

Bone Disease in CKD: A Focus on Osteoporosis Diagnosis and Management

Paul D. Miller, MD

Osteoporosis is defined as a condition of impairment in bone strength due to low bone mineral density and poor bone quality and predisposes individuals to an increased risk of fractures. Osteoporosis may coexist with chronic kidney disease—mineral and bone disorder (CKD-MBD) and osteoporotic fractures occur in all stages of CKD. Management of osteoporosis in CKD should consider the pathophysiology of both disorders. Diagnosis and management of osteoporosis in patients with stages 1-3 CKD and patients without CKD are similar, but diagnosis and management decisions differ greatly once patients have stages 4-5 CKD. Discriminating between osteoporosis and CKD-MBD is best accomplished with quantitative bone histomorphometry. Biochemical markers, especially intact parathyroid hormone and bone-specific alkaline phosphatase, also may be helpful. When the diagnosis of osteoporosis is established, management in stages 4-5 CKD may include antiresorptive or anabolic agents, though evidence for efficacy is marginal in advanced CKD.

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INDEX WORDS: Chronic kidney disease—mineral and bone disorder (CKD-MBD); osteoporosis; renal failure; bone histomorphometry; parathyroid hormone (PTH); bone-specific alkaline phosphatase.

CASE PRESENTATION

A 54-year-old white man with end-stage renal disease (ESRD) on peritoneal dialysis therapy for 5 years experienced a right hip fracture from a fall at home. His ESRD is related to kidney biopsy—documented idiopathic focal glomerulosclerosis. He also has had type 2 diabetes mellitus for 12 years, controlled by diet and exercise and oral antidiabetic therapy. After surgery and rehabilitation for hip surgery, he was referred for evaluation and management of metabolic bone disease.

The patient had no history of glucocorticoid exposure. He was not taking agents that could suppress parathyroid hormone (PTH) production. He had no history of weight loss or gastrointestinal diseases and no family history of osteoporosis. He did not smoke and consumed less than 2 ounces of alcohol weekly. There was no history of kidney stone formation.

On examination, the patient was 68" tall, weighed 154 lb, and had a good energy level and good proximal muscular strength, though his balance (tested by standing on 1 leg) was diminished. He had good peripheral vision and no neurologic, pulmonary, or cardiac findings.

The patient's laboratory data showed a normal biochemical profile. Specifically, total serum calcium level was 9.3 mg/dL; serum albumin, 4.1 g/dL; serum phosphorus, 4.5 mg/dL; total alkaline phosphatase (ALP), 85 (reference range, 10-120) IU/L; bone-specific ALP, 8 (reference range, 10-42) IU/L; and intact PTH, 154 (reference range, 15-65) pg/mL. Levels of biochemical markers of bone turnover, specifically serum CTX (carboxy-terminal crosslinking telopeptides of type I collagen) and PINP (procollagen type I amino-terminal propeptide), were 186

(reference range, 150-650) ng/mL and 54 (reference range, 20-108) µg/L, respectively. His 25-hydroxyvitamin D level was 30 (reference range, 0-100) ng/mL, and hemoglobin A_{1c} consistently was 7.8-8.8%. Femoral neck bone mineral density (BMD) classification by the World Health Organization (WHO) was T score of -3.8, defined as osteoporosis.

INTRODUCTION

Osteoporosis is defined by a consensus conference of the National Institutes of Health (NIH) as a condition of impairment in bone strength due to low BMD and poor bone quality (see Box 1 for a glossary of key terms).¹ Because bone quality cannot be measured in clinical practice, the operational definitions of osteoporosis are the occurrence of a low-trauma (fragility) fracture in women or men 50 years or older after other causes of bone fragility have been excluded (eg, osteomalacia and osteogenesis imperfecta).² In 1994, a second diagnostic criteria for osteoporosis was established. A working group of the WHO published their criteria for the diagnosis of osteoporosis by BMD criteria in individuals who have not yet had a fragility fracture.³ The osteoporotic label was called the T score (the number of standard deviations a person's BMD is below the mean BMD for the young healthy population) and the cutoff for the diagnosis was T score of -2.5 or lower. This cutoff was chosen based on the relationship between the lifetime risk of hip fracture in white women and the average T score from age 50-85 years is -2.5 at the hip. In other words, because the lifetime risk is 20% and assuming those 20% have the lowest T scores, the cutoff for osteoporosis was set at the threshold of the lowest T score quintile (ie, -2.5).⁴

The initial purpose of the BMD dual-energy photon densitometry (DEXA) WHO-derived classification

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

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Address correspondence to Paul D. Miller, MD, Colorado Center for Bone Research, Lakewood, CO 80227. E-mail: millercabr@aol.com

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Box 1. Glossary of Terms

- **Bone-specific alkaline phosphatase (bone ALP):** An osteoblast-derived bone formation marker; however, bone-specific alkaline phosphatase may be elevated in other diseases in which bone formation is not increased or normal (eg, osteomalacia, Paget disease, cancer in bone).
- **Procollagen type I amino-terminal propeptide (PINP):** A more specific osteoblast-derived bone formation marker.
- **Renal osteodystrophy:** A quantitative histomorphometric classification of the bone diseases accompanying CKD.
- **Chronic kidney disease—mineral and bone disorder (CKD-MBD):** A term that embraces the systemic nature of the interactions between the metabolic bone diseases that accompany CKD linked to the pathophysiologic processes of vascular/soft tissue calcification.
- **Adynamic bone disease:** A quantitative histomorphometric-defined bone disease characterized by absent or very low bone turnover.
- **Bone turnover markers:** Serum or plasma biochemical markers that reflect the systemic levels of bone turnover (formation/resorption).
- **Mixed renal bone disease:** A quantitative histomorphometric classification of bone histomorphometry in CKD; mixed renal bone disease is a combination of defects in bone mineralization with features of high bone turnover.
- **Osteitis fibrosa cystica:** A histologic feature of hyperparathyroid bone disease characterized by increased bone resorptive cavities, increased osteoclast number, marrow fibrosis, and increased cortical porosity.
- **Osteomalacia:** A quantitative histomorphometric metabolic bone disease of diverse etiologies characterized by an increase in osteoid (matrix) surface (>80%), wide osteoid seams (>10 μm), and delay in mineralization lag time (>100 d).
- **Osteoporosis:** A systemic metabolic bone disease of diverse causes characterized by impaired bone strength and increase in fragility fracture risk. The impairment in bone strength is due to a combination of reduced bone mineral density and altered bone quality. Clinically, osteoporosis can be diagnosed by the occurrence of a fragility fracture, or in patients without fracture, by the World Health Organization dual energy x-ray absorptiometry diagnosis (T score) of -2.5 or lower at the spine, femoral neck, total hip, or forearm.
- **Parathyroid hormone (PTH):** The peptide hormone in the blood stream that regulates multiple end-organ functions, most importantly, serum calcium concentration.
- **Fibroblast growth factor 23 (FGF-23):** A peptide that is secreted by osteocytes whose most important biological function is regulation of serum phosphorus concentration by inducing phosphaturia. FGF-23 also has recognized functions to affect kidney production of 1,25 dihydroxyvitamin D synthesis, PTH production, vascular calcification, and bone turnover.
- **Sclerostin:** A glycoprotein released by osteocytes that regulates osteoblast activity and influences bone remodeling.
- **Tartrate-resistant acid phosphatase (TRAP5b):** An osteoclast cellular product that influences bone remodeling. TRAP5b serum or plasma concentration is a measure not of bone resorption as much as it is a measure of osteoclast number.

