Osteoporosis
Clinical Updates
www.nof.org Clinical Information for Healthcare Professionals Fall 2014

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Osteoporosis and Chronic Kidney Disease
As the Baby Boom generation ages, primary care practitioners are increasingly tasked with caring for patients with age-related comorbid conditions that impact bone strength. Two of the most common are osteoporosis and chronic kidney disease (CKD). Both of these disorders grow more prevalent with age and both disorders increase susceptibility for fragile bones and fractures. However, their distinct etiologies and pathophysiologies call for distinct diagnostic and treatment approaches. In patients with kidney-disease-related bone disorders, typical osteoporosis treatment may be harmful, not helpful. Other therapy and nephrology co-management may be needed.

Standard bone density testing can easily misidentify renal bone disease as primary osteoporosis.

What is the practitioner to do? This issue of “Osteoporosis Clinical Updates” brings into focus this clinical conundrum. It provides tools and suggestions for identifying those CKD patients who would benefit from treatment for osteoporosis in a general practice setting and who would be better served by referral to a specialist with experience in renal-related bone disease.

Editor-in-Chief, Angelo Licata, MD, PhD.

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Bone Health in Patients with Chronic Kidney Disease

Osteoporosis and the fractures it causes are very common in the older adult population. About one out of every two Caucasian women will experience a fragility fracture at some point in her lifetime, as will approximately one in five men. Many of the same people are also at high risk for chronic kidney disease. According to the CDC, one in ten American adults, more than 20 million, has some level of recognized CKD, most in the early stages of disease. Undiagnosed CKD is estimated to be even higher. Unfortunately, although studies show an increased awareness of CKD, early intervention is not widespread in primary care. Prevalence of both osteoporosis and CKD increase with age. As the US population ages, primary care providers are going to see greater numbers of patients who have osteoporosis, CKD, or both concurrently. While cardiovascular disease is a universally recognized complication of CKD, renal bone disease is not usually identified outside of specialist practices. However, patients with renal bone disease may present in primary care and be difficult to distinguish from those with osteoporosis. Like osteoporosis, renal bone diseases can cause low bone density and fragility fractures; however, drugs used to treat osteoporosis may make renal-related bone diseases worse, increasing fracture risk rather than reducing it. In addition, dual x-ray absorptiometry (DXA), used to diagnose osteoporosis on the basis of bone mineral density (BMD), cannot discriminate complex renal bone disease from primary osteoporosis and so may lead to misdiagnosis. Screening for metabolic bone disease in CKD patients in primary care is currently low, while use of potentially harmful drugs is widespread. It is increasingly important that general internists, family physicians, and other primary care providers identify which of their patients need evaluation for renal bone disease and which are candidates for osteoporosis therapies.

Overview of Chronic Kidney Disease and Bone Health

National Kidney Foundation (NKF) guidelines define CKD as glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for three months or more or as kidney damage regardless of GFR. The stages of CKD are described by GFR ranging from high (stage 1 with GFR ≥90 and evidence of kidney damage [i.e., elevated serum creatinine/urinary protein]) down to low (stage 5 with GFR <15, the level at which dialysis or transplantation may be necessary). The NKF recommends the use of the GFR number for communication between primary care and specialist physicians. The GFR number is also a tool for patient education, empowering them to take control of their kidney health in the same way that blood pressure and cholesterol numbers are used.

GFR declines with age in healthy individuals who do not have kidney damage. A study of healthy men conducted by the NKF found progressive decline in mean GFR from 105 at age 40, to 93 at age 50, to 58 by age eighty. Some forms of kidney disease don’t affect GFR but may harm bone. Disorders of this kind are characterized by abnormalities of serum and urine (e.g., phosphorus leakage or amino acid loss, acidosis due to tubular damage, etc.). As GFR goes down, fracture risk goes up. The large Study of Osteoporotic Fracture involving 9000+ postmenopausal women found that with no intrinsic renal disease, age-related decline in kidney function was responsible for a near doubling of fracture risk in women.

**Activity Objectives**

Upon completion of this CE material, the participant should be able to:

- Identify populations of patients seen in primary care most at risk for chronic kidney disease.
- Compare osteoporosis with renal bone disease in terms of diagnosis, disease process, treatment, and impact on skeletal health.
- Distinguish CKD patients who may benefit from standard osteoporosis therapies from those who may be harmed by them.
- Apply recommendations for management of mild-to-moderate CKD patients diagnosed with osteoporosis.
- Co-manage the bone health of CKD patients in coordination with nephrology or renal bone disease specialists.
with GFR of less than 65 mL/min/1.73 m² as compared to age-matched women with normal GFR.³ For this reason, the NKF recommends patients with moderate to severe CKD (GFR <60) be assessed for markers of renal bone disease — serum PTH, phosphorus, and ionized calcium levels and proteinuria are the most commonly used of these biomarkers.²

### Diagnosis of CKD

CKD is diagnosed by presence of a biomarker of kidney damage (such as persistent proteinuria) or evidence of abnormal kidney function (GFR) persistent for three months or longer.

In general practice, measurement of serum creatinine concentration is the standard approach to assessing GFR. On its own, serum creatinine may not provide a complete picture of kidney health. Creatinine is a waste product of muscle that varies by age, gender, body size, and race. As a result, in people with low muscle mass, a condition very common in the elderly or infirm, serum creatinine may appear normal even in the presence of low GFR. Creatinine levels rarely exceed reference thresholds until more than 50% of kidney function has been lost. Estimating GFR using a prediction equation that factors in variables of gender, age, race, and body size provides a more reliable measure of renal sufficiency.¹⁰,¹¹,¹² Both the Cockcroft-Gault and the MDRD (modification of diet in renal disease) calculations of GFR are highly correlated to GFR determinations by 24-hour urinary creatinine clearance.

Most commercial laboratories now provide estimated GFR (eGFR) calculations with serum creatinine either routinely or at the health care provider’s request.

