Challenges in the diagnosis and management of Osteoporosis in CKD patients

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OSTEOPOROSIS

Osteoporosis is a disease that is characterized by poor bone quality and low bone mineral density (BMD) and strength, leading to risk of fractures.

The World Health Organization defines osteoporosis based on a decreased BMD T score ≤ −2.5; or, person's bone density 2.5 SD below the average value for persons aged 20- 29 years of the same sex.

Large systematic reviews document that persons with advanced chronic kidney disease are at 3 to 5 fold increased risk of osteoporosis and fractures compared with the general population.

NIH Consensus Development Panel on Osteoporosis Prevention D. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285(6):785-795. doi:10.1001/jama.285.6.785

World Health Organization. WHO Scientific Group on the assessment of osteoporosis at primary health care level: summary meeting report Brussels, Belgium, 5-7 May 2004. Accessed December 18, 2020. https://www.who.int/chp/ topics/Osteoporosis.pdf

Ball AM, Gillen DL, Sherrard D, et al. Risk of hip fracture among dialysis and renal transplant recipients. JAMA. 2002;288(23): 3014-3018. doi:10.1001/jama.288.23.3014

OSTEOPOROSIS

The diagnosis and management of osteoporosis in persons with advanced kidney disease is complex due to the highly variable pathophysiology of bone disease and due to limitations and unique side effects of the current therapeutic options.

In recognition of this, the European Renal Association–European Dialysis and Transplant Association recently released a consensus statement calling for standardized diagnostic and treatment practices to prevent fragility fractures in persons with advanced CKD.

Pazianas M, Miller PD. Osteoporosis and chronic kidney disease–mineral and bone disorder (CKD-MBD): back to basics. Am J Kidney Dis. 2021;78(4):582-589. doi:10.1053/j.ajkd. 2020.12.024

Evenepoel P, Cunningham J, Ferrari S, et al. European Renal Osteodystrophy (EUROD) Workgroup. European Consensus Statement on

OSTEOPOROSIS

Nearly all patients with CKD are high risk of osteoporosis.

Consequently, BMD testing is a critical element of the management of patients with CKD.

However, while BMD can provide information on bone density, volume, and fracture risk, it does not provide information on bone turnover, which is known to be abnormal in many patients with CKD and need direct treatment implications.

There are other imaging modalities that provide information on bone turnover or architecture, such as positron-emission tomography (PET) or high-resolution peripheral quantitative computed tomography (HRpQCT); however, these are not widely available and are primarily research tools.

Moe S, Drüeke 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):1945-1953. doi:10.1038/sj.ki. 5000414

Bone mineral density test

A bone mineral density (BMD) test measures how much calcium and other types of minerals are in an area of bone.

This test helps to detect osteoporosis or bone loss and predict risk of bone fractures.

Bone density testing can be done in several ways.

The most common and accurate way uses a dual-energy x-ray absorptiometry (DEXA) scan. DEXA uses low-dose x-rays. (You receive more radiation from a chest x-ray.)

There are two types of DEXA scans:

- Central DEXA -- patient lie on a soft table. The scanner passes over patient lower spine and hip. This scan is the best test to predict risk of fractures, especially of the hip.
- Peripheral DEXA (p-DEXA) -- These smaller machines measure the bone density in patient wrist, fingers, leg, or heel. These machines are found in some health care offices, pharmacies, shopping centers, and at health fairs.

Bone mineral density (BMD) tests are used to:

- 1- Diagnose bone loss and osteoporosis
- 2- See how well osteoporosis medicine is working
- 3- Predict risk for future bone fractures

