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Fragility fractures in chronic kidney disease: An opinion-based approach

ABSTRACT

When a patient with chronic kidney disease suffers a fragility fracture, a key question is whether the patient has osteoporosis or, instead, renal osteodystrophy. Bone densitometry does not help in this distinction: biochemical tests, and sometimes also bone biopsy, are needed. However, even if the patient has osteoporosis, we have little evidence to guide our treatment decisions in cases of advanced chronic kidney disease.

KEY POINTS

If the patient's glomerular filtration rate (GFR) is at least 30 mL/min/1.73 m² and if no biochemical test results suggest renal osteodystrophy, osteoporosis can be diagnosed if the T score is less than -2.5 or if the patient has had a fragility fracture. These criteria can also probably be applied, though with less certainty, if the patient's GFR is as low as 15.

If the patient's GFR is less than 15 or if he or she is on dialysis, biochemical profiling often cannot distinguish among the heterogeneous forms of renal bone disease. In some cases of severe chronic kidney disease with fractures, bone biopsy is needed to rule out renal osteodystrophy and to diagnose osteoporosis by exclusion.

In the author's opinion, in patients with severe chronic kidney disease and fractures who have "osteoporosis" by exclusion, off-label use of bisphosphonates is an option, but only after very careful consideration.

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WHEN A PATIENT with chronic kidney disease sustains a fracture that is not due to trauma, the potential causes are many (TABLE 1). Chronic kidney disease predisposes patients to a gamut of conditions that make the skeleton more fragile; these are collectively known as *renal osteodystrophy* if we are speaking strictly of bone morphology, or *chronic kidney disease–mineral and bone disorder* if we are talking about the systemic condition.

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But even in chronic kidney disease, many fractures are due to postmenopausal or age-related osteoporosis, and estrogen-deficiency osteoporosis is the most common cause of fragility fractures overall.^{1–3} Osteoporosis can be diagnosed only after other causes of skeletal fragility have been ruled out. And how to diagnose and treat osteoporosis in the most severe stage of kidney disease is a matter of opinion, as we have almost no data to guide us.

Nevertheless, in the pages that follow, I will outline my admittedly opinion-based approach to diagnosing and managing the causes of fragility fractures in patients with chronic kidney disease.

T SCORES DO NOT DISTINGUISH THE CAUSES OF FRAGILITY

The most common cause of fragility fractures is osteoporosis due to estrogen deficiency.^{1–3} But since many other medical conditions can lead to osteoporosis, simple diagnostic criteria have been difficult to find.

Before 1994, the diagnosis of osteoporosis

TABLE 1

Common metabolic bone diseases associated with fragility fractures

Osteoporosis

(including all secondary causes of osteoporosis, including steroid-induced osteoporosis, after solid organ transplantation)

Osteogenesis imperfecta

Osteomalacia

Osteitis fibrosa cystica (severe)

Pathologic fractures (malignancies)

Severe renal failure (renal osteodystrophy)

Osteoporosis

Osteitis fibrosa cystica

Osteomalacia

Mixed osteodystrophy

Adynamic bone disease, including aluminum bone disease

Amyloid bone disease

Osteopetrosis

Paget disease of bone

Even in chronic kidney disease, many fractures are due to postmenopausal or age-related osteoporosis

was made on the basis of low-trauma fractures.⁴ Now, we use the World Health Organization criteria,⁵ based on bone mineral density T scores:

- Normal—a T score of -1.0 standard deviations or higher
- Osteopenia—a T score of less than -1.0 but higher than -2.5
- Osteoporosis—a T score of -2.5 or less
- Severe osteoporosis—a T score of -2.5 or less with a fragility fracture.

However, fractures can also be due to metabolic bone diseases that are not osteoporosis, including renal bone diseases.⁶⁻⁷ While a low T score or a fracture provides a working diagnosis of osteoporosis, it does not help distinguish the different types of osteoporosis and nonosteoporotic metabolic bone diseases. For example, osteomalacia and osteogenesis imperfecta can also cause fragility fractures and can be associated with low bone density. Using these criteria to define osteoporosis is even more problematic in patients with chronic kidney disease.