### Table 2. Chronic Kidney Disease Stages and Probable Cause of Fragility Fracture

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR mL/min/1.73 m²</th>
<th>Probable Cause of Bone Loss/Fragility Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage# with normal or ↑ GFR</td>
<td>≥90</td>
<td>Primary/secondary osteoporosis</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage# with mild ↓ GFR</td>
<td>60-89</td>
<td>Primary/secondary osteoporosis</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>Primary/secondary osteoporosis/Renal bone disease</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>Primary/secondary osteoporosis/Renal bone disease</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
<td>Primary/secondary osteoporosis/Renal bone disease</td>
</tr>
<tr>
<td>5D</td>
<td>Kidney failure w/dialysis</td>
<td>&lt;15</td>
<td>Primary/secondary osteoporosis/Renal bone disease</td>
</tr>
</tbody>
</table>

# Damage due to injury, drugs, or disease. Markers of kidney damage include abnormal imaging, blood, or urine findings.
Easy-to-use calculators are also online and downloadable, such as the NKF’s estimator tool available at: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

The NKF endorses calculation of GFR by 24-hour urine assessment before management decisions are made regarding the use of bisphosphonates in patients with marginal eGFRs (e.g. ~25 mL/min).

Testing for excess urinary albumin (proteinuria) can be done with a spot urine (first morning is preferred) sample and urine dipstick (albumin/microalbumin). If positive, confirmation and follow up are indicated. The NKF and American Academy of Family Physicians recommend that, in general, patients with GFR below 30 or abnormal measures of PTH, phosphorus, or ionized calcium levels be referred to a nephrologist for further evaluation and management.\textsuperscript{16}

**Populations at highest risk for CKD**

There are multiple chronic medical conditions managed in primary care that cause or exacerbate CKD. Risk factors include family history of CKD, type 2 diabetes mellitus (T2DM), hypertension, heart disease, and advanced age (>60 years).

Other risk factors include obesity; autoimmune diseases; urinary tract and/or systemic infections; overuse of NSAID painkillers; and kidney loss, damage, injury, or infection. Women are at higher risk than men; and African Americans, Asians, Pacific Islanders, American Indians, and Hispanics are at higher risk than Caucasians.\textsuperscript{1,15} Socioeconomic factors also influence susceptibility to kidney disease. These factors include markers of poverty such as ethnic minority status, low birth weight, low income, and low educational attainment.

**Medical risk factors for CKD\textsuperscript{2}**

- Older age
- Family history of CKD
- Low birth weight
- Diabetes mellitus
- Hypertension
- Autoimmune diseases
- Systemic infections
- Urinary tract infections
- Urinary stones
- Lower urinary tract obstruction
- Cancer (either directly or resulting from nephrotoxic therapies)

- Nephrolithiasis
- Recovery from acute kidney injury
- Reduction in kidney size
- Exposure to certain drugs, toxins, and environmental factors

**Socioeconomic risk factors for CKD\textsuperscript{2}**

- U.S. racial minority status
- Low income
- Low educational attainment

Widespread underdiagnosis and undertreatment of CKD have been documented across the spectrum. In primary care, the patients most at risk with established risk factors such as diabetes are not being diagnosed with CKD, even when administered appropriate screening tests. This was the finding of a large study conducted by the NKF. The multisite cross-sectional study looked at survey, physical exam, medical history, and lab testing data for 9307 patients with diabetes. Five thousand of these patients had CKD (on the basis of urinary protein), but only 607 had been clinically identified. This pattern of underdiagnosis was evident regardless of clinician experience or number of patients seen per week.\textsuperscript{16}

Timely diagnosis and treatment of aggravating comorbidities, such as hypertension and diabetes, can help preserve kidney function and prevent complications that include stroke, cardiovascular disease, renal bone disease, fragility fracture, and kidney failure. Many of the chronic diseases linked to CKD are managed in

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**Figure 2. Causes of Kidney Failure.** This graphic shows data from the National Chronic Kidney Disease Fact Sheet, illustrating the breakdown of new cases of kidney failure by primary diagnosis in the United States in 2011. (Graphic source: Centers for Disease Control and Prevention (CDC). National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States, 2014. Atlanta, GA.)
primary care. As a result, renal function assessment of at-risk patients is an important component of primary care practice.

**Populations at High Risk for Osteoporosis**

There are many overlaps in risk factors for osteoporosis and CKD including older age, female gender, autoimmune disease, and type 2 diabetes. Many patients have both CKD and primary osteoporosis.

Risk factors for osteoporotic fracture included in the WHO Fracture Risk Assessment model [FRAX]:
- Advanced age (over 60 years)
- Female gender
- Prior fragility fracture — Any fracture in adulthood that occurred spontaneously or from low-impact trauma (a fall from standing height as opposed to a car accident). Fractures of face, fingers, and toes are excluded.
- Parental history of hip fracture — Hip fracture in the patient’s mother or father at any age.
- Current tobacco smoking — Only current tobacco smoking, not past.
- Long-term use of oral glucocorticoids — Current or past oral glucocorticoid use for 3+ months at ≥5mg/day prednisone (or equivalent).
- Low body mass index (BMI 18.5 kg/m²)
- Rheumatoid arthritis—Confirmed diagnosis.
- Other causes of bone loss—Type 1 (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption, and chronic liver disease.
- Daily alcohol consumption of three or more units daily — One unit roughly equals 8-10g of alcohol: 10 oz. beer (285mL), 1.5 oz. liquor (30mL), or 3-4 oz. wine (120mL).¹⁰,¹⁷

In addition to these risk factors, osteoporosis can be caused or made worse by a wide variety of medical conditions and medications used to treat them. For a list of risk factors, see Table 3.

Most patients with postmenopausal or age-related osteoporosis also have some decline in kidney function and may have mild to moderate CKD (GFR >30). While both osteoporosis and renal bone disease can lead to bone loss and fractures, these diseases have different etiologies and require different therapeutic approaches.