Normal Results

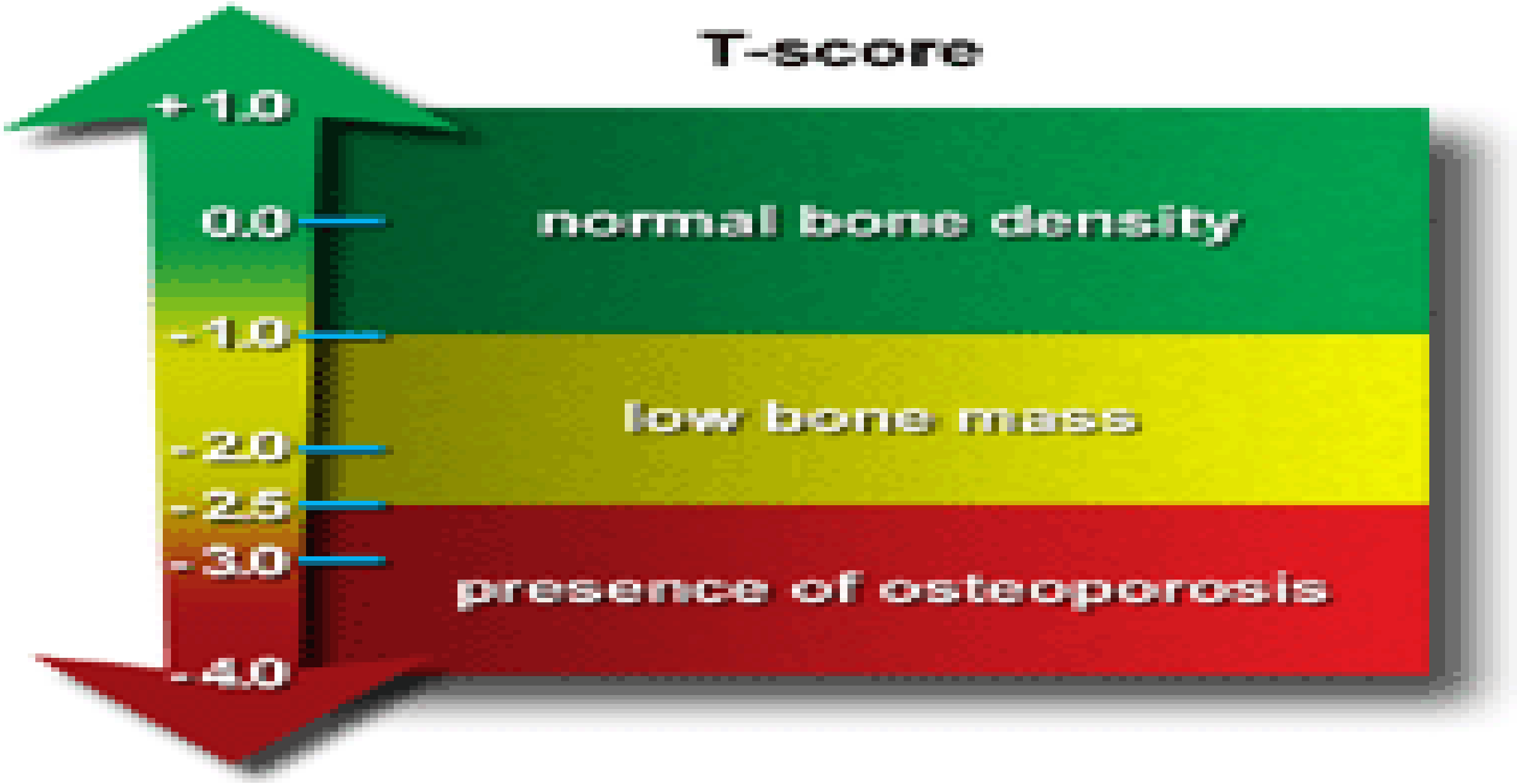
The results of test are usually reported as a T-score and Z-score:

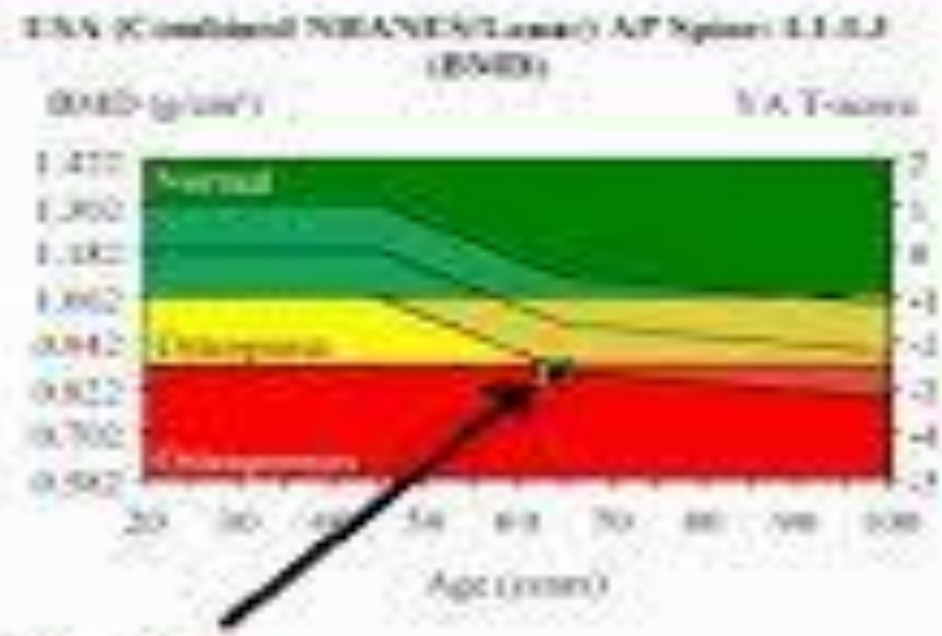
- T-score compares bone density with that of a healthy young woman.