was to determine the prevalence of osteoporosis in the world's population in order to aid in health-economic planning. Soon after 1994, the T score made its way

into clinical use and also was included in the *International Classification of Diseases, Ninth Revision (ICD-9)* as a second means of diagnosing osteoporosis in individuals who had not yet had a fragility fracture. The clinical utility of the T score lies in its use as a risk factor for osteoporotic fracture. Fracture risk approximately doubles for each standard deviation the BMD is below -2.5 in untreated postmenopausal women compared to the same population of the same age with a T score of zero.

One limitation of the T score is that it does not define the cause of low BMD, and it should not be used as a stand-alone risk factor for making management decisions.⁵ Because low BMD captures $\sim 50\%$ of bone strength and at the present time, bone quality (the contributing factor for the other 50% of bone strength) cannot be measured clinically,^{6,7} the T score must be applied along with other validated risk factors for fracture that are independent of BMD level.⁸⁻¹³ Thus, the WHO also funded the development of the largest and most robust validated risk model to predict 10-year risk for major (colles, humerus, vertebrae, hip, and tibia) and/or hip fracture in untreated postmenopausal women. Nine validated risk factors, each an independent risk factor for fracture, were identified and statistically validated in FRAX (fracture risk assessment modeling; Box 2).³ The FRAX calculator can be accessed at the University of Sheffield WHO Collaborating Centre for Metabolic Bone Diseases (www.shef.ac.uk/FRAX/tool.jsp) and also by the International Society for Clinical Densitometry (www.iscd.org) or the National Osteoporosis Foundation (www.nof.org) websites.

Glomerular filtration rate (GFR) or estimated GFR (eGFR) is not included in the FRAX model. Because the sample size was not large enough, the WHO working groups could not validate the threshold level of GFR/eGFR related to the lifetime risk of hip fracture (analogous to the T score threshold of -2.5 used to relate BMD to hip fracture risk). However, it is important to stress that since FRAX data were completed and implemented, additional independent risk factors for fracture have been identified, such that in clinical practice, adding fracture risk to the risk calculated by FRAX alone is an important adjunct in management decisions.¹⁴ Included in this additional risk-factor group are the magnitude of bone remodeling (turnover), fall frequency, number and/or severity of morphometric vertebral fractures, T score at the lumbar spine, and glucocorticoid dose. Newer measurements of bone strength, by quantitative computed tomography (CT)-derived finite element analysis or by DEXA-derived trabecular bone score, were not included because these technologies postdated FRAX.¹⁵⁻¹⁷

Despite the exclusion of GFR/eGFR from FRAX, there is extensive literature that supports chronic

Box 2. Nine Validated Independent Risk Factors for 10-Year Risk of Fractures in Untreated Postmenopausal Women Identified in FRAX

1. Prior low trauma osteoporotic fracture after the age of 50 years
2. Increased age
3. Low bone mineral density
4. Long-term glucocorticoid use (current use)
5. Smoking
6. Maternal or paternal history of hip fracture
7. Rheumatoid arthritis
8. Heavy long-term alcohol consumption
9. Secondary causes of osteoporosis

Abbreviation: FRAX, fracture risk assessment modeling.
Source: Kanis et al.⁸

kidney disease (CKD) as a risk factor for increased fracture risk. A number of population studies and expert editorials provide evidence that CKD, even as early as stage 3 CKD, may be associated with a greater fracture risk than observed in age- and BMD-matched patients without CKD.¹⁸⁻²⁷ This greater risk may be related to interactions among the multitude of pathophysiologic biological changes that accompany CKD, such as secondary hyperparathyroidism, abnormalities in 1,25-dihydroxyvitamin D synthesis, phosphorus retention, chronic metabolic acidosis, and elevated sclerostin and/or fibroblast growth factor 23 (FGF-23) levels.²⁸⁻³² These accompanying biochemical changes may independently or collectively alter bone remodeling (turnover) or mineralization. Before the KDIGO (Kidney Disease: Improving Global Outcomes) working group coined the term CKD-mineral and bone disorder (CKD-MBD) to embrace the systemic pathology that accompanies altered bone turnover in this population, classification of the bone diseases accompanying CKD was defined by quantitative bone histomorphometry.³³ These histomorphometric classifications are still scientific and valid.^{34,35} Quantitative histomorphometry requires double tetracycline labeling in order to define dynamic bone turnover parameters, which have specific criteria for the specific type of renal osteodystrophy.³⁶⁻⁴¹ In contrast, CKD-MBD is difficult to define in clinical practice and does not have a specific ICD-9 diagnostic code or known relationship to fracture risk. Although it is known that the biochemical abnormalities accompanying CKD-MBD alter bone turnover or mineralization, which can influence bone strength, the operational clinical differentiation among the diseases accompanying CKD lies in distinguishing between adynamic bone disease, hyperparathyroid bone disease, mixed renal bone disease, osteomalacia, and osteoporosis, all of which may have low BMD and/or be associated with fragility (including hip) fractures.⁴²⁻⁴⁵ The challenge for physicians managing fragility fractures in patients with

CKD is discriminating fractures due to osteoporosis from fractures due to the traditional bone diseases accompanying CKD.⁴⁶

BMD AND USE OF FRAX AT DIFFERENT STAGES OF CKD

Stages 1-3 CKD

There are a number of reasons why the WHO criteria for diagnosing osteoporosis can be used across the spectrum of stages 1-3 CKD (GFR = 110-30 mL/min). First, all the clinical trials submitted to the US Food and Drug Administration (FDA) for approval of treatments for postmenopausal osteoporosis have randomly assigned patients using WHO criteria. In all these trials, some form of kidney function assessment was used to include or exclude participants. Exclusion criteria varied: baseline serum creatinine concentration < 1.27 mg/dL for the alendronate trials, 1.1 times the upper limit of normal for the risedronate registration trials, < 2.4 mg/dL for the ibandronate trials, and eGFR > 30 mL/min for the zoledronic acid and denosumab trials.⁴² Second, measurable derangements in bone and mineral metabolism that suggest the presence of CKD-MBD, such as secondary hyperparathyroidism or hyperphosphatemia, are less pronounced at a GFR > 30 mL/min unless there also are nonrenal-related causes of secondary hyperparathyroidism^{28-30,43-45} (Box 3). Third, neither serum PTH nor serum phosphorus was systematically measured at randomization in the whole populations constituting the osteoporosis trials discussed. Compared to placebo, all the therapies approved for the treatment of postmenopausal osteoporosis have efficacy across the range of kidney function defined by the randomization criteria for each trial.

