Treatment of Osteoporosis in Chronic Kidney Disease and End-stage Renal Disease

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As glomerular filtration rate (GFR) declines from age-related bone loss or disease that specifically induces a decline in GFR, there are a number of metabolic bone conditions that may accompany the decline in GFR. These metabolic bone conditions span a spectrum from mild-to-severe secondary hyperparathyroidism in early stages of chronic kidney disease (CKD) to the development of additional heterogeneous forms of bone diseases each with its distinctly quantitative bone histomorphometric characteristics. Osteoporosis can also develop in patients with CKD and ESRD for many reasons beyond age-related bone loss and postmenopausal bone loss. The diagnosis of osteoporosis in patients with severe CKD or end-stage renal disease (ESRD) is not as easy to do as it is in patients with postmenopausal osteoporosis (PMO)—neither fragility fractures nor The World Health Organization bone mineral density criteria can be used to diagnose osteoporosis in this population since all forms of renal bone disease may fracture or have low "T scores". The diagnosis of osteoporosis in patients with CKD/ESRD must be done by first the exclusion of the other forms of renal osteodystrophy, by biochemical profiling or by double tetracycline-labeled bone biopsy; and the finding of low trabecular bone volume. In such patients, preliminary data would suggest that oral bisphosphonates seem to be safe and effective down to GFR levels of 15 mL/min. In patients with stage 5 CKD who are fracturing because of osteoporosis or who are on chronic glucocorticoids, reducing the oral bisphosphonate dosage to half of its usual prescribed dosing for PMO seems reasonable from known bisphosphonate pharmacokinetics, though we do need better scientific data to fully understand bisphosphonate usage in this population.

Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD), are associated with a whole range of distinctly different metabolic bone diseases and bring distinctly different decision-making challenges to the physician caring for these patients. CKD is defined as a glomerular filtration rate (GFR) less than 60 mL/minute (mL/min) and is a continuum down to a level of GFR that necessitates dialysis or transplantation (ESRD) [1••]. It becomes apparent, therefore, that CKD is a gradient of severity, progressing as GFR declines. Likewise, the nature of the metabolic bone pathophysiologic processes that alter bone and mineral metabolism during declining renal function also change as GFR declines.

Chronic kidney disease may be a result of many disease processes that affect the kidney or may be a result of a decline in renal function seen as a function of aging. Age-related decline in renal function is common. Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicates that otherwise healthy human beings have a steady decline in renal function, especially their GFR as age increases [2]. By the average age of 70 years, nearly 25% of otherwise seemingly healthy adult human beings have a GFR of less than 25 mL/min, without any specific concomitant renal disease. The high prevalence of CKD in otherwise seemingly healthy elderly patients becomes an important consideration for all physicians caring for patients with osteoporosis. Since the bisphosphonates are the only U.S. Food and Drug Administration (FDA) approved therapeutic agents for the treatment of osteoporosis in postmenopausal women, men, and for glucocorticoid-induced osteoporosis (GIOP), the use of bisphosphonates in these populations who may have a decrease in GFR are important management issues [3–13]. Currently, FDA product label strongly advises avoiding oral bisphosphonates in patients with GFR's less than 35 mL/min [14]. Patients without any known prior kidney disease may have CKD simply as a function of aging, and represent a large proportion of the population that may need treatment for osteoporosis. Most clinicians do not measure GFR in their patient population before initiating

Table 1. Metabolic bone diseases associated with renal disease

Osteitis fibrosa cystica
Osteomalacia
Vitamin D related
Nonvitamin D related
Chronic metabolic acidosis
Aluminum accumulation
Phosphate depletion
Adynamic bone disease
Mixed uremic osteodystrophy
Amyloid bone disease
Osteoporosis

(*Adapted from* Miller and Shane [18••].)

Table 2. Osteoporosis in dialysis patients

Chronic heparin
Steroids
Hypogonadism
Hyperprolactinemia
Poor nutrition
Vitamin D deficiency
Hyperparathyroidism
Metabolic acidosis

(*Adapted from* Miller and Shane [18••].)

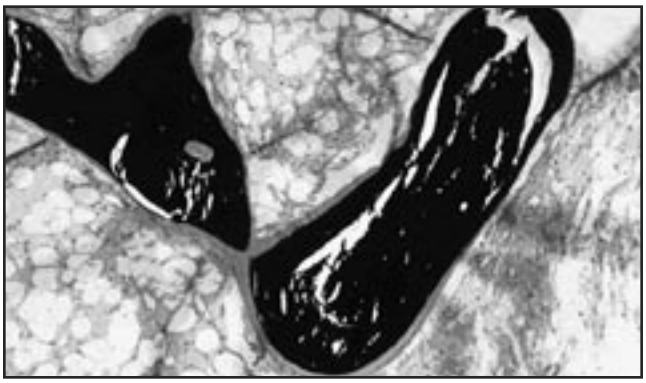

Figure 1. The criteria for osteomalacia are an increased osteoid surface percent greater than 80%, an increased osteoid seam thickness greater than 15 microns, and an increased mineralization lag time greater than 100 days. (*Adapted from* Miller and Huffer [19].)