- Z-score compares bone density with that of other people of Same age, sex, and race.

With either score, a negative number means you have thinner bones than the comparison group. The more negative the number, the higher risk of bone fracture.

A T-score is within the normal range if it is -1.0 or above.


T-score
+1.0
0.0
-1.0
-2.0
-2.5
-3.0
-4.0
normal bone density
low bone mass
presence of osteoporosis



T-score of - 2.6

Region	BMD	Young-Adult (%)	Young-Adult T-score	Age-Matched (%)	Age-Matched Z-score
L1	0.745 g/cm²	70%	-2.2	84%	-1.2
L2	0.699 g/cm²	74%	-2.6	88%	-1.0
L3	0.824 g/cm²	70%	-2.7	87%	-1.1
L4	0.743 g/cm²	65%	-3.7	78%	-2.2
L1-L3	**0.863 g/cm²**	**73%**	**-2.6**	**87%**	**-1.1**

BMD of spine showing osteoporosis

The bone density scan

FRACTURE RISK IN CHRONIC KIDNEY DISEASE

End-stage chronic kidney disease (CKD) is associated with an increased risk of fragility (low trauma) fractures that increases with the severity of CKD .

Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis 2000; 36:1115.

Danese MD, Kim J, Doan QV, et al. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. Am J Kidney Dis 2006; 47:149.

Kim SM, Long J, Montez-Rath M, et al. Hip Fracture in Patients With Non-Dialysis-Requiring Chronic Kidney Disease. J Bone Miner Res 2016; 31:1803.

The exact mechanism for this greater fracture risk in CKD is not clearly established, but there are biological changes in bone metabolism that render the skeleton in patients with progressive CKD more fragile .

These changes, **including**

1- phosphorus retention,

2- secondary hyperparathyroidism,

3- chronic acid loads,

4- elevated fibroblast growth factor 23 (FGF-23)

5- sclerostin overproduction,

Other risk factors include

1- glucocorticoid use,

2- hypogonadism,

3- hyperprolactinemia,

4- poor nutrition,

5- vitamin D deficiency,

6- inactivity .

Assessment of fracture risk

The assessment of fracture risk includes evaluation of

1-clinical risk factors for fracture,

2- measurement of bone mineral density (BMD) using dual-energy x-ray absorptiometry (DEXA).

Clinical risk factors for fracture

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption
Rheumatoid arthritis
Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Data from: Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005; 16:581.

Graphic 76445 Version 3.0

Bone mineral density

For patients with CKD, eGFR ≥30 mL/minute, and risk factors for fracture, BMD (DEXA) testing may be used to assess fracture risk.

- **Predialysis CKD –**

In cross-sectional studies, BMD by DEXA has been shown to be lower in patients with predialysis CKD who has fracture compared with those who do not.

In one study, for every standard deviation decrease in lumbar spine, total hip, femoral neck, and ultradistal radius BMD by DEXA, there was a significant increase in the risk of fracture (odds ratios [ORs] 1.93, 1.65, 1.86, and 2.29, respectively) .

Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. Clin J Am Soc Nephrol 2012; 7:1130.

Bucur RC, Panjwani DD, Turner L, et al. Low bone mineral density and fractures in stages 3-5 CKD: an updated systematic review and meta-analysis. Osteoporos Int 2015; 26:449.

West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. J Bone Miner Res 2015; 30:913.

Nickolas TL, Stein E, Cohen A, et al. Bone mass and microarchitecture in CKD patients with fracture. J Am Soc Nephrol 2010; 21:1371.