### Table 3. Medical Conditions Associated with Increased Risk of Osteoporosis

(For more detailed list see NOF’s Clinician’s Guide to Prevention and Treatment of Osteoporosis)

- AIDS/HIV
- Amyloidosis
- Ankylosing spondylitis
- Congestive heart failure
- Cushing syndrome
- Cystic fibrosis
- Diabetes mellitus
- Eating disorders (e.g. anorexia nervosa)
- Female athlete triad
- Gastrectomy
- Gastrointestinal bypass procedures
- Gaucher disease
- Hemochromatosis
- Hemophilia
- Hyperparathyroidism (primary or secondary)
- Hypogonadism, primary and secondary (e.g. amenorrhea)
- Idiopathic scoliosis
- Inflammatory bowel disease
- Kidney disease
- Lupus
- Lymphoma and leukemia
- Malabsorption syndromes (celiac disease and Crohn disease)
- Multiple myeloma
- Multiple sclerosis
- Organ transplants
- Parkinson’s disease
- Rheumatoid arthritis
- Severe liver disease, especially primary biliary cirrhosis
- Sickle cell disease
- Spinal cord injuries
- Stroke (CVA)
- Systemic mastocytosis
- Thalassemia
- Thyrotoxicosis

### Bone Disorders in Mild to Moderate CKD

Bone strength is dependent on a metabolic cycle of constant turnover through which old bone is removed and replaced with new bone. For this process to succeed in maintaining high-quality, fracture-resistant bone, turnover must balance removal with replacement, minerals must be deposited in a structurally sound matrix, and sufficient bone volume must be maintained to support skeletal demands. Any disruption of this complex process can lead to bones that are weak and susceptible to fracture.

**Renal Bone Disease.** Renal bone diseases results
Osteomalacia may occur in a setting of very high or very low bone turnover and is characterized by defective mineral deposition resulting from vitamin D deficiency and/or resistance. Post-transplantation syndrome is a multifactorial disorder due to pre-transplant bone disease and post-transplant hypophosphatemia, hypercalcemia, and immunosuppression.

**Osteoporosis.** In addition to these renal bone diseases, primary osteoporosis increases fracture incidence in patients at all stages of CKD. Primary osteoporosis is characterized by imbalanced remodeling in which resorption outperforms formation leading to progressive loss of bone mineral and strength.

Primary osteoporosis:
- Turnover: high
- Mineralization: low or normal
- Volume: low

In CKD patients with mild or moderate renal dysfunction (GFR >30), osteoporosis is the most likely cause of fragility fracture. In later stages of CKD (GFR <30), renal bone disease is a more significant cause. Fractures are particularly serious in these late-stage patients, in whom they confer a higher mortality risk than in persons with stage 1-3 CKD. Renal bone diseases can coexist with primary osteoporosis.

The National Kidney Foundation recommends that all patients with GFR <60 be evaluated for abnormalities associated with renal bone disease. These include serum PTH, phosphorus, ionized calcium levels, and urine protein/albumin. If any of these measures fall outside normal limits, referral to a nephrologist is generally recommended.

In women and men with normal kidney function, osteoporosis is diagnosed using World Health Organization (WHO) criteria based on measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) expressed in relation to a young-normal standard as a T-score, shown below.

<table>
<thead>
<tr>
<th>BMD T-score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score &gt;-1</td>
<td>Normal bone</td>
</tr>
<tr>
<td>T-score -1 to -2.4</td>
<td>Low bone mass (osteopenia)</td>
</tr>
<tr>
<td>T-score &lt;-2.5</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Low trauma fracture</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

While osteoporosis is readily identifiable in patients with mild renal impairment, it can be obscured in

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**Table 4. Medications Associated with Reduced Bone Mass in Adults**

(For more detailed list see NOF’s Clinician’s Guide to Prevention and Treatment of Osteoporosis)

- Aluminum
- Anticoagulants
- Anticonvulsants (phenobarbital, phenytoin)
- Aromatase inhibitors
- Cancer chemotherapeutic drugs
- Glucocorticoids and adrenocorticotropic
- Gonadotropin-releasing hormone agonists
- Heparin
- Immunosuppressants
- Lithium
- Progesterone (parental, long-acting)
- Proton pump inhibitors (PPIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Tamoxifen (premenopausal use)
- Thiazolidinediones

*Some risk associated with these medications is dose dependent.
patients with advanced CKD. In fracturing patients with GFR <60 with serum or urine abnormalities suggestive of renal disease, referral to a renal bone specialist is recommended.

In patients with early CKD (GFR >60) and no evident CKD-related urine or serum abnormalities, fragility fractures are far more likely to be due to osteoporosis than to renal bone disease.20,21 In patients with GFR <30, renal bone disease is the more likely cause. Consequently, the NKF recommends applying standard diagnostic criteria for osteoporosis in patients with early CKD (e.g. presence of low-trauma fracture and/or DXA T-score ≤-2.5) assuming there are no biochemical abnormalities to suggest the concomitant presence of renal bone disease.22 In this setting, DXA T-score is as predictive of fracture as it is in individuals with normal kidney function.4,23

It is generally recommended that patients with GFR <60 plus markers of kidney damage as well as all patients with GFR <30 be referred to nephrologists with expertise in renal bone disease. Bone biopsy is often used to identify specific forms of renal bone disease such as adynamic bone disease.

Options for Treating Osteoporosis in Patients with Mild to Moderate CKD

Determining whether a CKD patient’s fracture is caused by osteoporosis or a form of renal bone disease is the first step in identifying the most appropriate treatment. While GFR cannot definitively rule out renal bone disease, it should be measured before treating with an osteoporosis drug. This is critically important because the most widely prescribed osteoporosis medications slow bone turnover, which may actually increase fracture risk in a patient with adynamic bone disease or osteomalacia.4 Markers of renal bone disease should be measured in patients with GFR <30. Those with abnormal levels of serum PTH, phosphorus, and ionized calcium or persistent proteinuria should be referred for further evaluation.

