EDITORIAL

MARIA COCO, MD, MS
Professor of Clinical Medicine, Renal Division, Montefiore Medical Center, Bronx, NY

Treating the renal patient who has a fracture: Opinion vs evidence

MANAGING BONE HEALTH IN patients with chronic kidney disease presents unique challenges. While the common end point—a fracture—is comparable to that in patients with osteoporosis, the underlying metabolic conditions differ from patient to patient with chronic kidney disease and may be dramatically different from those in patients who have osteoporosis without chronic kidney disease.

See related article, page 715

In chronic kidney disease, underlying conditions differ from patient to patient

Renal osteodystrophy is not osteoporosis

Renal osteodystrophy is not osteoporosis. While osteoporosis in people without kidney disease is defined clinically on the basis of bone mineral density (measured by bone densitometry), renal osteodystrophy is a histologic diagnosis made on bone biopsy: it is a continuum between frankly low-turnover-bone disease—encompassing adynamic bone disease and osteomalacia—and frankly high-turnover-bone disease, with severe secondary hyperparathyroid bone disease and osteitis fibrosa. Histologically, there may or may not be low trabecular bone volume or loss of connectivity typical of the bone loss in osteoporosis.

Patients at both ends of the spectrum of bone turnover in renal osteodystrophy may have the same bone mineral density on densitometry. Low bone mineral density may reflect inadequate mineralization (seen in osteomalacia and adynamic bone disease) or increased peritrabecular fibrosis (seen in secondary hyperparathyroid bone disease). High bone mineral density readings may capture extraosseous calcifications, which are very common in chronic kidney disease.

doi:10.3949/ccjm.76a.09075

Renal osteodystrophy is part of the syndrome called chronic kidney disease-mineral and bone disease,[1] which is not limited to bone fractures but may also affect vascular health. Abnormal calcium deposits in vascular tissue—consistent with calciphylaxis and associated with increased morbidity and mortality rates in chronic kidney disease—may occur with low bone turnover.

The diagnosis of osteoporosis in the general population is based on clinical evidence: the measured bone mineral density is compared with normalized scores. Histologically, the bone of the osteoporotic patient shows osteopenia with increased bone turnover and a shift toward increased bone resorption, resulting in loss of connectivity of the trabeculae, as well as decreased trabecular volume. These conditions are common in advanced age and in certain pathologic states (eg, steroid therapy, metastatic bone disease, Paget disease of bone).

It is well accepted that the risk of fracture in osteoporosis increases as measured bone mineral density decreases. Conversely, increasing bone mineral density has been correlated with fewer fractures. The clinician is often guided by biomarkers of bone metabolism such as urinary N-terminal cross-linked telopeptides of collagen (NTx) in diagnosing and treating bone breakdown.

Can bisphosphonates be used in chronic kidney disease?

Bisphosphonates are antiresorptive agents that bind to the hydroxyapatite of bone. They poison the osteoclast (the bone-resorbing cell), causing its death and thereby halting the resorption of bone. Osteoblasts—the bone-forming cells—are presumably not affected,

and the bone continues to make osteoid, which is subsequently mineralized. Bone turnover is dramatically decreased. The net effect is increased bone density in people with osteoporosis. The half-life of these agents is years.

In the general population, bisphosphonate therapy has been associated with decreased risk of fragility bone fractures. However, the long-term effects are not yet known. Indeed, jaw necrosis—possibly due to low bone turnover—is being reported with increasing frequency.[2] Fractures associated with low bone turnover in patients without chronic kidney disease treated with bisphosphonates long-term are now being reported.[3,4]

In an article in this issue of the *Journal*,[5] the author advocates the use of bisphosphonate therapy in patients with chronic kidney disease who have low bone mineral density. However, treating patients who have chronic kidney disease on the basis of low bone mineral density with bone-suppressing agents may further depress bone turnover and lead to more extraosseous calcifications as the turned-off bone is unable to accept serum calcium.[6]

Further, it is unclear how long "long-term" would be in a patient with advanced chronic kidney disease: Would the half-life of the bisphosphonates be tremendously increased, leading to adverse events sooner? Would adynamic bone disease promptly develop, leading to rampant jaw necrosis and bone fractures? Would vascular calcification flourish?

Opinions abound, but without adequate evidence to back them up

Bone biomarkers are hard to interpret in chronic kidney disease

In chronic kidney disease, the interpretation of biomarkers of bone metabolism is notoriously unreliable. The usual chemistry values associated with clinical osteoporosis in the general population—ie, elevated levels of urinary NTx, serum C-terminal cross-linked telopeptides of collagen (CTx), osteocalcin, and bone-specific alkaline phosphatase—are not valid in patients with chronic kidney disease, for obvious reasons: with declining renal function, the various markers accumulate in the serum. Urinary NTx does not apply in patients with advanced chronic kidney disease or end-stage renal disease.

How should renal osteodystrophy be treated?

Nephrologists currently focus therapy on reducing hyperphosphatemia (associated with increased morbidity across all stages of chronic kidney disease), replenishing vitamin D as much as possible without causing hyperphosphatemia and hypercalcemia, and suppressing parathyroid hormone secretion.

However, there is not enough evidence on what the goal should be with respect to parathyroid hormone in patients with chronic kidney disease who are not on dialysis. Although in the recent past many believed that parathyroid hormone goals should be 150 to 300 pg/mL in dialysis patients, the latest guidelines suggest that perhaps this goal is too narrow and may lead to more adynamic bone disease. Similarly, there is no consensus on the use of synthetic parathyroid hormone analogues.

Bisphosphonate therapy, particularly with pamidronate (Aredia) and zolendronic acid (Reclast), has been associated with adverse renal effects even in patients without chronic kidney disease. There are no prospective studies of the effects of these agents in patients with depressed renal function.

The patient with chronic kidney disease who has a fracture remains a unique problem for the nephrologist, primary care physician, and subspecialist. Efforts should be concentrated on preventing and treating metabolic bone disease in its entire spectrum, with rational, prospective studies, and should not depend on anecdotal reports. Opinions abound, without adequate evidence to back them up. ■

REFERENCES

1. **Moe S, Drüeke T, Cunningham J, et al; Kidney Disease: Improving Global Outcomes (KDIGO)**. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 69:1945–1953.
2. **Rustemeyer J, Bremerich A**. Bisphosphonate-associated osteonecrosis of the jaw: what do we currently know? A survey of knowledge given in the recent literature. Clin Oral Investig 2009; Epub ahead of print.
3. **Armamento-Villareal R, Napoli N, Diemer K, et al**. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int 2009; 85:37–44.
4. **Ali T, Jay RH**. Spontaneous femoral shaft fracture after long-term alendronate. Age Ageing 2009; Epub ahead of print.
5. **Miller PD**. Fragility fractures in chronic kidney disease: an opinion-based approach. Cleve Clin J Med 2009; 76:713–721.
6. **Toussaint ND, Elder GJ, Kerr PG**. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin J Am Soc Nephrol 2009; 4:221–233.

***ADDRESS**: Maria Coco, MD, MS, Renal Division, Montefiore Medical Center, 111 East 210 Street, Bronx, NY 10467; e-mail mcoco@montefiore.org.*