FIVE STAGES OF CHRONIC KIDNEY DISEASE

The National Kidney Foundation⁸ classifies the severity of chronic kidney disease on the basis of the glomerular filtration rate (GFR), as measured by 24-hour urine for creatinine clearance, or as estimated by the Cockcroft-Gault equation or, preferably, the Modification of Diet in Renal Disease (MDRD) equation (calculators are available at www.kidney.org/professionals/kdoqi/gfr_calculator.cfm):

- Stage 1—GFR 90 mL/minute/1.73 m² or higher
- Stage 2—GFR 60 to 89
- Stage 3—GFR 30 to 59
- Stage 4—GFR 15 to 29
- Stage 5—GFR lower than 15, or if the patient is on dialysis. (Another stage, called 5D, was added to the list to denote patients on dialysis, since the metabolic derangements in bone and systemic biology may differ between patients on dialysis vs those not on dialysis.)

This staging system is relevant to the discussion of bone fragility that follows.

CHRONIC KIDNEY DISEASE IS COMMON IN THE ELDERLY

The third National Health and Nutrition Examination Survey⁹ found that, at least as estimated by the Cockcroft-Gault equation, the GFR declines with age, so that by the age of 70 at least 20% of the US population has stage 4 or 5 chronic kidney disease.

Although the Cockcroft-Gault and MDRD equations may yield lower GFR values in the general population than one would get by measuring creatinine, inulin, or iothalamate clearance,^{10,11} the point is that both osteoporosis and chronic kidney disease are common.

THE GAMUT OF RENAL OSTEODYSTROPHY

In kidney failure (stage 5 chronic kidney disease), all forms of renal osteodystrophy may be associated with fragility fractures. Renal osteodystrophy can be defined by quantitative bone histomorphometry.^{12,13} The systemic conditions that may be associated with the

bone disease and systemic vascular disease (chronic kidney disease–mineral and bone disorder) are characterized by one or more of the following¹⁴:

- Abnormalities of calcium, phosphorus, parathyroid hormone, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft-tissue calcification.

The National Kidney Foundation¹⁴ classifies renal osteodystrophy on the basis of:

- Turnover—high, normal, or low
- Mineralization—normal or abnormal
- Volume—high, normal, or low.

Although this system helps us understand these diseases better, it does not provide a working diagnosis of osteoporosis.¹⁴

■ WHAT IS OSTEOPOROSIS?

In an attempt to define osteoporosis by a pathophysiologic mechanism, the National Institutes of Health¹⁵ have held two consensus conferences and have stated that “osteoporosis is a skeletal disorder characterized by impairment in bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality.”¹⁵ However, the consensus statement also does not provide a working diagnosis of osteoporosis—one that clinicians can apply to management decisions, and one that is also accepted by the US International Classification of Disease codes for reimbursement purposes.

The 1994 World Health Organization criteria offer the most pragmatic operational definition of osteoporosis, and they can be applied in both men and women, as well as in younger patients with medical conditions associated with increased risk of low-trauma fracture.^{5,16} Although the main purpose of these criteria was to advise international health authorities of the potential future economic impact of osteoporosis, the T score also became the pragmatic diagnostic threshold for defining normal, osteopenia, and osteoporosis in clinical practice.

The T score also calls attention to an important observation: of people who have fractures and subsequently undergo bone den-

sitometry, more are found to have osteopenia than osteoporosis. The reasons are that there are more people with osteopenia than osteoporosis,^{17,18} and many other factors independent of low bone mineral density contribute to bone strength.^{19,20}

How is osteoporosis diagnosed in stage 1–3 chronic kidney disease?

In patients with chronic kidney disease who develop fragility fractures, the reasonable question is: Is the cause of the fracture osteoporosis or some other metabolic bone disease associated with chronic kidney disease?

The National Kidney Foundation guidelines¹⁴ say that the diagnosis of osteoporosis can be established in patients with stage 1, 2, or 3 chronic kidney disease on the basis of either of the World Health Organization criteria, ie, a T score of -2.5 or lower or fragility fractures, as in the postmenopausal population, as long as there are no biochemical abnormalities that suggest chronic kidney disease–mineral and bone disorder.

How is osteoporosis diagnosed in stage 4 or 5 chronic kidney disease?

The answer is neither straightforward nor clearly defined in severe (stage 4 or 5) chronic kidney disease.