Markers of renal bone disease (NKF recommends testing if GFR <60):

- Serum: Abnormal levels of PTH, phosphorus, ionized calcium, and vitamin D
- Urinalysis: Abnormal random spot urine test for proteinuria

CME Program Eligibility

Method of Participation in the Learning Process: Clinician learners will read and analyze the subject matter, conduct additional informal research through related internet searches on the subject matter, and complete a post-test assessment of knowledge and skills gained as a result of the activity.

After participating in this activity, the reader has the option of taking a post-test with a passing grade of 70% or better to qualify for continuing education credit for this activity. It is estimated it will take 1.0 hour(s) to complete the reading and take the post-test. Continuing education credit will be available for two years from the date of publication.

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Due to the lack of data from large-scale controlled clinical trials, uncertainty exists regarding the safety and effectiveness of pharmacologic therapy for osteoporosis in patients with advanced CKD. However, pivotal osteoporosis drug trials randomized patients down to GFR of 30 (stage 1 to mild stage 3). As a consequence, it is generally accepted that pharmacologic management of osteoporosis in patients GFR >30 and normal PTH, calcium, and phosphate does not differ from that of postmenopausal women with normal GFR. Data do not exist to support use of these medications in patients with stage 1-3 CKD who have abnormal PTH and mineral indices and/or patients with stage 4-5 CKD. In general, these patients should have renal/metabolic abnormalities corrected under specialist care.

There are multiple FDA-approved drugs for prevention and/or treatment of osteoporosis in people with normal GFR—in alphabetical order: bisphosphonates, conjugated estrogens/bazedoxifene, denosumab, estrogens and/or hormone therapy, estrogen agonist/antagonist, raloxifene, and teriparatide. All of these medications require adequate calcium and vitamin D for maximal efficacy.

Bisphosphonates. (alendronate, alendronate plus D, ibandronate, risedronate, and zoledronic acid). The use of bisphosphonates to treat osteoporosis in populations with mild to moderate renal disease (GFR 90-30) requires first ruling out or correcting metabolic disturbances (vitamin D, phosphorus, PTH, calcium). Current US FDA product labeling strongly advises against using oral bisphosphonates in patients with GFRs below 30 mL/min (late stage 3 to stage 5 CKD). In patients with moderate to severe CKD (stages 3-5D, GFR <30 mL/min), bisphosphonates have traditionally been avoided because they rely on renal elimination. However, recent analysis of pivotal trials and their extension studies of bisphosphonates have reported no evidence of renal deterioration or damage in patients on oral alendronate, risedronate, and ibandronate for postmenopausal osteoporosis. Transient elevation in serum creatinine has been reported in patients receiving intravenous ibandronate and zoledronic acid; however, studies show treatment with these agents does not result in long-term renal deterioration or accelerated disease progression. (There have been a few case reports of renal failure in CKD patients with IV bisphosphonate drugs.)

The graphics below reflect data from one of the post-hoc analyses of oral risedronate safety and efficacy in patients with compromised renal function, from mild CKD (GFR 80-50 mL/min) down to severe CKD (GFR <30 mL/min). As you can see, a daily dose of 5 mg risedronate over two years, while not significantly changing creatinine clearance, did significantly reduce fractures equally across all stages of CKD.

Several osteoporosis therapeutics do not require renal clearance and so may be safer for CKD patients. These include conjugated estrogen/bazedoxifene, denosumab, estrogen, salmon calcitonin, and teriparatide.

Conjugated Estrogens/Bazedoxifene. Sold under the brand name Duavee®, conjugated estrogens/
Salmon Calcitonin. Salmon calcitonin, sold under the brand names of Miacalcin and Fortical, can be prescribed in this population regardless of CKD stage of renal function. However, it has also been shown to have a less robust effect on vertebral fracture risk than other agents and, because calcitonin has not been shown to reduce risk of non-vertebral fracture, it has limited benefit for patients at higher risk for non-vertebral fracture.\textsuperscript{35,36}

Prescribing information for Miacalcin\textsuperscript{®} and Fortical\textsuperscript{®} products was revised in 2014. New language states that since fracture reduction efficacy has not been demonstrated, these drugs should be reserved for patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies).\textsuperscript{36}

New labeling also includes a warning of increased overall malignancy risk associated with Miacalcin\textsuperscript{®}/Fortical\textsuperscript{®} as observed in meta-analysis of 21 clinical trials.\textsuperscript{36} The magnitude of this increased risk was (4.1\%) compared with placebo-treated patients (2.9\%).

Raloxifene. Raloxifene is in a class of drugs called estrogen agonist/antagonists (formerly known as SERMs). Sold under the brand name Evista\textsuperscript{®}, raloxifene is approved by the FDA for prevention and treatment of osteoporosis in postmenopausal women. Raloxifene is potentially a good choice for treating osteoporosis in CKD patients. Analysis of data from the large three-year multicenter, randomized, placebo-controlled MORE trial found raloxifene’s documented benefits to bone were similar in women with normal kidney function and in those with CKD, regardless of estimated GFR. In addition, rates of adverse effects were comparable for placebo and raloxifene groups across all CKD levels. (Patients with more severe CKD had more adverse events with or without raloxifene.)\textsuperscript{31}

Prospective studies will define the potential renal safety for denosumab in patients with even more severe renal failure.\textsuperscript{33}

Estrogen. Data from the Women’s Health Initiative confirm the efficacy of estrogen in reducing the risk of both vertebral and hip fracture.\textsuperscript{34} It is possible that lower-dose estrogen may be effective in preventing bone loss in postmenopausal women with CKD. However, since estrogen may increase the risk for endometrial bleeding, stroke, and deep vein thrombosis, it should be used with caution, especially in the stage 5 CKD population due to CKD-related cardiovascular complications.