- **Dialysis dependent –**

BMD is also lower in dialysis-dependent patients who has fracture, as illustrated by the findings of a meta-analysis of six cross-sectional studies, which included 683 patients on dialysis .

Compared with patients without fracture, patients with fracture had significantly lower BMD

Jamal SA, Hayden JA, Beyene J. Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. Am J Kidney Dis 2007; 49:674

In the study of Japanese dialysis patients, low hip BMD (DEXA) was predictive of any type of incident fracture when the parathyroid hormone (PTH) was below the median value 204 pg/mL.

In patients with advanced CKD and elevated PTH levels, the bone density is lost primarily from the cortical bone, and it may be increased in the cancellous bone.

Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients--a single-center cohort study. Nephrol Dial Transplant 2012; 27:345.

Limitations of DEXA scan

1-DEXA measures areal BMD, rather than volumetric BMD.

2- it cannot distinguish between cortical and cancellous bone,

3-it cannot assess bone microarchitecture or bone turnover.

Thus, new technologies have been developed that allow noninvasive, three-dimensional evaluation of bone microarchitecture (high resolution microcomputed tomography [microCT] and micromagnetic resonance imaging [microMRI], hip structural analysis, finite element analysis).

they are not available in most clinical settings.

Wehrli FW, Leonard MB, Saha PK, Gomberg BR. Quantitative high-resolution magnetic resonance imaging reveals structural implications of renal osteodystrophy on trabecular and cortical bone. J Magn Reson Imaging 2004; 20:83.

DIAGNOSIS

In the general adult population, the clinical diagnosis of osteoporosis is made in one of two ways:

1- the presence of a low trauma fracture independent of the prevailing bone mineral density (BMD) or, in the absence of a preexisting fracture,

2- a certain level of BMD defined in standard deviation score terms, the T-score .

- **In patients with chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) ≥30 mL/minute, the World Health Organization (WHO) criteria for BMD (T-score -2.5 standard deviations or the presence of a fragility fracture) may be used for the diagnosis of osteoporosis, assuming that there are no accompanying biochemical abnormalities.**

(eg, hyperparathyroidism, hyperphosphatemia) that indicate the possible coexistence of renal osteodystrophy or CKD-MBD (mineral bone disorder).

●In patients with GFR <30 mL/minute, **bone physiology is more complex and features of CKD-MBD may predominate**.
In this setting, a **diagnosis of osteoporosis can only be made by excluding renal osteodystrophy.**

Laboratory assessment

- **eGFR> = 30 mL/minute –**

For this patients with a history of a fragility fracture and/or low BMD (DXA T-score ≤-2.5), we initially measure serum:

- **Calcium**
- **Phosphorus**
- **Parathyroid hormone (PTH)**
- **25-hydroxyvitamin D**
- **Alkaline phosphatase**

In those patients with eGFR ≥30 mL/minute with normal initial biochemical tests, (absence of coexisting CKD-MBD), we make the diagnosis of osteoporosis as in patients without CKD.

In patients with eGFR ≥30 (ie, G3a and G3b) with abnormalities on initial testing suggestive of CKD-MBD **management and monitoring of renal osteodystrophy prior to consideration of osteoporosis therapy, is necessary**.

eGFR <30 mL/min –

For patients with an eGFR <30 mL/minute with a history of a fragility fracture and/or low BMD (DXA T-score ≤-2.5), we measure:

- **Bone-specific alkaline phosphatase (BSAP)**
- **Calcium**
- **Phosphorus**
- **PTH**
- **25-hydroxyvitamin D**

Bone-specific alkaline phosphatase

In clinical practice, the marker that has the most value in discriminating bone turnover in CKD is BSAP. In particular, a high BSAP may be helpful in excluding the presence of adynamic bone disease.

Garrett G, Sardiwal S, Lamb EJ, Goldsmith DJ. PTH--a particularly tricky hormone: why measure it at all in kidney patients? Clin J Am Soc Nephrol 2013; 8:299

Delanaye P, Souberbielle JC, Lafage-Proust MH, et al. Can we use circulating biomarkers to monitor bone turnover in CKD haemodialysis patients? Hypotheses and facts. Nephrol Dial Transplant 2014; 29:997

In a cross-sectional study evaluating the ability of serum BSAP to predict bone turnover in 492 dialysis patients who had bone biopsy, a BSAP level of <33.1 Unit/L best discriminated low from non-low bone turnover (AUROC 0.76) . The combination of intact PTH and BSAP was better able to discriminate bone turnover than BSAP alone.