Thus, there seems to be an understanding in the metabolic bone community that the WHO criteria for the diagnosis of osteoporosis can be applied in a similar manner in patients with stages 1-3 CKD as long as there are no kidney-related biochemical abnormalities suggesting CKD-MBD. Likewise, there is agreement that given the same list of risk factors, FRAX can be applied to stages 1-3 CKD in a manner

Box 3. Causes of Secondary Hyperparathyroidism

Familial hypercalcemia hypocalciuria
Vitamin D deficiency
Acute kidney injury
Chronic kidney failure
Lithium use
Celiac disease
Small-bowel diseases/resection
Hypercalciuria
Hypocalcemia

Source: Miller.³⁰

similar to that in the postmenopausal osteoporosis populations without known CKD, recognizing that more severe stage 3 (eg, stage 3B) CKD may have a greater risk for fracture than is seen in earlier phases of stage 3 (eg, stage 3A).⁴⁵⁻⁴⁸ The biology of bone in patients without CKD with osteoporosis is clearly different from that of patients with CKD with osteoporosis because measurable changes in molecules that affect bone metabolism (PTH, FGF-23, and serum phosphorus) may be seen in early CKD, even stage 2.^{31-34,47} However, it is unknown to what extent these early increases in levels of serum phosphorus regulatory peptides affect the ability to differentiate clinically between osteoporosis and CKD-MBD.

Stages 4-5 CKD

By the time a patient progresses to stages 4-5 CKD, derangements in bone metabolism become so dominant that the WHO criteria for the diagnosis of osteoporosis or the use of FRAX without a clinical adjustment for the greater fracture risk than calculated by FRAX alone become invalid. The WHO working group in 1994³ and the analysis of risk factors for fracture (FRAX) in 2001⁸ were confined to the condition of postmenopausal osteoporosis, and KDIGO's CKD-MBD guideline in 2009³³ was established 17 years after the T score was conceived in 1992. In addition, it took another decade after the pivotal WHO postmenopausal osteoporosis population studies for clinical societies, led by the International Society for Clinical Densitometry (ISCD) and the International Osteoporosis Foundation (IOF; which met in Bucharest, Romania, in October 2011), to acquire data that established the clinical capacity of the WHO criteria to be applied to specific populations other than postmenopausal osteoporosis, including elderly men and persons younger than 50 years if secondary conditions influencing bone strength were coexistent.¹⁵ The most recent ISCD Position Development Conference dealt with how to incorporate data into FRAX that had not been validated by the original WHO analysis⁴⁹; however, they concluded that they still did not have enough data to add CKD to the clinical risk log for calculating fracture risk. Nevertheless, clinical recognition of the higher fracture risk that is observed in severe (stages 4-5) CKD is useful because it emphasizes the additional risk that CKD-MBD derangements in bone metabolism add to management decisions that are intended to reduce risk. Therefore, it is critical that physicians faced with managing patients with CKD who have a fracture make the correct diagnosis. Management decisions differ if the patient has osteoporosis, as opposed to having one of the metabolic bone diseases, such as renal osteodystrophy or CKD-MBD, as defined by the KDIGO working group.

DEXA underestimates fracture risk in stages 4-5 CKD.^{21,29,43,45} However, more sensitive methodologies for measuring cortical bone of the radius or tibia, such as peripheral quantitative CT or high-resolution quantitative CT, perform better than 2-dimensional DEXA at discriminating between patients with and without fracture with stages 4-5 CKD (giving a receiver operating characteristic curve value of 0.78).⁴⁵ This greater differentiation may be related to the improved capacity of high-resolution 3-dimensional modalities to define bone size, bone microarchitecture, and cortical porosity compared to 2-dimensional (DEXA) measurements.

High-resolution radiologic tools that are capable of quantifying bone microarchitecture are scientifically valid and very important for research into bone quality measurements. However, they are not clinically useful or reimbursable at this time, and data derived from quantitated CT have not been validated in the same way FRAX has been validated, using central DEXA. Routine quantitative CT of the spine or femur has shown risk prediction for osteoporotic fractures similar to central (spine and hip) DEXA.^{16,45} Prospective studies need to be performed in large sample sizes of both sexes comparing 2- and 3-dimensional radiologic techniques, including the hip-derived quantitative CT bone strength analysis, finite-element analysis, and vertebral-derived trabecular bone score^{15,16} across a spectrum of CKD in order for there to be widespread application of 3-dimensional bone architecture measurement techniques in clinical practice.

Implications for Case

The 54-year-old man with ESRD presented in the clinical case introduced previously has osteoporosis, both as defined by WHO criteria and by the occurrence of a low-trauma hip fracture. As discussed in the previous sections, the 2 clinical criteria for the diagnosis of osteoporosis cannot be applied to stage 5 CKD. The diagnosis of osteoporosis in stages 4-5 CKD at the present time can only be an exclusionary one by excluding the other forms of renal bone disease that also may accompany CKD. Currently, this exclusion can be accomplished in 2 ways: by profiling biochemical markers of bone turnover or by double tetracycline-labeled quantitative bone histomorphometry (eg, transiliac bone biopsy).

BIOCHEMICAL MARKERS OF BONE TURNOVER

The human body remodels (turns over) bone at both cortical and cancellous sites. Bone remodeling is regulated by both systemic factors (eg, PTH, phosphorus, 1,25-dihydroxyvitamin D, circulating sclerostin, and perhaps FGF-23), as well as by local bone microenvironment factors (RANKL [receptor-activated

nuclear factor- κ B ligand], osteoprotegerin, sclerostin, insulin growth factors, and ephrin-B2/ephrin-B4).⁵⁰⁻⁵⁷ One major purpose of remodeling is to repair the microdamage that occurs in the skeleton with daily mechanical stress on bone. In clinical practice, there are a number of biochemical markers of bone turnover that can be measured in serum.⁵⁻⁶⁴ Bone resorption and bone formation markers can be measured. Data suggest that levels of specific serum bone-turnover markers, including serum PTH, may be able to help discriminate among the heterogeneous forms of renal bone disease.⁶⁵⁻⁶⁸ These serum bone turnover marker levels are valuable in assessing systemic bone turnover in postmenopausal osteoporosis, as well as in assessing the body's response to anti-resorptive agents (which inhibit bone turnover) or anabolic agents (which stimulate bone turnover).^{58,59,63,64,69,70} Box 4 lists bone turnover markers and divides measureable bone turnover markers into resorption and formation markers, recognizing that either group may be used interchangeably due to the inherent coupling between bone cell types, that is, osteoclasts, osteoblasts, and osteocytes.⁶⁹