Denosumab. Denosumab (Prolia\textsuperscript{™}) a human monoclonal antibody that specifically targets a mediator of bone turnover is approved for treatment of osteoporosis in postmenopausal women at high risk of fracture (e.g., history of osteoporotic fracture or multiple risk factors for fractures) and when other treatments have failed or are not tolerated. Denosumab may prove to be an attractive option for patients with CKD because it is not cleared by the kidney and has a fast on-set/off-set mechanism of action on bone tissue.\textsuperscript{31} In addition, post-hoc analysis of the registration clinical trial, found denosumab safe and effective for three years in patients with eGFR down to 15 mL/min.\textsuperscript{32} Prospective studies will define the potential renal safety for denosumab in patients with even more severe renal failure.\textsuperscript{33}

Bazedoxifene is a tissue-selective estrogen complex that combines conjugated estrogen with bazedoxifene, an estrogen agonist/antagonist.

In pivotal trials, conjugated estrogen/bazedoxifene increased mean lumbar spine BMD (1.51\%) and hip BMD (1.21\%) at 12 months compared to placebo in women who had been postmenopausal between one and five years.\textsuperscript{26,27,28,29} Like other products containing estrogen, it should be used for the shortest duration consistent with treatment goals and risks for the individual woman. When using this drug only for the prevention of osteoporosis, such use should be limited to women who are at significant risk of osteoporosis after considering alternatives that do not contain estrogen.

Subgroup analysis performed on data from pivotal randomized placebo controlled trials of bazedoxifene stratified by baseline eGFR observed no significant association between GFR and drug benefits or adverse events.\textsuperscript{30} It must be borne in mind that this study has limitations and that further investigation is needed to establish long-term safety and fracture benefit in CKD patients.

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**Teriparatide.** The only bone anabolic FDA approved for osteoporosis treatment is teriparatide, a recombinant formulation of human parathyroid hormone (1-34), sold under the brand name Forteo. Data from clinical trials on safety and effectiveness of teriparatide at 20 or 40 µg/day show no adverse effect on GFR in patients with mild to moderate impairment of renal function (eGFR down to 30 mL/min). In fact, GFR goes up a little because PTH is a vasodilator and increases renal blood flow. Contraindications to teriparatide treatment in patients with mild to moderate CKD include elevated pretreatment PTH, hypercalcemia, and unexplained elevated bone-specific alkaline phosphatase. There is currently no data on use of PTH in patients with GFR <30 mL/min.

**Other Management Considerations**

Treatment of patients with concomitant osteoporosis and CKD should include the broader recommendations of calcium and vitamin D intake applicable to patients with postmenopausal osteoporosis: 1200-1500 mg/day of elemental calcium and adequate vitamin D to maintain 25-hydroxyvitamin D levels at least to values of 30 µg/mL. Pharmacologic vitamin D analogues and/or cinacalcet, a calcimimetic, that are used by nephrologists to reduce PTH levels in patients with CKD should be employed only by specialists familiar with their use.

**Patient Cases: Management of Osteoporosis in CKD Patients**

Diagnosing and treating osteoporosis in patients with kidney disease is a complex process. In patients with mild to moderate CKD (GFR 30-90), renal bone disease is excluded by normal urinary protein, serum PTH, phosphate, and calcium levels. With renal bone disease ruled out, diagnosis and treatment with an FDA-approved osteoporosis drug can proceed as it would in patients with normal GFR.

In patients with more severe disease (GFR <60) or those with persistent proteinuria and/or derangements of PTH, phosphate, and calcium, a form of renal bone disease should be suspected and referral to a nephrologist is recommended.

In the following case vignettes, we will examine typical patients and discuss the pros and cons of various pharmacologic options for treating bone loss and preventing fragility fractures in patients with chronic kidney disease.

**Case 1: 72-Year-Old Postmenopausal Woman**

The first patient we will discuss is a healthy 72-year-old African American postmenopausal woman who consults her clinician following wrist ultrasound measurement done as a part of a community health screening. The patient is otherwise healthy and was surprised that the ultrasound T-score indicated osteoporosis. (Note: The United States Prevention Services Task Force recommends osteoporosis screening in all postmenopausal women 65 and older regardless of additional risk factors).

The patient’s medical history is as follows:
- Age: 72 years
- Height by stadiometer: 5’2” (at age 25 baseline 5’5”)
- Weight: 102 lbs (low BMI)
- Race: African American
- Mild hypertension controlled by ACE inhibitor
- Natural menopause at age 52 years
- Lives at home with husband
- No family history of hip fracture
- Drinks fewer than 5 alcoholic beverages/week
- Has never smoked
- Takes 500 mg calcium/day as calcium carbonate
- Takes 400 units vitamin D daily (in calcium tablets)
- Rarely exercises, but has active life gardening, walking dog, etc.
- No hormone replacement
- No history of falls
- No history of fracture as adult
- No history of serum abnormalities (creatinine, BUN, CBC, etc.)

Should this patient be diagnosed with osteoporosis on the basis of the wrist ultrasound?

No. Peripheral screening tests cannot accurately diagnose osteoporosis. A central DXA test of the hip and spine is needed.

Are there factors in her clinical assessment that indicate elevated risk for osteoporosis?

Yes. The patient has been postmenopausal for 22 years and has not taken hormone replacement or other medications that prevent bone loss. She has low BMI. She has a stadiometer-measured height of 5’2” and reports a height of 5’5” at age 25 years. Assuming accuracy
Is there reason for the clinician to suspect CKD?
Yes. The patient has several risk factors for CKD. She is female and African American; she is hypertensive and over age 70. Currently, measurement of GFR is not a standard of care for patients presenting with postmenopausal osteoporosis who have serum creatinine concentration within the laboratory’s normal reference range. However, since GFR may be below 30 mL/min in many seemingly healthy postmenopausal women over age 70 it would be useful to determine eGFR.

What tests would help the clinician get a clearer picture of this patient’s bone health?
The clinician orders a comprehensive blood and urine workup: CBC, ESR, CRP, and metabolic panel, including serum creatinine and markers of CKD-induced bone disease and proteinuria. Estimated GFR is requested.