In stage 5 and especially in patients on dialysis, the derangements in bone and mineral metabolism become serious enough to impair bone strength and increase the risk of low-trauma fractures. The risk of hip fracture in stage 5 may be four times higher than in age-matched controls.^{21–24}

Adynamic, severe hyperparathyroid bone disease as well as osteomalacia can be associated with a higher risk of fragility fractures than in aged-matched controls in population studies of postmenopausal women or elderly men. These are bone fragility conditions that are not osteoporosis but that can mimic osteoporosis by the World Health Organization criteria.

Thus, when a patient in stage 5 has severe fragility fractures that by themselves may be life-threatening, it is reasonable to ask if the drugs that reduce the risk of fractures in many other osteoporotic conditions (postmenopausal, steroid-induced, elderly male osteoporosis,

More people who have fractures have osteopenia than osteoporosis by World Health Organization criteria

In stage 5 chronic kidney disease, the risk of hip fracture is up to 5 times higher

after solid organ transplantation) can also be used in patients with advanced chronic kidney disease.

The diagnosis of osteoporosis in these patients has no universally accepted criteria. The diagnosis is best suggested by excluding other forms of renal osteodystrophy by quantitative histomorphometry or by attempting to classify the form of renal osteodystrophy by noninvasive means of assessing bone turnover, mineralization, and volume. However, we lack clinical tools to make these distinctions in individual patients.

While many promising radiologic techniques that examine bone microarchitecture offer hope of being able to define turnover, mineralization, and volume noninvasively in severe chronic kidney disease, they are investigational and unproven at this time in discriminating between renal osteodystrophy and osteoporosis.^{6,25–27} As we increase our understanding of the relationships between turnover, mineralization, volume, and bone strength, these noninvasive imaging technologies may become the means to correlate turnover, mineralization, and volume to bone strength and open up an entirely new way to classify skeletal strength.

In the meantime, the clinician is left with quantitative bone histomorphometry (which requires biopsy) and biochemical markers of bone turnover to characterize the bone disease that may be responsible for low-trauma fractures in stage 5 chronic kidney disease. The clinician should first use biochemical markers before bone biopsy to distinguish the form of renal osteodystrophy, as this distinction may be able to prevent unnecessary biopsy.

Biochemical markers of bone metabolism

In chronic kidney disease, the bone biochemical tests that nephrologists usually assess during the course of declining renal function are the serum levels of:

- Phosphorus
- Parathyroid hormone
- Calcium
- Other electrolytes
- Total alkaline phosphatase or bone-specific alkaline phosphatase
- 1,25 dihydroxyvitamin D.

In postmenopausal osteoporosis, the bio-

chemical markers of bone turnover that are measured to reflect baseline levels of bone turnover or change in bone turnover in response to drug therapy are:

- The serum or urine collagen cross-links N-telopeptide (NTx) and C-telopeptide (CTx), markers of bone resorption
- Bone-specific alkaline phosphatase (an osteoblast activity marker)
- Serum osteocalcin, a bone formation marker
- Propeptide type 1 collagen (PINP), a marker of osteoblast activity, highly correlated with bone formation
- 25-hydroxyvitamin D levels.

Biochemical markers of bone turnover cannot be used to diagnose osteoporosis. They can, however, provide clinical guidance as to whether a patient has high or low bone turnover and whether therapy is affecting bone turnover.^{28–36} Although these markers have value in making these distinctions in groups of patients, they are less sensitive and specific for classifying an individual patient's bone turnover status.

In the renal field, bone-specific alkaline phosphatase and parathyroid hormone are generally considered the most useful markers for characterizing a patient's bone turnover, and their application for group classification is outlined in **TABLE 2**.^{37,38} The other markers used for management decisions in postmenopausal osteoporosis (NTx, CTx, PINP) have not as yet been shown to be valuable in assessing bone turnover in stage 4 or 5 chronic kidney disease.^{39–42} Tartrate-resistant acid phosphatase 5b (TRAP 5b), a marker of osteoclast activity, holds promise for assessing the activity of this bone remodeling cell in patients with chronic kidney disease—mineral and bone disorder.

Bone-specific alkaline phosphatase, parathyroid hormone, and adynamic bone disease

If a patient's bone-specific alkaline phosphatase level is elevated, adynamic bone disease is highly unlikely. Assuming that other causes of this elevated level (eg, Paget disease of bone, metastatic cancer) have already been excluded, the elevated level could represent either osteomalacia or hyperparathyroid bone disease.