bisphosphonate treatment. Measuring GFR in daily clinical practice is not a standard of care in the management of the osteoporotic population. The measurement of the serum creatinine concentration is more routinely done and all of the clinical trials done for the FDA registration of all osteoporotic-specific pharmacologic agents did exclude patients with baseline serum creatinine concentrations above 2.0 mg/dL and did not require prerandomization GFR determinations. Yet, many clinicians know that many elderly patients who have low body weights and muscle mass may have serum creatinine concentrations that fall within a "normal" laboratory reference range and yet have GFR values less than 35 mL/min. This poor relationship between measured serum creatinine concentration and GFR in elderly patients with low muscle mass is related to the fact that creatinine is derived from the breakdown of muscle-derived creatine [15–17]. Hence, the evaluation of renal and bone disease and the potential use and safety of bisphosphonates in practice are important considerations.

Patients with CKD and/or ESRD may have a heterogeneous group of metabolic bone diseases (Table 1) [18••]. In addition patients with CKD or ESRD may also develop osteoporosis and may do so for many more reasons than the osteoporosis of aging or postmenopause (Table 2) [18••]. The challenge then for the clinician faced with a patient with CKD or ESRD who has a low bone mineral density (BMD) or fragility fractures is to first make the diagnosis of osteoporosis as opposed to some other form of renal metabolic bone disease. While antiresorptive therapy may be appropriate for osteoporosis, antiresorptives, especially bisphosphonates, may be contraindicated in certain nonosteoporotic forms of renal osteodystrophy (osteomalacia or adynamic renal bone disease; Figs. 1 and 2) [19]. Thus, the first decision is to make the discrimination between osteoporosis or nonosteoporosis bone disease in patients with CKD or ESRD.

How Is the Diagnosis of Osteoporosis Made in Patients with CKD or ESRD?

The diagnosis of osteoporosis in postmenopausal women is based on BMD criteria established in 1994 by The World Health Organization (WHO; T score of -2.5 or lower) or the presence of the fragility fractures [20]. However, these criteria cannot be used to diagnose osteoporosis in the patient with CKD or ESRD because all of the various forms of renal osteodystrophy that are not osteoporosis also have low T scores and may develop fragility fractures [21–28]. The only way to make the diagnosis of osteoporosis in a patient with CKD or ESRD is by excluding the other forms of renal osteodystrophy. How is the exclusion done? It can be done to some degree by biochemical profiling, measuring in particular the parathyroid hormone (PTH) level and the bone-specific alkaline phosphatase (BSAP) [29••,30,31]. To be truly accurate in the diagnosis, double tetracycline-labeled quantitative bone histomorphometry is the best diagnostic test, since each specific form of renal bone disease is defined by specific criteria established by standard committees on nomenclature [19,32–37]. While bone biopsy is invasive and more expensive to perform, with experience in the transiliac procedure performed with the use of minimal awareness