Her test results are as follows.
Serum creatinine concentration is measured as 1.3 mg/dL (normal laboratory reference range: 0.5-1.5 mg/dL). Her eGFR is 29 mL/min (stage 4 CKD), a normal PTH, ionized calcium, phosphate, normal urinary protein and negative workup for secondary causes of osteoporosis.

The patient’s DXA results show BMD diagnostic of osteoporosis by WHO criteria:
Hip: 0.67 g/cm² and 0.68 g/cm²; T-score -3.3/-3.2 (left/right femoral neck)
Lumbar spine: 0.78 g/cm²; T-score -2.8
The x-ray reveals two vertebral compression fractures.

Does the patient have osteoporosis?
Based on WHO criteria this patient has severe osteoporosis. The presence of vertebral fractures, even when asymptomatic, signals a much greater risk for future vertebral and non-vertebral fractures.43,44,45

What factors could be affecting this patient’s GFR?
Many elderly patients have a low GFR as a function of aging. As a result, a large proportion of the elderly population we treat for postmenopausal osteoporosis may have a low GFR even to levels where oral bisphosphonates are not advised by the FDA. Yet these low GFR levels may go undetected because of serum creatinine concentrations in the normal reference range. (Creatinine won’t usually exceed normal values until GFR has declined by half.)

Should this patient be referred to a renal specialist?
Even though this patient has eGFR diagnostic of stage 4 CKD (GFR 15-30) she may not need an in-depth work-up for renal bone disease because her serum and urine labs are unremarkable. If she had abnormal serum and urine markers of renal disease or GFR below 15 (stage 5 CKD), she would definitely be referred to a specialist.

If her follow-up spot urine checks are normal, the patient could be diagnosed with primary osteoporosis and age-related renal function decline.

What pharmacological therapy for postmenopausal osteoporosis would be best suited to this patient?
This is a complex problem. FDA guidelines warn against prescribing antiresorptive drugs for patients with such low GFR (<30) regardless of etiology. It would be best to refer this patient to a specialist for appropriate care and follow up. Because she is at high risk for additional fractures based on her age, low BMD, and prevalent vertebral fractures, this patient may benefit from bone preserving therapy under specialist care. This therapy may involve treatment with a nonbisphosphonate antifracture drug such as denosumab or teriparatide, along with adequate calcium and vitamin D.

What else can be done to reduce her fracture risk?
Given her low hip BMD and lack of extra body fat (at only 102 pounds), probably the greatest risk for fracture in this patient is falling. Protective hip pads could significantly reduce her risk if she does fall. Exercise that improves strength and balance would help her avoid falls, as would fall-proofing her house according to the earlier measurement, the patient has lost 3˝ in height. A loss of 3˝ in height is a “red flag” for osteoporosis as it may signify compression fractures of the spine.
to guidelines provided by the National Osteoporosis Foundation (at http://nof.org/articles/17 nof.org). Also of importance will be nutritional support that focuses on increased intake of protein, adequate calcium (from foods, preferably), and supplemental vitamin D as needed to raise serum 25-hydroxyvitamin D to optimal levels.

Case 2: 81-Year-Old Caucasian Male

The second case we will discuss is an example of co-management of a CKD patient by primary care and nephrology specialist. The patient is an 81-year-old Caucasian male. Two years ago, he was diagnosed with osteoporosis after suffering a hip fracture from a fall. At that time he was prescribed weekly 70 mg alendronate. His physical examination is significant for “frailty” defined clinically and a body mass index of 19 kg/m² (weight 110 pounds and height of 5’11”).

The patient’s medical history is as follows:

- Age: 81 years
- Height by stadiometer: 5’11” (at age 50 baselines 6’1”)
- Weight: 110 lbs
- Low BMI (19)
- Race: Caucasian
- Diagnosed with osteoporosis 2 years ago
- Personal history of hip fracture
- Takes proton pump inhibitor for GERD
- Currently on weekly 70 mg alendronate (2 years duration)
- Baseline BMD (2 years ago)
- Hip: 0.50 g/cm² and 0.51 g/cm²; T-scores -5.0/-4.9 (left/right femoral neck)
- Lumbar spine: 0.73 g/cm²; T-score -2.7
- Current BMD
- Hip: 0.52 g/cm² and 0.50 g/cm²; T-scores -4.8/5.0 (left/right femoral neck)
- Lumbar spine: 0.72 g/cm²; T-score -2.8
- Lives in retirement community with at home health support
- Drinks fewer than 5 alcoholic beverages/week
- Smokes cigarettes
- Sedentary lifestyle
- Personal history of falls
- eGFR 32 mL/min/1.73 m² (stage 3 CKD)
- Treated by renal specialist for CKD
His CKD is being managed by a nephrologist who reports a history of normal urinalysis, no proteinuria, a normal renal ultrasound, and no clinical risk factors for renal bone disease. The nephrologist recommends discontinuing bisphosphonate treatment because of the patient’s CKD and because his BMD had not changed (“not responding to treatment”).

The current patient’s serum and urine lab work was consistent with stage 4 CKD with normal serum creatinine concentration. In addition, his PTH is mildly elevated, which is consistent with the decrease in GFR. His lab values are remarkable for low calcium, low vitamin D, and high PTH.