However, a "normal" bone-specific alkaline

phosphatase level does not exclude adynamic bone disease, whereas a low level is more often associated with low bone turnover.

An elevated parathyroid hormone level does not exclude adynamic renal bone disease, but a low level (< 150 pg/mL) suggests a low-bone-turnover state. A level six times or more greater than the upper limit of normal is far more likely to be associated with high bone turnover.

Thus, in clinical practice, patients with stage 4 or 5 chronic kidney disease who have elevated bone-specific alkaline phosphatase or very high parathyroid hormone values do not have adynamic bone disease. Furthermore, once other causes of these aberrant biochemical abnormalities have been defined, then “high-bone-turnover osteoporosis” may be a consideration. Certainly, in my opinion, if bone turnover markers suggest low bone turnover, bone biopsy is necessary before starting an antiresorptive agent.³⁵

Quantitative bone histomorphometry

Double tetracycline-labeled quantitative histomorphometry is still the only accepted way to measure turnover, mineralization, and volume in clinical practice.^{43–45} A committee of the American Society for Bone and Mineral Research has developed histomorphometric criteria for distinguishing among the different types of metabolic bone diseases (osteomalacia, adynamic bone disease, hyperparathyroid bone disease).¹² These criteria can be used to distinguish among the various metabolic bone diseases that accompany stage 5 chronic kidney disease, including adynamic bone disease.^{43,46–48}

For patients in stage 5 who have had a fragility fracture, adynamic bone disease should be excluded before the off-label use of an osteoporosis drug that reduces bone turnover, such as a bisphosphonate, calcitonin, estrogen, a selective estrogen receptor modulator, or denosumab (anti-RANK ligand antibody). While there is no evidence, for example, that starting a bisphosphonate in a patient who already has adynamic bone disease is detrimental to either bone strength or systemic vascular calcification (which may be linked to low bone turnover),⁴⁹ it seems unreasonable to do so until solid prospective data clarify the

TABLE 2

Parathyroid hormone and bone-specific alkaline phosphatase levels in specific forms of renal osteodystrophy

DISORDER	SERUM INTACT PARATHYROID HORMONE	BONE-SPECIFIC ALKALINE PHOSPHATASE
Hyperparathyroidism		
Mild	200–400 pg/mL	Normal
Moderate	350–800 pg/mL	Normal or elevated
Severe	> 700 pg/mL	Elevated
Aluminum bone disease	10–500 pg/mL (mostly < 100)	Normal
Adynamic bone disease	< 100 –150 pg/mL	Normal to low
Osteomalacia	Normal or mildly elevated	Mildly elevated

In groups of patients, the parathyroid hormone and bone-specific alkaline phosphatase levels can distinguish the various histologic forms of renal osteodystrophy. In individual patients, however, the values often overlap.

DATA FROM MILLER PD, LERMA EV. RENAL BONE DISEASES. IN: KLEEREKOPER M, SIRIS E, MCCLUNG M, EDITORS. THE BONE AND MINERAL MANUAL—A PRACTICAL GUIDE. 2ND ED. BURLINGTON, MA: ELSEVIER ACADEMIC PRESS; 2005:127–138; AND MILLER PD, SHANE E. MANAGEMENT OF TRANSPLANTATION RENAL BONE DISEASE: INTERPLAY OF BONE MINERAL DENSITY AND DECISIONS REGARDING BISPHOSPHONATE USE. IN: WEIR MR, EDITOR. MEDICAL MANAGEMENT OF KIDNEY TRANSPLANTATION. PHILADELPHIA, PA: LIPPINCOTT WILLIAMS & WILKINS; 2004:359–375.

harm or benefit.⁵⁰ Preliminary experimental and clinical data suggest that bisphosphonates may even reduce progression of extraosseous calcification and inhibit the development of atherosclerosis.⁵⁰

Hence, quantitative bone histomorphometry can discriminate among the various forms of renal osteodystrophy. If a distinct form of renal osteodystrophy is not present in a patient with stage 4 or 5 chronic kidney disease who has had a fracture and who, on biopsy, has a low trabecular bone volume, the patient probably has osteoporosis by exclusion.