Sprague SM, Bellorin-Font E, Jorgetti V, et al. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. Am J Kidney Dis 2016; 67:559.

Bone Biopsy

Bone biopsy at the iliac crest remains the gold standard for diagnosing bone turnover and underlying pathology in patients with CKD.

Bone biopsy is typically performed after tetracycline double-labeling.

In addition to bone turnover, histomorphometric analysis provides information on mineralization and volume.

Nonetheless, few CKD patients receive bone biopsies.

Tomiyama C, Carvalho AB, Higa A, et al. Coronary calcification is associated with lower bone formation rate in CKD patients not yet in dialysis treatment. J Bone Miner Res 2010; 25:499.

Hernandez JD, Wesseling K, Pereira R, Gales B, Harrison R, Salusky IB. Technical approach to iliac crest biopsy. Clin J Am Soc Nephrol. 2008;3(suppl 3):S164-S169. doi:10.2215/CJN. 00460107

Considering that imaging and BTMs cannot reliably predict bone turnover or mineralization in most patients with CKD, bone biopsy should be pursued more broadly than is common in current clinical practice.

This may require collaboration with colleagues in orthopedics and interventional radiology in order to implement this procedure more broadly.

Additionally, considering that many centers lack expertise in histomorphometry interpretation, collaborations with larger pathology departments need to be pursued as well for sample processing and interpretation

Table 1. Markers of Bone Turnover

Biomarker Class	Renal Clearance	Hemodialysis Clearance	Association With Turnover Type[a]
Bone metabolism			
PTH	Yes	Yes (Fragments)	High
FGF-23	Yes	No	High
α-Klotho	Yes	No	Low
Sclerostin	Yes	Yes	Low
Bone formation			
BSAP	No	Yes	High
Osteocalcin	Yes	Yes	High
P1NP/P1CP	No	Yes	High
Bone resorption			
NTX/CTX	Yes	Unknown	High
TRAP5b	No	No	High

Abbreviations: BSAP, bone-specific alkaline phosphatase; CTX, β-C-terminal telopeptide; FGF-23, fibroblast growth factor 23; NTX, cross-linked N-telopeptides of type I collagen; P1NP, procollagen type 1 C-terminal propeptide; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; TRAP5b, tartrate-resistant acid phosphatase.

[a]Higher concentrations of bone turnover markers are associated with high or low bone turnover.

Management

INTRODUCTION —The management of osteoporosis in these patients is more complex than in patients without CKD and depends upon whether the patient also has coexisting chronic kidney disease-mineral and bone disorder (MBD).

1- LIFESTYLE MEASURES — including **adequate calcium and vitamin D, exercise, cessation of smoking, avoiding excessive alcohol intake, and fall prevention,** are important in all patients at high risk for fracture.

A- Calcium and vitamin D — An optimal diet for the prevention of fracture includes an adequate intake of calories (to avoid malnutrition), calcium, and vitamin D.

- **eGFR ≥30 mL/minute** – and **no biochemical evidence of CKD-MBD** (mineral bone disorder) (eg, no evidence of hyperparathyroidism, hyperphosphatemia) **should have similar calcium and vitamin D intake as patients without CKD**

- **eGFR <30 mL/minute –** For patients with eGFR <30 mL/minute, a total calcium intake (diet plus supplement) of 1200 mg/day, with 500 mg/day provided by calcium supplementation.

Since dairy products also contain phosphorus, nondairy sources of calcium (calcium-fortified juice, soy products, vegetables) may be preferred in some patients.

We also suggest 800 international units of vitamin D (cholecalciferol or ergocalciferol) daily

Fall prevention — **Fall prevention strategies are particularly important in patients with eGFR <15 mL/minute**, who are often frail and have a high frequency of falling. Patients with severe CKD often have sarcopenia, a systemic condition of muscle mass deficiency and poor muscle strength, receiving more attention by the National Institutes of Health and various professional societies [5,6].