**Laboratory findings:**

- Ionized calcium ................. 6.9 mg/dL  
  (normal 8.5-10.9 mg/dL)
- Phosphorus ...................... 3.5 mg/dL  
  (normal 2.4 - 4.1 mg/dL)
- Bone-specific alkaline phosphatase .... 100 U/L  
  (normal 20-140 IU/L)
- 25(OH) vitamin D .................. 20 ng/mL  
  (normal 30 – 80 ng/mL)
- PTH .................................. 80 pg/mL  
  (normal 10 - 65 pg/mL)
- Creatinine ...................... 1.3 mg/dL  
  (normal: 0.8-1.5 mg/dL)
- Hct ............................. 45%  
  (normal 40-50%)
- BUN .............................. 10 mg/dL  
  (normal 7-20 mg/dL)
- Serum Albumin .................. 4.5 g/dL  
  (normal 3.4-5.4 g/dL)
- Urine albumin .................... 6 mg/dL  
  (normal 0 to 8 mg/dL)
- eGFR ............................. 32  
  (stage 3 CKD: GFR 30-59)
- Serum Albumin .................. 4.5 g/dL  
  (normal 3.4-5.4 g/dL)
- Urine albumin .................... 7 mg/dL  
  (normal 0 to 8 mg/dL)
supplemental calcium only as needed to raise his total intake to the target of 1200 mg/day.

Calcium citrate is recommended over the patient’s calcium carbonate for its superior bioavailability in a setting of low gastric acidity. He is sent home with a handout of calcium rich foods (see end of article).

In addition, he is advised to take a daily vitamin D supplement of 600 units. His vitamin D serum level will be checked in a few months. This dosage may need to be increased to bring his level up to the recommended level of ≥30 µg/mL. Calcium and vitamin D repletion should help lower the patient’s PTH and have a net positive impact on his bone density.

**What management plan can be recommended?**
Assuming that secondary causes of osteoporosis have been excluded and the patient is compliant, it is probably not necessary to change anything at this time. It may be worthwhile to consider switching to daily injectable teriparatide after the patient has been on alendronate for five years as risk for rare adverse events increases with duration of alendronate treatment.

The clinician will continue to monitor BMD, fractures, and serum creatinine over time and reassure the patient. Urine and serum bone resorption markers can also be measured as an indicator of bone resorption suppression. It is possible that specific serum biomarkers of bone resorption may be preferable in a patient with low GFR because they are not affected by renal function. However, resorption markers should be interpreted with caution since most of the published data has not prespecified a population with GFR under 30 mL/min.

**What can this patient do to protect himself from future fracture?**
The biggest threat to this patient’s independence is falling again and breaking a hip. In someone his age, with a previous hip fracture, he is at high risk. Fortunately, the retirement community in which he lives conducts group exercise classes that are designed to build balance and strength in frail and elderly individuals like our patient. The clinician enthusiastically encourages the patient to pursue these classes, emphasizing the potential benefits of independence, overall health, and longer life.

**Case 3. 66-year-old Caucasian Woman with T2DM**
The third patient we will discuss is a 66-year-old Caucasian woman whose medical history is remarkable for type 2 diabetes (T2DM) and hypertension controlled by medication. She is concerned about her risk of osteoporosis following the hip fracture of her older sister. She has never had her GFR estimated from serum creatinine. She has also not had a bone density scan.

The patient’s medical history is as follows:
- Age: 66 years
- Height by stadiometer: 5’3” (at age 58 baseline 5’5”)
- Weight: 160 lbs
- Race: Caucasian
- Natural menopause at age 55 years
- Lives at home with husband
- Family history of hip fracture
- Drinks fewer than 5 alcoholic beverages/week
- Has never smoked
- Eats balanced calcium-rich diet and supplements with 500 mg calcium/day as calcium citrate
- Takes 400 units vitamin D daily (in calcium tablets)

**STEP 1: Estimate calcium intake from calcium-rich foods**

<table>
<thead>
<tr>
<th>Product</th>
<th># of Servings/d</th>
<th>Estimated calcium/serving, in mg</th>
<th>Calcium in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (8 oz.)</td>
<td>X 300 =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogurt (6 oz.)</td>
<td>X 300 =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheese (1 oz. or 1 cubic in.)</td>
<td>X 200 =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortified foods or juices</td>
<td>X 80 to 1,000** =</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal =</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2: Total from above + 250 mg for non-dairy sources</th>
<th>+250 =</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Calcium =</strong></td>
<td></td>
</tr>
</tbody>
</table>

* About 75 to 80 percent of the calcium consumed in American diets is from dairy products.
** Calcium content of fortified foods varies.

**Figure 4. Patient-friendly calcium estimator.**
• Rarely exercises  
• Hypertension controlled with ACE inhibitor  
• Type 2 diabetes mellitus 10 years duration. Under good glycemic control.  
• No hormone replacement  
• No history of falls  
• No history of fracture as adult

Is this patient at risk for fragility fracture?
This patient has four prominent factors linked to increased fracture risk:  
• Diabetes type 2 (increased risk of hip fracture even with normal to high BMD)  
• Possible hypertension-, diabetes-, and/or age-related kidney function decline (increased risk of fracture independent of BMD)  
• Osteoporosis due to age and postmenopausal estrogen loss  
• Family history of hip fracture

What tests would help the clinician devise a management plan for this patient?
Blood and urine workup: CBC, ESR, CRP, and comprehensive metabolic panel, including estimated GFR by serum creatinine, markers of CKD-induced bone disease, and urinalysis.

She is referred for bone density scan by DXA and scheduled for a follow-up visit to discuss test results. She will have repeat spot urine protein check at that time. (Persistence of proteinuria over three or more spot tests is significant for kidney dysfunction.)

The patient’s test results related to markers of CKD, renal bone disease, and osteoporosis are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>25</td>
<td>stage 4 CKD</td>
</tr>
<tr>
<td>Total calcium</td>
<td>8.5 mg/dL</td>
<td>normal 8.5-10.9 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.8 mg/dL</td>
<td>normal 2.4 - 4.1 mg/dL</td>
</tr>
<tr>
<td>Bone-specific alkaline phospatase</td>
<td>490 U/L</td>
<td>normal 20-140 IU/L</td>
</tr>
<tr>
<td>25(OH) vitamin D</td>
<td>10 ng/mL</td>
<td>normal 30 – 80 ng/mL</td>
</tr>
<tr>
<td>PTH</td>
<td>565 pg/mL</td>
<td>normal 10 - 65 pg/mL</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>4.5 g/dL</td>
<td>normal 3.4-5.4 g/dL</td>
</tr>
<tr>
<td>Urine albumin</td>
<td>10 mg/dL</td>
<td>normal 0 to 8 mg/dL</td>
</tr>
</tbody>
</table>

Her DXA scan results are diagnostic of osteoporosis by WHO criteria: Hip 0.75 g/cm², T-score -2.5; Lumbar spine 0.79 g/cm², T-score: -2.1.

