclast number and function, include tartrate-resistant acid phosphatase 5b (Trap-5b) and C-terminal telopeptides of type I collagen (CTX).

Table 2.

TMV classification system for renal osteodystrophy

Turnover	Mineralization	Volume
Low	Normal	Low
Normal	Abnormal	Normal
High		High

From: Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 69(11):1945–53.

NEFROLOGIA. 2018;38(5):476–490

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Review

Osteoporosis, bone mineral density and CKD–MBD complex (I): Diagnostic considerations☆

Jordi Bover[a,], Pablo Ureña-Torres[b], Josep-Vicent Torregrosa[c], Minerva Rodríguez-García[d], Cristina Castro-Alonso[e], José Luis Górriz[f], Ana María Laiz Alonso[g], Secundino Cigarrán[h], Silvia Benito[a], Víctor López-Báez[a], María Jesús Lloret Cora[a], Iara daSilva[a], Jorge Cannata-Andía[i]*

Table 1 – Fracture risk factors.

Major risk factors (RR ≥ 2)	BMD ≤ −2.5 Previous fracture (hip, spine, wrist) Age ≥ 65 years BMI ≤ 20 kg/m^2 History of hip fracture in a first-degree relative Corticosteroid therapy (≥5 mg/day of prednisone or equivalent for ≥3 months) Untreated premature ovarian failure Falls in the previous year (≥2) Hyperparathyroidism Eating disorder Chronic malnutrition or malabsorption syndromes
Minor risk factors	Female gender Early menopause (40–45 years) Current smoker Consumption of ≥3 units of alcohol/day Type 1 diabetes mellitus Rheumatoid arthritis Hyperthyroidism

BMD measured as T-*score* (number of standard deviations from BMD of women aged 20–29) exponentially increases the risk of fracture.[146] Osteopenia (T between −1 and −2.5): doubles the risk of fracture (2×); osteoporosis (T ≤ −2.5): 4×; established osteoporosis (T ≤ −2.5 and fracture); severe osteoporosis (T < −3.5). The Z index (i.e. ≤−2) should be used for diagnostic purposes in the assessment of BMD in *pre*-menopausal women and men under 50 years of age.[101] The Z value indicates the relationship with the "expected" value for the patient's age. In the absence of BMD measurement, this could be indicated by the presence of a major risk factor (other than age) or 2 minor risk factors, or, according to different guidelines, 2 major or 1 major + 2 minor. Other risk factors important for nephrologists would be (among others, and by different mechanisms): the use of loop diuretics, chronic use of heparin or anticoagulants, proton pump inhibitors, antihistamines, selective serotonin reuptake inhibitors, oestrogen and testosterone blockers, antiepileptics, aromatase inhibitors, etc.[147–150] As fractures occur at a younger age in CKD, SEN 2011 Spanish guidelines suggested that, in addition to transplant patients, densitometry should be performed in women over 50 years of age and men >65 years of age with CKD (unlike the usual indication in women >65 years of age and men >70 years of age).[101]
BMD: bone mineral density; BMI: body mass index; RR: relative risk.

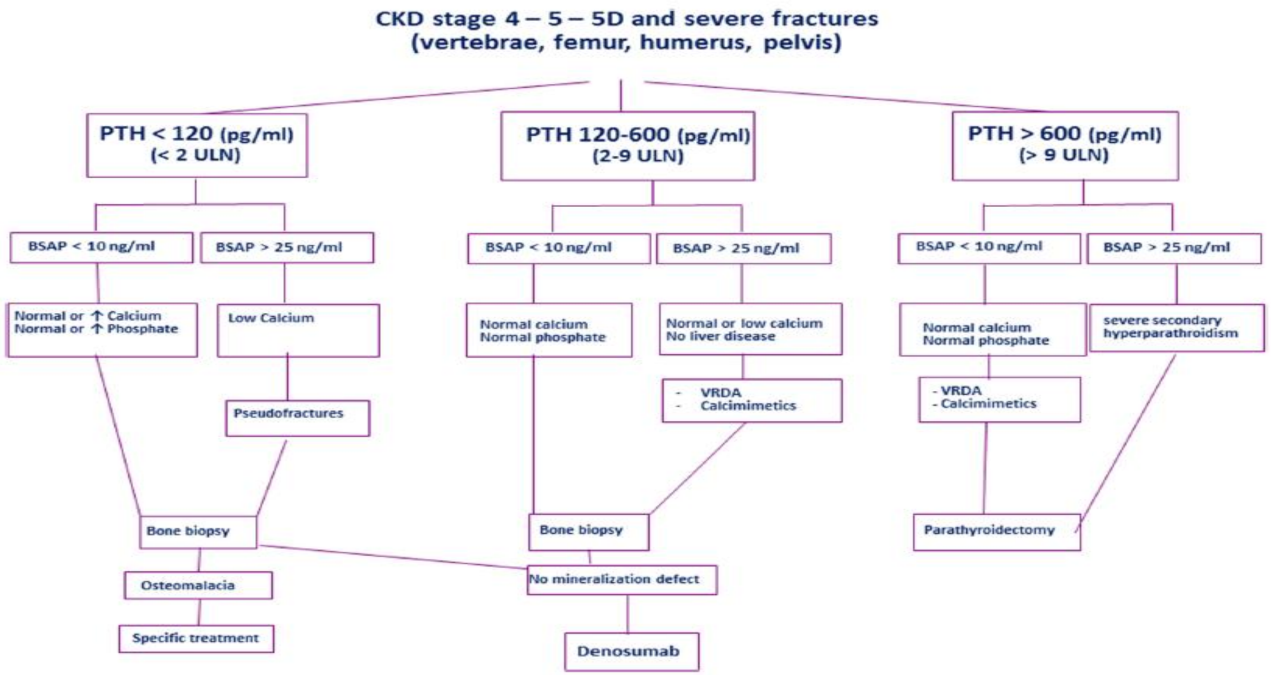

Figure 2

Proposed algorithm for treatment decision in patients with CKD and fracture. Treatment decisions are dependent of the levels of parathyroid hormone (PTH) and bone specific alkaline phosphatase (BSAP) levels. The different conditions are shown, to guide treatment decisions appropriately.

Nephrol Dial Transplant (2021) 36: 42–59
doi: 10.1093/ndt/gfaa192
Advance Access publication 24 October 2020

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

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

Drugs	Renal retention	Efficacy Preclinical	*Post hoc* (postmenopausal women)	Clinical trial (advanced CKD)	Safety (postmenopausal women)	Comments
Nitrogen-containing bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid)	Yes [118, 119]	Yes [129, 157]	Fracture ↓ [120–122]	BMD (↑) [123–127]	Atypical fracture, ONJ, oesophagitis, (hypocalcemia, renal dysfunction) [131, 137–139]	Dose adjustments?
Denosumab	No [141]	Yes [145]	Fracture ↓ [142]	BMD ↑ [126, 143, 144, 147, 156]	Atypical fracture, ONJ, hypocalcaemia [138, 143]	Beware: offset of effect [150]
PTH analogues (teriparatide, abaloparatide)	No	Yes [157]	Fracture ↓ [158, 159]	BMD ↑, in patients with ABD or hypoparathyroidism [123, 160, 161]	Hypotension [160]	Dose adjustments? Therapy to be limited to a maximum of 2 years
Romosozumab	Unlikely	Yes, low PTH only [162]	No data	No data	Cardiovascular adverse events ↑ [165] (hypocalcaemia)	Beware: offset of effect