Kim SM, Long J, Montez-Rath M, et al. Hip Fracture in Patients With Non-Dialysis-Requiring Chronic Kidney Disease. J Bone Miner Res 2016; 31:1803.
Nitsch D, Mylne A, Roderick PJ, et al. Chronic kidney disease and hip fracture-related mortality in older people in the UK. Nephrol Dial Transplant 2009; 24:1539

2- TREATMENT OF HYPOGONADISM —

Estrogen is an option for the prevention of osteoporosis in hypogonadal, premenopausal women with chronic kidney disease (CKD).

If estrogen replacement therapy is indicated, no dosing adjustments are required in most women with CKD.

However, women with G5D kidney disease should receive approximately 50 percent of the dose typically prescribed to women with less severe renal impairment.

No longer consider estrogen a first-line therapy for osteoporosis in postmenopausal women who are more than 10 years past menopause,

Jamal SA, West SL, Miller PD. Fracture risk assessment in patients with chronic kidney disease. Osteoporos Int 2012; 23:1191.

Hypogonadism is also common in men with CKD and estimated glomerular filtration rate (eGFR) ≤30 mL/min.

For men with CKD and symptomatic hypogonadism, testosterone therapy is indicate (in the absence of other contraindications).

The dose of testosterone does not need to be adjusted based upon renal function. In men with CKD, observational data suggest that **testosterone replacement improves hypogonadal symptoms and anemia.**

Premenopausal women and men with CKD who are taking hormone replacement therapy may not require additional pharmacologic therapy for osteoporosis.

Fried LF, Biggs ML, Shlipak MG, et al. Association of kidney function with incident hip fracture in older adults. J Am Soc Nephrol 2007; 18:282.

Dooley AC, Weiss NS, Kestenbaum B. Increased risk of hip fracture among men with CKD. Am J Kidney Dis 2008; 51:38.

CANDIDATES FOR PHARMACOLOGIC TREATMENT

The ultimate goal of treating osteoporosis is to prevent fracture. Therefore, selection of patients for pharmacologic therapy for osteoporosis is based upon fracture risk, (primarily determined by history of fragility fracture and bone mineral density (BMD),) and the presence or absence of chronic kidney disease-mineral and bone disorder (CKD-MBD) (eg, adynamic bone disease).

CHOICE OF DRUG

Estimated glomerular filtration rate ≥30 mL/minute —
Patients with osteoporosis and eGFR ≥30 mL/minute who do not have evidence of CKD-MBD can be managed as patients without CKD.

Medication (reference)	Indication(s) in PMO	Pivotal trial name (reference)	Statistically significant relative fracture risk reductions vs. control			Administration	Dose
			Vertebral	Non-vertebral	Hip		
Alendronate (49)	Treatment and prevention of osteoporosis in postmenopausal women	FIT I (50)	√	X	√	Oral	5 mg daily for prevention of osteoporosis; 10 mg daily (alternatively 70 mg once weekly) for treatment
		FIT II (51)	√	X	X		
Risedronate (52)	Treatment and prevention of osteoporosis in postmenopausal women	VERT NA (53)	√	√	NR	Oral	5 mg daily (alternatively 35 mg once weekly or 150 mg once monthly) for prevention and treatment
		HIPS (54)	NR	NR	√		
Zoledronic acid (55)	Treatment of osteoporosis in	HORIZON (56)	√	√	√	Intravenous	5 mg as single 15–30

Denosumab (11)	Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy	FREEDOM (48)	√	√	√	Subcutaneous	60 mg every 6 months
Raloxifene (37)	Treatment and prevention of osteoporosis in postmenopausal women	MORE (36)	√	X	X	Oral	60 mg daily
Estrogen replacement therapy*	Varies by formulation	WHI (57)	√	NR	√	Oral or transdermal	Daily

Teriparatide (58)	Treatment of postmenopausal women with severe osteoporosis who are at high risk of fracture or who have failed or are intolerant to previous osteoporosis therapy	FPT (59)	√	√	NR	Subcutaneous	20 mcg daily

Estimated glomerular filtration rate <30 mL/minute —

There are few data in patients with eGFR between 15 and 30 mL/minute (G4).

Bisphosphonates are generally not recommended for those with eGFR below 30 and should only be considered by specialists in CKD-MBD and after biochemical testing and/or bone biopsy (for patients with eGFR <15 mL/minute) exclude renal osteodystrophy.