Is she at elevated risk for fragility fracture?
Yes. She has low BMD, diabetes, and probable CKD, all of which increase her fracture risk. Data show that T2DM increases risk of fracture independent of BMD (which tends to be higher than in patients without T2DM). It is speculated that fracture risk may be raised by diabetes-related bone deterioration and/or to falls caused by diabetes-related neuropathy and vision disorders.

Should she be treated for osteoporosis?
Not at this juncture. Her eGFR of 25 plus abnormal serum and urine albumin need further investigation. She is referred to a nephrologist for renal workup. She may have a form of renal bone disease that requires specialist management.

What can the clinician do to help this patient reduce her fracture risk?
There are many nonpharmacologic interventions that may significantly reduce fracture risk in this patient including the following:

Vitamin D and calcium repletion  
• Diet first, supplement as needed

Fall prevention  
• Fall-proofing home environment  
• Balance and strength training  
• Vision correction

Vitamin D repletion may help correct high PTH and alkaline phosphatase levels, slowing bone loss. In addition, fall prevention will be key. To this end, the patient is sent home with written instructions for fall-proofing her home. She will be monitored closely for peripheral neuropathy and advised to engage in exercise that increases balance and strength, such as dance, yoga, or swimming. Her vision will be checked and any appropriate corrections made.
Summary
As the U.S. population ages, primary care clinicians will see greater numbers of patients with impaired kidney function who suffer fragility fractures. Determining which of these patients would benefit from osteoporosis treatment and which should receive specialist treatment for a form of renal bone disease is essential to preventing fractures. Renal bone disease must be excluded before osteoporosis therapies can be employed. In patients with GFR 90-30 (stages 1-3 CKD), management decisions are the same as in patients with normal GFR as long as there are no biochemical abnormalities suggesting renal bone disease. In patients with GFR <30 (stage 4-5 CKD) and in high-risk patients who appear to have osteoporosis and not renal forms of bone disease, specialist use of off-label osteoporosis drugs for a limited period of time may be considered. All patients with GFR <15 and patients who have abnormalities of urine and serum suggestive of renal bone disease should be referred for specialist evaluation before initiating any antifracture therapy. All patients should be assessed for calcium and vitamin D status. Calcium should be acquired from food as much as possible with supplementation only as needed to reach daily target intake. Vitamin D should be supplemented as needed to reach target serum level of ~30 µg/mL. Because falls are the single most common cause of hip fracture in patients with skeletal fragility, measures to prevent falls are critical. All patients can benefit from regular exercise to improve balance and strength as well as correction of vision deficits, which can lead to falls.

References
6  Levey AS, Eckardt KU, TsukamotoY, et. al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease:


34 Cauley JA, Robbins J, Chen Z, Cummings SR, et. al; Women's Health Ini-


**Patient Education Resources**


National Osteoporosis Foundation. *Calcium and Vitamin D: What You Need to Know*. Available online at: http://nof.org/articles/10#CALCIUMSOURCES.
## Calcium-Rich Foods Patient Handout

<table>
<thead>
<tr>
<th>Calcium-Rich Food, serving size</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified oatmeal, 1 packet</td>
<td>350</td>
</tr>
<tr>
<td>Sardines, canned in oil, with edible bones, 3 oz.</td>
<td>324</td>
</tr>
<tr>
<td>Cheddar cheese, 1 1/2 oz. shredded</td>
<td>306</td>
</tr>
<tr>
<td>Milk, nonfat, 1 cup</td>
<td>302</td>
</tr>
<tr>
<td>Milkshake, 1 cup</td>
<td>300</td>
</tr>
<tr>
<td>Yogurt, plain, low-fat, 1 cup</td>
<td>300</td>
</tr>
<tr>
<td>Soybeans, cooked, 1 cup</td>
<td>261</td>
</tr>
<tr>
<td>Tofu, firm, with calcium, 1/2 cup</td>
<td>204</td>
</tr>
<tr>
<td>Orange juice, fortified with calcium, 6 oz.</td>
<td>200-260 (varies)</td>
</tr>
<tr>
<td>Salmon, canned, with edible bones, 3 oz.</td>
<td>181</td>
</tr>
<tr>
<td>Pudding, instant (chocolate, banana, etc.) made with 2% milk, 1/2 cup</td>
<td>153</td>
</tr>
<tr>
<td>Baked beans, 1 cup</td>
<td>142</td>
</tr>
<tr>
<td>Cottage cheese, 1% milk fat, 1 cup</td>
<td>138</td>
</tr>
<tr>
<td>Spaghetti, lasagna, 1 cup</td>
<td>125</td>
</tr>
<tr>
<td>Frozen yogurt, vanilla, soft-serve, 1/2 cup</td>
<td>103</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified with calcium, 1 cup</td>
<td>100-1000 (varies)</td>
</tr>
<tr>
<td>Cheese pizza, 1 slice</td>
<td>100</td>
</tr>
<tr>
<td>Fortified waffles, 2</td>
<td>100</td>
</tr>
<tr>
<td>Turnip greens, boiled, 1/2</td>
<td>99</td>
</tr>
<tr>
<td>Broccoli, raw, 1 cup</td>
<td>90</td>
</tr>
<tr>
<td>Ice cream, vanilla, 1/2 cup</td>
<td>85</td>
</tr>
<tr>
<td>Soy or rice milk, fortified with calcium, 1 cup</td>
<td>80-500 (varies)</td>
</tr>
</tbody>
</table>

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