Two markers that are not cleared by the kidney are the resorption marker (or more accurately, the osteoclast cellular number marker) tartrate-resistant acid phosphatase (TRAP5b; encoded by the *ACP5* gene) and the formation marker (or more accurately, the osteoblast activity marker) bone-specific ALP. For the osteoblast-derived marker PINP, there are 2 types of assays: one that measures the total (monomer and trimer) form of PINP (Roche Diagnostics) and one that measures only the intact trimeric form of PINP (IDS-iSYS Intact PINP chemiluminescent immunoassay [Immunodiagnostic Systems] and Orion Uni-Q PINP radioimmunoassay, available through Immunodiagnostic Systems). The trimer is not cleared by the kidney, whereas the monomer is cleared by the kidney. Currently, there are insufficient data to determine whether the difference in clearance between the 2 forms of PINP is enough to influence clinical use of the intact PINP in determining

osteoblast activity.⁷⁰ However, according to the pooled clinical teriparatide trial data, an increase in PINP level $> 10 \mu\text{g/L}$ at 3-4 months after the initiation of teriparatide therapy (20 $\mu\text{g/d}$) is highly correlated with improvement in BMD and/or bone microarchitecture.⁷⁰ The only FDA-approved assay for PINP, the Orion radioimmunoassay, is able to accomplish this important surrogate anabolic measurement because it measures the trimeric form.

Recently, a pivotal publication assessed the ability of serum PTH and/or bone ALP to discriminate among the different forms of renal bone disease.⁷¹ In this study, a large sample size of quantitative bone histomorphometry was analyzed along with the assays for tissue-specific ALP and serum PTH. The authors concluded that serum PTH level $< 150 \text{ pg/mL}$ (and even more so, $< 100 \text{ pg/mL}$) in dialysis patients not receiving therapies to lower serum PTH levels had a high positive predictive value for renal adynamic bone disease. Likewise, adynamic bone disease was suggested by a tissue-specific ALP level in the lower quartile of the laboratory reference range. At the other end of the spectrum, a high (6 times above the upper limit of the reference range) serum PTH level had a high positive predictive value for hyperparathyroid bone disease (osteitis fibrosa cystica), as did a high level of bone ALP. However, it should be kept in mind that a high bone ALP concentration also may be seen in a number of metabolic bone diseases that are not hyperparathyroid bone disease and can coexist in patients with stage 5 CKD, such as Paget disease or metastatic cancer of bone (Box 5). In the management of patients with stages 4-5 CKD and low T scores or fractures, adynamic bone disease probably is the most important disease to exclude, and here, the lower PTH and bone ALP levels may have discriminatory value. Discrimination between adynamic bone disease and osteoporosis is most important in the context of management of the patient with fracture with stages 4-5 CKD because in theory, the anti-resorptive agents used to treat osteoporosis would lower bone turnover when bone turnover is low to begin with.

Box 4. Bone Turnover Markers

Anabolic Markers

- Bone-specific alkaline phosphatase (bone ALP)
- Serum osteocalcin
- Serum or plasma procollagen type I amino-terminal propeptide (PINP)

Resorption markers

- Serum carboxy-terminal crosslinking telopeptides of type I collagen (CTX)
- Urinary amino-terminal crosslinking telopeptides of type I collagen (NTX)
- Tartrate resistant acid phosphatase (TRAP5b)

Source: Civitelli et al.⁵⁹

Box 5. Causes of Elevated Bone-Specific Alkaline Phosphatase

- Hyperthyroidism
- Hyperparathyroidism
- Osteomalacia
- Paget disease of bone
- Metastatic cancer in bone
- Recent large bone fracture
- Treatment with anabolic agents
- Space travel
- Severe immobilization

Source: Miller.³⁰

Implications for Case

Our patient's bone ALP level was in the lower quartile of the reference range and his serum PTH level was 154 pg/mL, values close to those suggestive of adynamic bone disease. He also has diabetes mellitus, a condition often associated with low bone turnover,⁷²⁻⁷⁴ and is on peritoneal dialysis therapy, also linked to low bone turnover.⁷⁵ Because his biochemical profiling and clinical conditions were both suggestive of adynamic bone disease, the gold standard for discrimination among the heterogeneous forms of renal bone disease was performed: quantitative bone histomorphometry.

BONE BIOPSY FOR QUANTITATIVE PURPOSES

Transiliac bone biopsy done with prior double tetracycline labeling is the most sensitive and specific means of discrimination among the various renal bone diseases³⁶⁻⁴¹ and, by exclusion, of making the diagnosis of osteoporosis.^{76,77} Transiliac bone biopsies are safe and have very low morbidity when performed by experienced operators. Tetracycline goes into bone attached to calcium and because it fluoresces under a fluorescent microscope, it is used as a means of quantifying certain dynamic parameters of bone turnover. The science underpinning quantitative histomorphometry is rooted in robust data sets defining normal bone turnover and abnormalities in bone turnover.^{34,35,40} Whereas hyperparathyroid bone parameters have a spectrum of histomorphometry according to the severity and longevity of the hyperparathyroid disorder, osteomalacia has a clear set of criteria required for its definition, and adynamic bone disease generally is considered to be a turnover disorder best defined by the absence of any single or double tetracycline labels (Fig 1).³⁷

Though bone biopsy is definitive in the diagnosis of osteomalacia, the disease also always has a biochemical

cause³⁰ (Box 6). Hence, if a patient has an unexplained elevated bone ALP level and has no other cause for it (Box 5), osteomalacia may be the most probable cause. If there are no identifiable biochemical abnormalities suggesting a cause for osteomalacia, bone biopsy is a definitive means for making the diagnosis.

Implications for Case

Our patient had levels of bone turnover markers that were not discriminatory enough to distinguish the cause of bone turnover, so a transiliac biopsy was performed and adynamic renal bone disease was diagnosed. Therefore, both the low T score and large fragility fracture were due in part to adynamic bone disease. The NIH definition of osteoporosis encompasses bone quality components associated with microarchitectural changes in bone, and in that regard, a component of our patient's impairment in bone strength might be due to osteoporosis as defined by the NIH. Adynamic bone disease is an important disorder to diagnose because there may be modifiable risk factors associated with it. In addition, treatment of osteoporosis in the presence of adynamic renal bone disease may allow for consideration of off-label use of an anabolic agent instead of an antiresorptive agent due to the pre-existence of absent bone turnover to begin with. Based on our patient's biopsy-proven adynamic bone disease of unknown cause ("idiopathic"), he received teriparatide off label. Use of this agent for adynamic bone disease is not evidence based, but may be considered in very high-risk patients with proven adynamic bone disease because it is the only FDA-approved agent at this time that has putative mechanism(s) of action to stimulate bone formation, including the inhibition of sclerostin binding to the osteoblast.^{52,53} Because osteocyte-derived sclerostin