The basis for the eGFR contraindications include the fact that bisphosphonates are cleared by the kidney .
Due in part to unknown effects of greater bone retention of bisphosphonates in patients with impaired renal function, the US Food and Drug Administration (FDA) established a creatinine clearance cut point of <30 mL/minute to avoid bisphosphonate exposure.
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Without evidence of CKD-MBD —

If there is no biochemical evidence of CKD-MBD (hyperparathyroidism, hyperphosphatemia) or clinician is certain that the type of MBD causing the fracture is not adynamic bone disease, then **choices for intervention include oral bisphosphonates, denosumab, or raloxifene** (for postmenopausal women).

Without evidence of CKD-MBD

- **eGFR 15 to 30 mL/minute –**

Some experts consider first-line therapy to be an oral bisphosphonate because of decades of clinical experience in this patient population, lower cost, and existing clinical trial data.

Other experts do not administer bisphosphonates to patients with eGFR <30 mL/min.

If bisphosphonates are administered, the dosing interval and duration should be modified (typically risedronate 35 mg every other week [ie, half the usual dose] and for not more than three years).

Denosumab is an attractive option because it is not cleared by the kidney, but there is limited clinical experience in patients with severe CKD and denosumab administration in hemodialysis patients has been associated with clinically significant hypocalcemia .
It is unknown whether denosumab influences vascular calcification; information is needed before widespread administration in patients with eGFR <30 mL/minute.
Other therapies for skeletal health, such as raloxifene and calcitonin, are usually not considered in G4 CKD,

National Osteoporosis Foundation. Osteoporosis and chronic kidney disease updates, 2010 http://www.nof.org/sites/default/files/clinicalupdates/Issue20KidneyDisease/kidney.html (Accessed on September 25, 2012).
Naylor KL, Garg AX, Zou G, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. Clin J Am Soc Nephrol 2015; 10:646.
Miller PD, Jamal S, West S. Bone mineral density in chronic kidney disease-use and misuse. Clin Rev Bone and Mineral Metab 2012; 10:163. http://www.springerlink.com/content/0364267gmnm85147/ (Accessed on September 25, 2012).
Kanis JA, Hans D, Cooper C, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int 2011; 22:2395

●eGFR <15 mL/min –

Clinical experience is limited, but some experts suggest that in patient with eGFR <15 mL/minute whose osteoporotic fracture is associated with a very high risk of recurrent fracture and mortality, a bisphosphonate or denosumab should be considered instead of no treatment.

Patients with this degree of renal impairment who fracture, should have bone biopsy prior to consideration of osteoporosis therapy.

If biopsy does not show evidence of renal osteodystrophy, we prefer an oral bisphosphonate, typically risedronate 35 mg every other week (ie, half the usual dose), and for not more than three years.

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) http://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf (Accessed on November 08, 2017).

Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. Clin J Am Soc Nephrol 2012; 7:1130.

With evidence CKD-MBD

—

For patients with eGFR between 15 and 30 mL/minute (G4) or <15 mL/minute (G5 or G5D) and evidence of CKD-MBD, **antiresorptive osteoporosis drugs should not be administered.**
The principal goal **in this setting is to prevent or manage renal osteodystrophy, largely by controlling secondary hyperparathyroidism**; **preventing over suppression of PTH**,; and **treating acidosis and vitamin D deficiency.**

With evidence CKD-MBD

Some experts consider anabolic agents (eg, parathyroid hormone [PTH]) for patients with history of fragility fracture and low PTH .

However, this option should only be considered by specialists in CKD-MBD and after biochemical testing and/or bone biopsy (for patients with eGFR <15 mL/minute) with evidence of non iatrogenic adynamic bone disease.

Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients--a single-center cohort study. Nephrol Dial Transplant 2012; 27:345.

PRETREATMENT EVALUATION —

Serum vitamin D and calcium levels must be assessed prior to administration of bisphosphonates or denosumab.

Patients who have hypocalcemia should not receive bisphosphonates or denosumab until hypocalcemia is corrected. Patients with vitamin D deficiency should be replaced with vitamin D prior to administering denosumab.

MONITORING THERAPY —

●eGFR ≥30 mL/min –
monitoring is similar to patients without chronic kidney disease (CKD).

Serial bone mineral density (BMD) measurements are typically performed to assess the clinical response to therapy.

●eGFR <30 mL/min –measuring the following blood tests every months and also approximately 10 days after denosumab administration:

- Calcium
- Phosphorus
- 25-hydroxyvitamin D
- Parathyroid hormone (PTH)

EFFICACY

— There are few data evaluating fracture prevention efficacy and long-term adverse effects of pharmacologic therapy in patients with reduced renal function.