TREATING OSTEOPOROSIS IN STAGE 1–3 CHRONIC KIDNEY DISEASE

As previously mentioned, patients who have fragility fractures in stage 1, 2, or 3 chronic kidney disease are more likely to have osteoporosis than renal osteodystrophy as the cause

In clinical trials, osteoporosis drugs were effective in people with GFRs as low as 30 mL/min

of their impaired bone strength. Although several articles have described a higher risk of fragility fractures in patients with age-related reduction in renal function than in age-matched patients with normal renal function, the specific metabolic bone disease other than osteoporosis accounting for this bone fragility has not been defined.⁶

Hence, patients with osteoporosis who are in stage 1, 2, or 3 chronic kidney disease and do not have a known biochemical abnormality that might suggest some form of renal osteodystrophy can and should be considered for treatment with approved drugs that reduce the risk of fractures in postmenopausal, male, or glucocorticoid-induced osteoporosis.^{51–53} In clinical trials, these agents were shown to be effective in patients with serum creatinine concentrations as high as 2.0 mg/dL or a GFR as low as 30 mL/min, as estimated by the Cockcroft-Gault equation.

While all of the approved agents show evidence of reducing the risk of vertebral fractures, patients at higher risk of fractures or those who have already suffered a nonvertebral fracture are more often considered candidates for treatment with a bisphosphonate or teriparatide (Forteo), both of which have shown evidence of reducing the risk of all fractures.

Bisphosphonates in stage 1–3 chronic kidney disease

There is prospective evidence that patients with an age-related reduction in GFR down to 30 mL/min benefit from oral and intravenous bisphosphonates, since all of the clinical trials that led to the approval of bisphosphonates included patients with GFRs as low as this.^{54–57} Bisphosphonates seem to have an excellent safety profile as measured by renal adverse events in patients with a GFR of 30 mL/min or greater.^{52–59}

From the intravenous bisphosphonate studies, it appears that ibandronate (Boniva) at the approved dose of 3 mg intravenously every 3 months and zoledronic acid (Reclast) 5 mg once a year given over 15 minutes are safe in patients with a GFR greater than 30 or 35 mL/min.

However, the safety of these drugs might not be the same in patients with preexisting

renal parenchymal disease (eg, in diabetes) or in patients using other agents that could affect renal function (eg, nonsteroidal anti-inflammatory drugs). Therefore, caution is still needed when deciding to use intravenous bisphosphonates in specific higher-risk renal subpopulations.

In the clinical trials of zoledronic acid, a substantial proportion of patients had diabetes, and no difference was seen in adverse renal effects between diabetic and nondiabetic patients. Also, GFRs declined equally between the treated and placebo groups over time and were no different at the end of 3 years.⁵⁵ However, in patients in whom serum creatinine was measured 9 to 11 days after the infusion of zoledronic acid, there was a small but statistically significant transient increase in serum creatinine concentration (0.5–2.0 mg/dL above baseline) after the second annual infusion.⁵⁸ The serum creatinine concentrations returned to their baseline values in all of these patients before the next annual infusion.

It is important that infusions of zoledronic acid be given no faster than over 15 minutes. More rapid infusion has been associated with acute renal failure, suggesting that the tubular damage that mimics acute tubular necrosis is related to the maximal concentration and not to the area under the curve. I infuse zoledronic acid over 30 minutes in patients with normal renal function or in those with stage 1, 2, or 3 chronic kidney disease.

Teriparatide

Teriparatide's approval trial did not require baseline measurements of GFR, but patients were enrolled only if their baseline serum creatinine concentrations were less than 2.0 mg/dL.⁶⁰ In a post hoc analysis, a small subset of patients had GFRs as low as 30 mL/min as estimated by the Cockcroft-Gault equation. In these patients, teriparatide 20 or 40 µg/day had an anabolic effect as measured by increases in osteoblast activity markers and bone mineral density, similar to that seen in patients with higher estimated GFRs and without any adverse renal effects.⁶¹

There are no data on using teriparatide in stage 4 or 5 chronic kidney disease, and I emphasize that in all of the clinical trials of teriparatide, all patients, even those with esti-

mated GFRs as low as 30 mL/min, had normal baseline serum intact parathyroid hormone levels. It is possible that the bone biologic response could differ between patients with chronic kidney disease who have an elevated as compared with a normal serum parathyroid hormone level. This issue should be investigated.