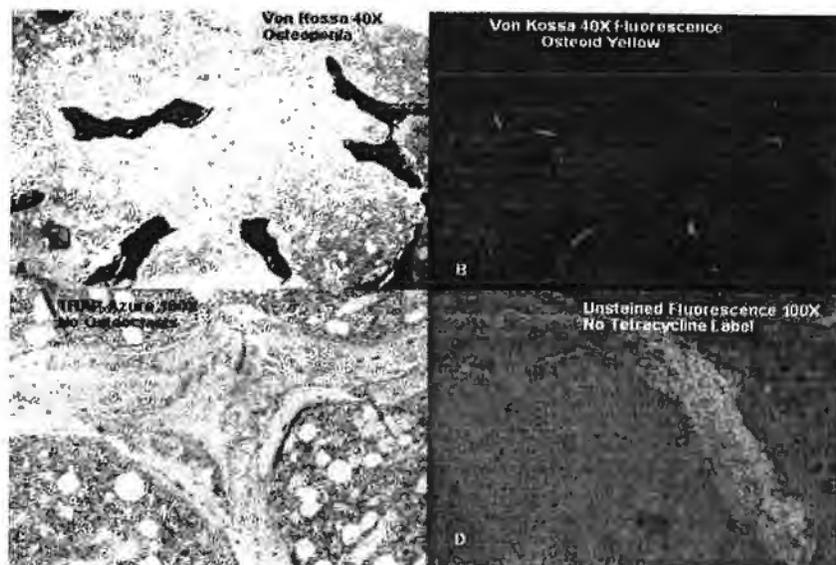


Figure 1. Histomorphometric characteristics of renal adynamic bone disease. (A) Von Kossa stain for calcified bone (small trabecular bone volume). (B) Von Kossa fluorescent osteoid (matrix) stain with very little osteoid; (C) TRAP Azure osteoclast stain with no osteoclasts. (D) Unstained fluorescence of a trabeculae with no tetracycline labels.

Box 6. Causes of Osteomalacia

Severe (<8 ng/mL) 25-hydroxyvitamin D deficiency
Low 1,25-dihydroxyvitamin D levels (with normal 25-hydroxyvitamin D)
Chronic hypophosphatemia
Renal tubular acidosis
Aluminum accumulation in bone
Long-term exposure to high fluoride levels
Oncogenic osteomalacia
Chronic kidney failure

Source: Miller.³⁰

serum levels have been shown to increase in CKD, it is possible that teriparatide might provide a bone formation benefit in patients with CKD with fractures.³²

TREATMENT OF OSTEOPOROSIS IN STAGES 1-3 CKD

Osteoporosis management and treatment for patients with stages 1-3 CKD should not differ from management and treatment for patients without CKD as long as there are no biochemical markers suggestive of the presence of CKD-MBD. All FDA-approved or off-label pharmacological therapies for osteoporosis were based on trials that contained individuals across the spectrum that defines stages 1-3 CKD (Table 1). Although greater detail for the use of bisphosphonates, denosumab, and teriparatide is described in the next section, mention should be made with regard to the use of calcitonin, estrogens, androgens, and selective estrogen receptor modulators here. Recently, an FDA advisory panel suggested that marketing of salmon calcitonin for osteoporosis be discontinued due to data suggesting a possible increase in the risk of gastrointestinal cancers. Estrogens are still approved for the prevention of osteoporosis, though the FDA suggests that other bone active agents are preferred over estrogens due to concerns that estrogen carries an increased risk of cardiovascular and breast cancer events. The selective estrogen receptor modulator raloxifene is FDA approved for treating postmenopausal osteoporosis, as well as invasive breast cancer.⁷⁸ Raloxifene has been documented to reduce the risk of vertebral fracture, but not of nonvertebral or hip fracture. Androgens also are of benefit to the skeleton and muscle (sarcopenia) and should be considered in hypogonadal men. However, the ratio of androgen benefit to risk should be considered with caution in the CKD population due to the relationship between androgen exposure and increased risk of prostate cancer.⁷⁹

TREATMENT OF OSTEOPOROSIS IN STAGES 4-5 CKD

Treatment of osteoporosis is an important consideration for patients who have experienced a fragility

fracture, due to the high mortality and morbidity associated with osteoporotic fractures, and even more so in the CKD population. Population data have confirmed the short- and long-term mortality associated with all fractures, including vertebral fractures, in both sexes.⁸⁰ This mortality is even greater in patients with CKD, probably associated with the overall greater mortality from all causes in severe CKD.

The main limitation of the FDA-approved pharmacological choices for osteoporosis is the lack of evidence for fracture risk reduction in patients with severe (stages 4-5) CKD, with the exception of a few post hoc analyses in smaller sample sizes of the trial cohorts for postmenopausal osteoporosis. This review focuses on the most widely used treatments: the antiresorptive agents (bisphosphonates and denosumab) and the only available anabolic agent, teriparatide.

Antiresorptive Agents

Antiresorptive agents are a class of agents that have a common pathway resulting in the inhibition of bone resorption.⁸¹ FDA-approved antiresorptive agents include calcitonin, estrogens, selective estrogen receptor modulators, bisphosphonates, and denosumab. Each antiresorptive agent has its own unique mechanism of action. Because bisphosphonates and denosumab are the most widely used antiresorptive agents for osteoporosis, they are focused on in this review.

Bisphosphonates are biological analogues of naturally occurring pyrophosphates, which in turn are degradation products of adenosine triphosphate metabolism. Pyrophosphates are metabolized rapidly by the ubiquitous presence of pyrophosphatases, whereas bisphosphonates are not metabolized. When they enter the blood stream, bisphosphonates are taken up rapidly by bone, the only tissue that binds bisphosphonates due to the physiochemical attachment.^{82,83} In bone, bisphosphonates inhibit bone resorption in 2 ways: by the physiochemical process of stabilizing the calcium-phosphorus surface and by the cellular process of inhibiting osteoclast activity (Fig 2).⁸² Bisphosphonates are cleared by the kidney by both filtration and active proximal tubular secretion.^{42,84,85} They are retained in bone in the remodeling resorption cavity and the amount of bisphosphonate retained probably is a function of the baseline remodeling space, the long-term rate of bone turnover, and GFR.