In a systematic review of trials evaluating the benefits and harms of osteoporosis medications in patients with chronic kidney disease (CKD), there was insufficient evidence to determine efficacy among patients with G3 to G5 CKD .

Miller PD. Diagnosis and treatment of osteoporosis in chronic renal disease. Semin Nephrol 2009; 29:144.

EFFICACY

Antiresorptive agents Bisphosphonates

- **Compared with placebo-treated women, alendronate and risedronate increased bone mineral density (BMD) and prevented vertebral fracture regardless of degree of renal impairment.**

Thus, oral bisphosphonates appear to be effective in individuals with moderately reduced renal function.

- Zoledronic acid –

, **there were too few patients in the zoledronic acid .**
Zoledronic acid is contraindicated in patients with a creatinine clearance <30 mL/minute or in patients with evidence of acute renal impairment.

Coen G. Adynamic bone disease: an update and overview. J Nephrol 2005; 18:117.

Ibandronate – Ibandronate is also available in an IV preparation (3 mg IV every three months). However, there are no direct fracture efficacy data for IV ibandronate.

Denosumab — Denosumab, unlike bisphosphonates, is not cleared by the kidney and there is no restriction of its use in patients with creatinine clearances below 30 mL/minute, for whom bisphosphonates are considered contraindicated.
However, patients with CKD are at higher risk for hypocalcemia following denosumab administration than patients with normal renal function.
Thus, patients with CKD and creatinine clearance <30 mL/min should be monitored for hypocalcemia.

EFFICACY

Raloxifene is a less potent antiresorptive agent than bisphosphonates.

Compared with placebo, raloxifene improved BMD and reduced vertebral fractures, irrespective of kidney function. Within each category of kidney function, adverse events were similar between raloxifene and placebo.

In two small, short-term trials, raloxifene was effective in maintaining bone density in patients with G5 and G5D CKD.

Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. Nat Rev Endocrinol 2012; 8:529.
Tomiyama C, Carvalho AB, Higa A, et al. Coronary calcification is associated with lower bone formation rate in CKD patients not yet in dialysis treatment. J Bone Miner Res 2010; 25:499

Anabolic agents

— The administration of anabolic agents should be limited to patients with biopsy evidence of noniatrogenic adynamic bone disease and only by specialists in the field of CKD-MBD

Teriparatide — PTH 1-34 (teriparatide) is an effective antiosteoporosis drug that increases BMD and reduces fracture risk by stimulating bone formation

Teriparatide may be beneficial in patients with adynamic bone disease.

In a case report, teriparatide (20 mcg by subcutaneous injection daily) was administered to a patient with dialysis-dependent CKD who presented with multiple painful fractures and bone histomorphometry showing low-turnover bone disease. Bone pain resolved within six months, and after 24 months, bone histomorphometry showed improvement in parameters of bone formation.

The teriparatide-induced improvement in parameters of bone formation may be mediated by its effect on sclerostin. Idiopathic renal adynamic bone disease is associated with elevated serum sclerostin, an osteoblast inhibitor.

PTH inhibits sclerostin binding to osteoblasts, thereby promoting bone formation.

In addition, the development of monoclonal antibodies to sclerostin, currently in phase III clinical development, might offer a targeted therapy for idiopathic renal adynamic bone disease.

Gal-Moscovici A, Popovtzer MM. New worldwide trends in presentation of renal osteodystrophy and its relationship to parathyroid hormone levels. Clin Nephrol 2005; 63:284.

Martin KJ, Olgaard K, Coburn JW, et al. Diagnosis, assessment, and treatment of bone turnover abnormalities in renal osteodystrophy. Am J Kidney Dis 2004; 43:558.

Abaloparatide — Abaloparatide (PTH-related peptide [PTHrP] analogue) is a second anabolic agent available for the treatment of osteoporosis.

Through different mechanisms of action than teriparatide, abaloparatide may have comparable effects to increase bone formation while inducing less bone resorption.

Abaloparatide's effect has not yet been examined in patients with GFR <30 mL/min.

Miller PD. Unrecognized and unappreciated secondary causes of osteoporosis. Endocrinol Metab Clin North Am 2012; 41:613.

THE END THANK YOU