■ TREATING OSTEOPOROSIS IN STAGE 4 OR 5 CHRONIC KIDNEY DISEASE

Treatment decisions are more difficult in patients with stage 4 and especially stage 5 chronic kidney disease who have had fragility fractures. This is even the case when the clinician has determined to the best of his or her ability that the patient has osteoporosis rather than renal osteodystrophy.

There are no prospective data showing any of the approved drugs to be effective in treating osteoporosis in patients whose GFRs are lower than 30 mL/min. However, a post hoc analysis of pooled data from nine clinical trials⁶² found that risedronate (Actonel) 5 mg/day reduced the incidence of new vertebral fractures. Another post hoc analysis, from the Fracture Intervention Trial,⁶³ found that alendronate (Fosamax) 5 mg/day for the first 2 years and 10 mg/day for the 3rd year reduced the incidence of all clinical fractures. In neither of these post hoc analyses did the drug affect the serum creatinine concentration. The patients—postmenopausal women—had GFRs as low as 15 mL/min as estimated by the Cockcroft-Gault equation. Similar post hoc data have been published on raloxifene (Evista).⁶⁴

There are no data on the efficacy (reduction in fracture risk) or safety of any bisphosphonate in patients with GFRs lower than 15 mL/min (stage 5 chronic kidney disease). Nevertheless, the question often arises when fragility fractures occur in this population. Here, only opinion and controversy exist, and we fervently await good science and randomized prospective data.

How to manage renal bone disease after transplantation is a distinctly separate issue in which bisphosphonate use may be even more controversial than in end-stage renal disease.^{65,66}

In my opinion, patients without fractures with stage 5 chronic kidney disease should not be given bisphosphonates or teriparatide off-label. Treating only on the basis of low bone mineral density and other risk factors seems to be associated with greater risk than benefit.

In stage 5 patients suffering fragility fractures, a bisphosphonate may be considered, but only after renal osteodystrophy has been thoroughly ruled out, which most often requires a bone biopsy.^{43,67,68} In skilled hands, transiliac bone biopsy is a safe procedure with little morbidity.

If osteoporosis appears to be the cause of the fracture, and if one chooses to use a bisphosphonate and the patient gives his or her informed consent, then I would give half the usual dose and restrict the therapy to no more than 3 years. The reason for halving the dose is based on the known pharmacokinetics of bisphosphonates in people with normal renal function: 50% of a given dose goes to bone and 50% is excreted by the kidney. Furthermore, the dialyzability of bisphosphonates has not been well studied. Limiting the treatment to 3 years is based on the unknown but probably greater bone retention of bisphosphonates when excretion is impaired.

I must emphasize that these approaches are not based on any evidence of efficacy, but rather are considered in extreme cases of often-recurrent fragility fractures in which the fractures per se pose a great risk of morbidity and death. These approaches should be clearly discussed with the patient, undertaken by specialists knowledgeable in complex metabolic bone disease management, and initiated only after the skeletal fragility disorder is well characterized.

■ SUMMING UP

No consensus exists on the criteria for diagnosing osteoporosis in stage 4 or 5 chronic kidney disease.

In higher-risk patients in stage 1, 2, or 3 chronic kidney disease who have osteoporosis, it appears that any drug approved for osteoporosis can be used, eg, a bisphosphonate, teriparatide, or both.

Considerations for management are far more complex in stage 4 or 5 because of the

Zoledronic acid infusions should be given no faster than 15 minutes

increased prevalence of other metabolic bone diseases and renal osteodystrophy, and because the World Health Organization criteria cannot be used to diagnose osteoporosis. In stage 5, the differential diagnosis requires careful analysis of a broad range of biochemical markers of bone turnover and, at times, quantitative bone histomorphometry, especially if one is considering using a bisphosphonate. It is unknown if bisphosphonates, by reducing bone turnover in a preexisting low-bone-turnover state, would help or harm bone or would lead to less or more cardiovascular disease. These questions must be addressed by better science and prospective data.

In the future, newer noninvasive radiologic tools to measure microstructure and mineralization of bone promise to help us better understand osteoporosis and renal osteodystrophy in a noninvasive manner.

In clinical practice, at the current time and with current limited knowledge, treatment of osteoporosis in stage 4 or 5 chronic kidney disease is opinion-based. Nevertheless, in very specific clinical cases of severe fragility fractures that, by themselves, may cause disability and death, bisphosphonates should be considered by experts in bone metabolism and, as with any off-label application, after careful informed discussions with the patient. ■

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