Although oral bisphosphonates are poorly absorbed (<1% of a single dose) and 50% of that is excreted by the kidney, intravenous bisphosphonate shows 100% bioavailability (again, with 50% of the intravenous dose excreted by the kidney). Oral bisphosphonates have never been shown to have kidney toxicity, whereas intravenous bisphosphonates, especially

Table 1. Pharmacological Agents Approved for the Treatment of Osteoporosis

Agent	Dose	Dose Adjustment in CKD	Use in CKD4-5	Mechanism	Notes
Injectable calcitonin (Calcimar)	0.5 mL/d SC	None	No adjustment	Inhibits bone resorption	No data for efficacy in CKD4-5
Nasal calcitonin (Miacalcin)	200 µg spray/d	None	No adjustment	Inhibits bone resorption	No data for efficacy in CKD4-5
Alendronate (Fosamax)	70 mg/wk	No adjustment for eGFR ≥ 30 mL/min; avoid for eGFR < 30 mL/min	Off-label use ^a	Bisphosphonate; inhibits bone resorption	Consider limiting exposure to <3 y in CKD
Ibandronate (Boniva)	150 mg/mo	No adjustment for eGFR ≥ 30 mL/min; avoid for eGFR < 30 mL/min	Off-label use ^a	Bisphosphonate; inhibits bone resorption	Consider limiting exposure to <3 y in CKD
Risedronate (Actonel or Atelvia)	150 mg/mo or 35 mg/wk	No adjustment for eGFR ≥ 35 mL/min; avoid for eGFR < 35 mL/min	Off-label use ^a	Bisphosphonate; inhibits bone resorption	Consider limiting exposure to <3 y in CKD
Zoledronic acid (Reclast)	5 mg/y IV over 15 min	Contraindicated for eGFR < 35 mL/min	Off-label use ^a ; only consider in very high-risk patients; reduce infusion rate to 30 min	Bisphosphonate; inhibits bone resorption	Slow infusion rate down to 30-60 min in advanced CKD
Denosumab (Prolia)	60 mg SC every 6 mo	None	Insufficient safety and efficacy data	Monoclonal antibody with affinity for RANKL; reduces osteoclast activity	Ensure normal vitamin D levels and calcium intake
Teriparatide (Forteo)	20 µg/d SC	None	Insufficient data on efficacy or safety in CKD4-5	Recombinant human PTH; stimulates osteoblast activity	Uncertain efficacy in advanced CKD; patients should have normal or explained bone ALP and not be hypercalcemic
Raloxifene (Evista)	60 mg/d	None	Use with caution	Selective estrogen receptor modulator; inhibits osteoclast activity	Safety and efficacy not established in patients with moderate or severe decreased kidney function

Abbreviations: ALP, alkaline phosphatase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IV, intravenous; PTH, parathyroid hormone; RANKL, receptor-activated nuclear factor-κB ligand; SC, subcutaneous.

^aOff-label use of IV bisphosphonates in patients with stages 4-5/5D CKD with osteoporosis and prevalent fractures: no dose adjustments; low infusion rate down to minutes.

zoledronic acid, may acutely reduce GFR by a tubular lesion that mimics acute tubular necrosis.⁸⁶ Although intravenous ibandronate, the only other intravenous bisphosphonate approved for osteoporosis, has not been shown in either clinical trials or postmarketing reports to have a negative effect on the kidney, there have never been head-to-head studies comparing effects on the kidney of these 2 bisphosphonates in healthy individuals or those with decreased GFR.^{42,87} Even zoledronic acid, when administered slower than the 15 minutes recommended by the product label, seems safe in clinical experience in patients with decreased GFR. Data from the zoledronic acid cancer trials suggest that the potential kidney damage that

can be observed with zoledronic acid may be related to dose and rate of infusion.^{88,89} Zoledronic acid given as a dose of 8 mg monthly versus 4 mg monthly and given over 5 minutes versus 15 minutes induced a large proportion of acute kidney failure not seen with the lower dose and slower infusion rate. These data would suggest that from a pharmacokinetic profile, the kidney damage might be related to the peak concentration of the drug, rather than to the area under the curve. Nevertheless, because 50% of absorbed bisphosphonates are cleared by the kidney and because of the lack of clinical trial data in patients with GFRs < 30 mL/min, bisphosphonates carry either a warning or a contraindication label for use in

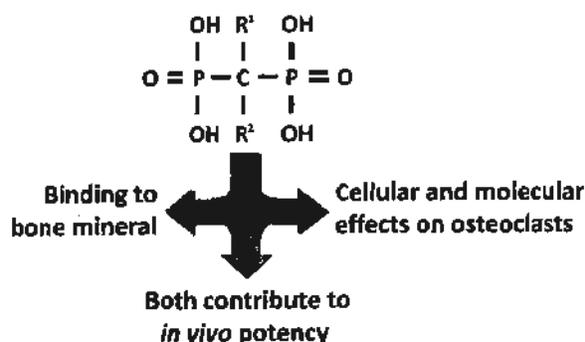


Figure 2. Mechanisms of action of bisphosphonates: physicochemical and cellular. Source: Russell et al.⁹²

patients with GFRs < 30-35 mL/min. Thus, use of bisphosphonates in patients with stages 4-5 CKD is an off-label use, but if given, they should be administered very slowly (eg, over 60 minutes).

In 2 post hoc analyses, one a pooled analysis of risedronate from 9 trials⁹¹ and the other an analysis of alendronate from the fracture intervention trial,⁹⁰ both these oral bisphosphonates in their original registration formulations (5 mg/d of risedronate and 10 mg/d of alendronate) were used in approximately 600 patients per trial (300 treated and 300 placebo) to treat patients with postmenopausal osteoporosis with estimated creatinine clearance (calculated by the Cockcroft-Gault formula) of 15-30 mL/min. In both trials, both bisphosphonates reduced the incidence of either morphometric vertebral fractures or all clinical fractures significantly compared to placebo over an average of 2.6 years' duration without any change in kidney function.^{90,91} The initial clinical trials developed for the FDA approval process did not require or measure eGFR or GFR as inclusion/exclusion criteria in any preplanned design, but only serum creatinine concentration. It took the osteoporosis community longer than the nephrology community to realize that a serum creatinine concentration may fall within a normal laboratory reference range, yet a patient with low body mass index may still have a significant reduction in GFR. Only the FDA approval studies for zoledronic acid and denosumab used eGFR as randomization criteria.

Bisphosphonates as a class should be administered for 3-5 years and then discontinued in lower risk patients, which sometimes is referred to as a bisphosphonate drug holiday. The FDA advises this strategy based on the lack of efficacy of bisphosphonates on fracture risk reduction beyond 5 years, as well as the appearance of bisphosphonate-associated atypical femur fractures with long duration of use, especially beyond 5 years.⁹² Although these atypical fractures are rare, they have a large morbidity. In addition, the risk for these atypical subtrochanteric

femur fractures decreases by at least 70% within the first year of bisphosphonate discontinuation, although the pharmacology of bisphosphonates indicates they are still being recycled.⁹³ The biological answer to why risk declines despite continual reduction in bone turnover is not known, but it is important for physicians to be aware that even though risk declines, it does not disappear. In that regard, patients should be made aware of a prodrome symptom that may precede the fracture displacement weeks before the break: a deep anterior thigh or groin pain that does not go away with rest or a supine position. In these cases, x-ray of the femoral shaft may reveal the classic stress fracture and periosteal reaction. In high-risk patients (those with femoral neck T scores -2.5 or lower) who have been on bisphosphonate therapy for 3-5 years, the FLEX (Fosamax [alendronate] Long-term Extension) trial suggests that the benefit of continuation seems to far outweigh the risks.⁹⁴ Recent publications on the bisphosphonate benefit to risk ratio provide helpful reviews of the large benefit that bisphosphonates may provide in postmenopausal osteoporosis when used in the right population for the right duration.^{95,96} For patients at high risk who have discontinued bisphosphonate therapy, the FDA advises switching to a different approved osteoporosis therapy with a different mechanism of action. Although there are no data for duration of bisphosphonate use in more advanced CKD, it seems logical that because bone retention may be greater in CKD, duration of use ideally would be shorter than 3-5 years.

Finally, there is a growing amount of retrospective cohort data suggesting that bisphosphonates may be associated with a reduction in all-cause mortality, including cardiovascular mortality.⁹⁷ If there is such a link, the mechanism is unknown, though bisphosphonates have been shown to alter cellular pathways in vascular endothelial cells that influence vascular calcification.⁹⁸⁻¹⁰⁰ These data are relevant to the issue of bone turnover and vascular calcification in CKD. Because there may be a link between low bone turnover and greater risk for vascular calcification in severe CKD,¹⁰¹ pharmacological lowering of bone turnover should be done in this population only if very low (eg, adynamic) bone disease has been excluded.

Denosumab is a fully human monoclonal antibody that binds to the osteoblast- (and osteocyte)-derived glycoprotein RANKL, inhibiting it from binding to the osteoclast membrane receptor RANK and thereby inhibiting osteoclastogenesis.^{102,103} Denosumab was FDA approved for postmenopausal osteoporosis in June 2010 and is a powerful and reversible inhibitor of bone turnover, which substantially reduces bone turnover marker levels and induces a transient complete loss of the histomorphometric appearance of

osteoclasts on biopsy.¹⁰⁴ Denosumab clinical trial data show complete reversibility of both bone turnover markers and BMD effect 6 months after administration of the 60-mg dose and a return to responsiveness with repeat administration (Fig 3).¹⁰⁵ The registration trials show strong evidence for fracture risk reduction in postmenopausal osteoporosis of all fractures (hip, nonvertebral, and vertebral) with the registered dose of denosumab (60 mg subcutaneously every 6 months).¹⁰⁶ In the extension trials of denosumab that have now been reported out through 8 years, there is a continual increase in BMD.^{107,108}

Because denosumab is metabolized (in the reticuloendothelial system) and the biological effect wanes after 6 months, it seems, but is not established to date, that denosumab treatment must be continued indefinitely to have a benefit. One of the fundamental limitations of all osteoporosis clinical trials is that the placebo arms cannot be continued indefinitely, especially in high-risk patients, so that after 3-5 years in most trials, the continual fracture benefit is always compared to the reduction in fracture risk seen with the original randomly assigned population.

From a safety standpoint, denosumab seems to be safe with long-term exposure. In the original clinical trial, the only significantly different safety signal in the treated group as opposed to the placebo arm were reports of skin "cellulitis," most of which cleared with topical or antibiotic therapy.¹⁰⁸ Nevertheless, because denosumab is a biologic and the RANKL-RANK system is ubiquitous throughout the body, general

immune suppression must be a safety consideration, especially in patients with immune suppression, including patients treated by other biologics and those who are posttransplantation. There is a paucity of data in these groups.

In addition, it has been observed that in hemodialysis patients, denosumab may induce significant hypocalcemia.¹⁰⁹ This hypocalcemic effect may be mitigated by ensuring adequate 25-hydroxyvitamin D levels and calcium intake.

In addition, for the population with kidney disease, there are additional considerations related to denosumab use. On quantitative bone histomorphometry in the original registration trials, there were significantly more patients who had no single tetracycline labels in the treated as opposed to the placebo groups.¹⁰⁴ Although absent single tetracycline labels may be seen in <5% of healthy individuals, the preponderance of absent labels with denosumab treatment suggests the absence in a subset of the clinical trial patients of bone mineralization during the drug administration. Though levels of bone turnover markers rebound to even greater than baseline within 6 months after discontinuation of denosumab therapy, it is unknown whether mineralization returned in the original registration cohort. In a separate nonregistration study, STAND (the Study of Transitioning From Alendronate to Denosumab), double labels were seen in patients exposed to denosumab after its discontinuation.¹⁰⁸ However, it is unknown whether these patients had absent labels at baseline. The point is that if

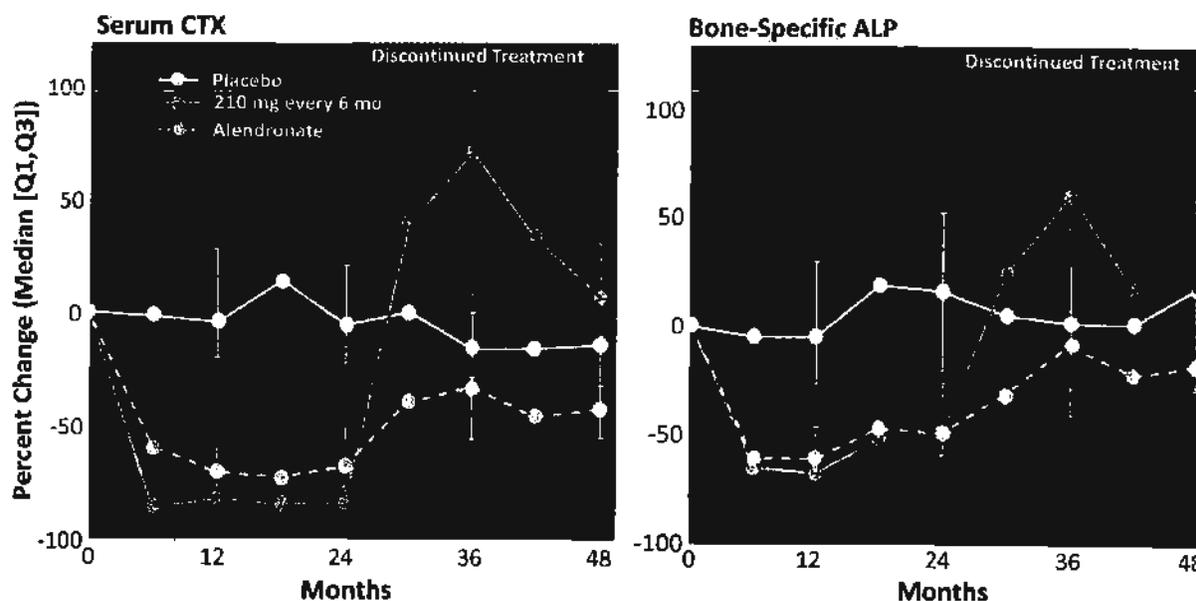


Figure 3. The rapid off-set of denosumab (anti-RANK [receptor-activated nuclear factor- κ B] ligand antibody) as assessed by an increase in the bone resorption marker C-telopeptide (CTX). For serum CTX graph, $*P < 0.001$ at month 36 and $P = 0.05$ at month 48 versus placebo. For bone-specific alkaline phosphatase (ALP) graph, $*P = 0.008$ at month 36 versus placebo. Data from Miller et al.¹⁰⁵

suppression of remodeling is a concern in patients with kidney disease with adynamic bone disease, and until we have more definitive data, denosumab should be avoided in stages 4-5 CKD unless the managing physician knows that the patient does not have pre-existing adynamic bone disease. The challenge is compounded in that denosumab has no FDA-mandated lower GFR warning or contraindication because denosumab is not cleared by the kidney. In addition, in post hoc analysis from the original denosumab registration trial, denosumab significantly increased BMD and reduced incident vertebral fractures in patients with GFRs as low as 15 mL/min.¹¹⁰ However, the issues of efficacy versus safety in these populations are separate considerations.

Finally, because vascular calcification is the major factor associated with death in the CKD population, a discussion of the data for vascular calcification in the denosumab trials is warranted. This is important because serum osteoprotegerin levels increase with denosumab administration as a regulatory response when RANK pathways are inhibited. There are conflicting and opposing data with regard to the influence of osteoprotegerin on vascular calcification.^{111,112} In the denosumab registration trial, vascular calcification was assessed by lateral lumbar spine x-rays done in order to assess for incident vertebral compression fractures. Data recently published suggest that vascular calcification scores did not change between the treated versus the placebo groups over the 3-year duration of the trial.¹¹³ Larger prospective trials are being designed to examine the relationship between denosumab use and vascular calcification, using a variety of more sensitive means to measure vascular calcification.

Anabolic Agents

The only anabolic agent FDA approved for the treatment of osteoporosis in women and men, as well as for the treatment of glucocorticoid-induced osteoporosis, is a recombinant protein encompassing the first 34 amino acids of human PTH (teriparatide).¹¹⁴⁻¹¹⁷ Teriparatide stimulates the formation of new bone by other cellular and regulatory pathways.¹¹⁸ The initial trial completed for FDA approval for postmenopausal osteoporosis lasted 18 months, 16 months shorter than the FDA requires for the approval of treatments for osteoporosis.¹¹⁹ The teriparatide trial was cut short in part due to the appearance of osteogenic sarcoma in the Fischer strain of rat, an animal model that predominately models rather than remodels bone. After many FDA advisory board hearings, the FDA concluded that this specific tumor is a rat-specific issue and wanted the sponsor (Eli Lilly and Co) to restart the trial, but many of the participants, now 6 months off the trial, had been started on other approved osteoporosis therapies. Hence, the

FDA granted approval based on 18-month data, due in part to their own decision to temporarily halt the trial and in part to the significant reduction in vertebral and nonvertebral fracture incidence seen in the registration trial by the 18th month.

The teriparatide registration trial, like other registration trials for osteoporosis, did not randomly assign participants with known stages 4-5 CKD. However, like the previously mentioned post hoc analysis for alendronate, risedronate, and denosumab that had subsets of the randomly assigned population with eGFRs as low as 15 mL/min, the teriparatide trials had small subsets with eGFRs as low as 30 mL/min.¹²⁰ In these subsets, there were similar increases in BMD and PINP values across tertiles of eGFR. Fracture numbers were too small to have power for statistical analysis across these 3 tertiles. There were no changes in kidney function as assessed by changes in serum creatinine or serum calcium concentrations as a function of eGFR during the registration trial with the approved 20- μ g/d or the higher 40- μ g/d doses of teriparatide. Although 24-hour urine calcium excretion increased on average ~50 mg/d greater than in the placebo group, there was no greater risk of clinical nephrolithiasis, though pre-existing kidney stones were an exclusionary criterion for trial randomization. Serum uric acid levels increased significantly more than in the placebo group, though the clinical consequences of this change in serum uric acid levels over the trial duration are unknown.

There are no data for the effect of teriparatide in individuals with stages 4-5 CKD or in individuals with bone biopsy-proven adynamic renal bone disease. The use of teriparatide in stages 4-5 CKD is off label and its use in known adynamic bone disease is predicated only on the knowledge that an anabolic agent can increase bone turnover and improve bone microarchitecture, shows a strong correlation with increases in BMD and fracture risk reduction, and is a disease for which there are no known therapies.¹²¹⁻¹²⁴ Hence, it is possible, though unproved, that teriparatide may have a beneficial role in idiopathic renal adynamic bone disease. It also is unknown whether teriparatide will have the same anabolic effect in patients with pre-existing secondary hyperparathyroidism. Baseline PTH levels were measured in only a small subset of the teriparatide postmenopausal osteoporosis registration trials and were normal. Hence, it is unknown whether sustained and uncorrected elevated PTH levels could mitigate the anabolic effect of teriparatide.

Implications for Case

Our patient, with biopsy-proven idiopathic renal adynamic bone disease, was administered teriparatide,

20 µg/d. Although there have been no additional fractures over the 2-year period, his PINP level increased 60 µg/L from baseline and his bone ALP level doubled from baseline 4 months after teriparatide therapy initiation, suggesting an anabolic response. In the postmenopausal osteoporosis registration trials for teriparatide, lumbar spine BMD returned to baseline 12 months after discontinuation of teriparatide therapy unless the patients were using a bisphosphonate, though there seemed to be maintenance in fracture risk reduction.¹²⁵ Our patient was started on treatment with low-dose risedronate (35 mg every other week) due to his low GFR and due to evidence in prior clinical trials that the 2.5-mg/d risedronate dosage reduced vertebral or hip fractures to the same degree as the registered 5.0-mg/d dosage.^{126,127}

CONCLUSIONS

The management of patients with fragility fractures across the spectrum of CKD should not differ between persons without reductions in eGFR or persons with stages 1-3 CKD, at least as it pertains to patients with age-related reductions in GFR. This suggestion is predicated on the absence of information that could suggest the presence of CKD-MBD. In patients with stages 4-5 CKD who have fragility fractures, the first management step is making the correct diagnosis. Diagnosis of osteoporosis in stages 4-5 CKD is an exclusionary one. Exclusion is best made by quantitative histomorphometry, a clinical science that is underused. Biochemical markers of bone turnover, in particular serum PTH and tissue-specific ALP, may provide differentiation between biopsy-proven adynamic renal bone disease, hyperparathyroid bone disease, and/or osteomalacia. The exclusion in particular of renal adynamic bone disease is important because 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 the beneficial or nonbeneficial effect of registered therapies for postmenopausal, male, or steroid-induced osteoporosis in very high-risk patients with stages 4-5 CKD who have sustained a low-trauma fracture.

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