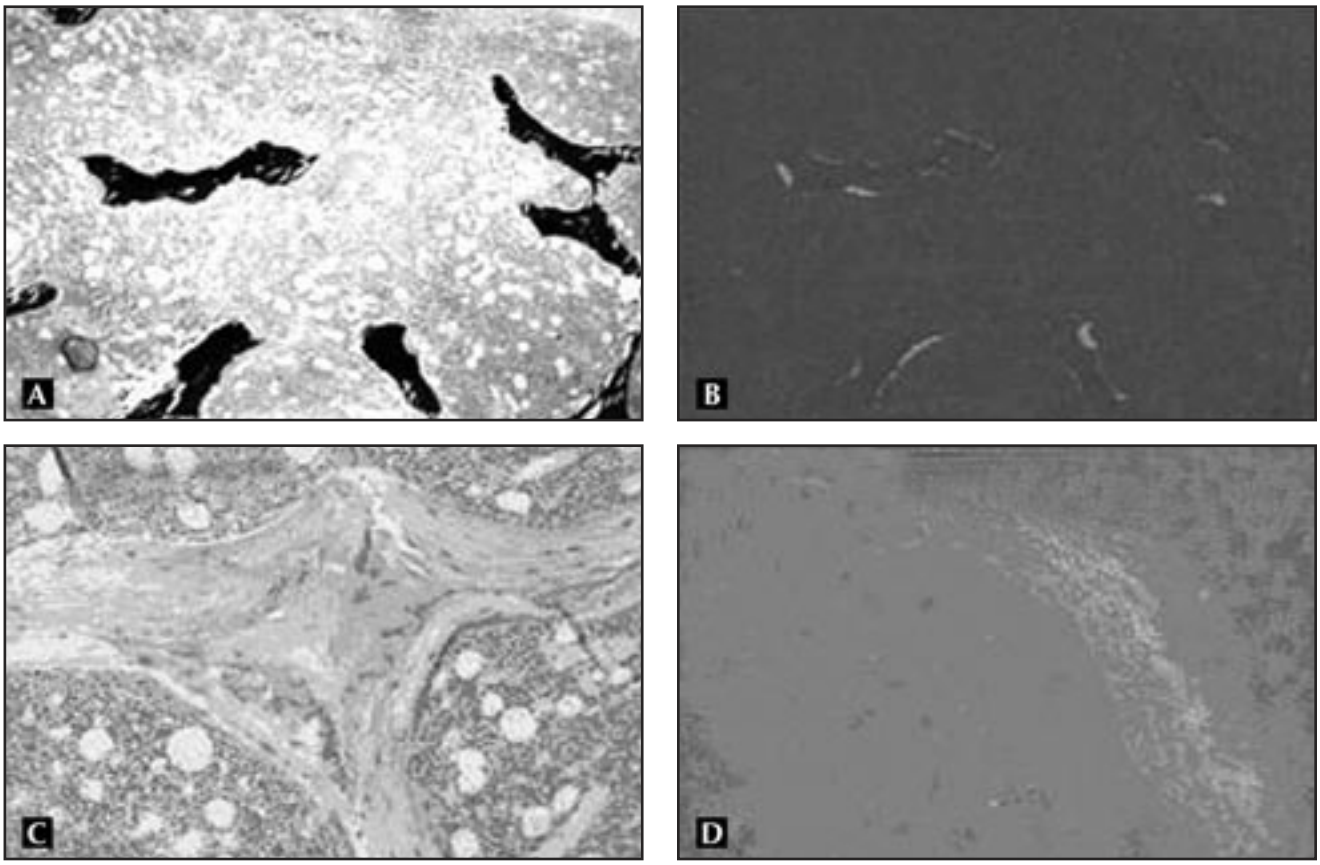

Figure 2. Adynamic bone disease. **A**, Very little calcified bone. **B**, Very little noncalcified bone (osteoid). **C**, No osteoclasts seen on osteoclast (tartrate resistant acid phosphatase) stain. **D**, No Tetracycline seen under fluorescent stain. (*Adapted from* Miller and Huffer [19].)

consciousness anesthesia, the biopsy itself is safe and the postoperative pain and morbidity are negligible. Transiliac bone biopsy removes the guess-work that is invariably associated with the biochemical differentiation between the various forms of renal bone disease. Biochemical profiling discriminates between the various forms of renal bone disease in groups of patients. However, there may be enough overlap in biochemical values in individual patients such as the specific diagnosis may not be clear by biochemical testing. For example, even though the intact PTH level is usually less than 200 pg/mL in most patients with adynamic bone disease, there are subsets of patients with adynamic bone disease that have PTH levels greater than 500 pg/mL. This latter group may have higher levels of 7-84 PTH, that is catabolic to bone, and may be responsible for the low bone turnover observed in these patients despite the presence of a high anabolic 1-84 PTH [38•]. The general biochemical profiles of the various renal bone diseases are shown in Table 3 [18••]. If a physician considering using a bisphosphonate to treat "osteoporosis" in a patient with CKD or ESRD is uncertain that the patient may have osteomalacia or adynamic bone disease, diseases where bisphosphonates may be contraindicated, a bone biopsy should be performed prior to therapy. For example, if the BSAP is low or elevated, the former value suggesting adynamic bone disease and the latter hyperparathyroid or osteomalacic bone disease, quantitative bone histomorphometry can make the discrimination. Hence, the diagnosis of osteoporosis is made in a patient with CKD or ESRD first by excluding the other forms of renal bone disease and then the finding of a low trabecular bone volume on biopsy or by use of WHO criteria or the occurrence of a fragility fracture in a patient where other types of renal bone disease have been eliminated.

It is important to point out that adynamic bone disease, one of the most prevalent forms of renal osteodystrophy, does not occur in the earlier stages of CKD. Adynamic renal bone disease may be seen in advance stages of CKD, with levels of GFR reductions so severe that it really is ESRD. Adynamic bone disease may have reversible etiologies (Table 4) [39]. For the ESRD patient with adynamic bone disease, this low bone turnover may be reversible if the factor(s) responsible for the low bone turnover is removed (excess PTH suppression by vitamin D metabolites or possibly even cinacalcet, for example) [40]. Yet because adynamic bone disease is not seen before ESRD levels of renal failure (stage 5), for the patient in a rheumatology practice on glucocorticoids with concomitant CKD, where the physician wants to

Table 3. Biochemical profiling in patients with severe chronic kidney disease

Disorder	Serum iPTH levels (pg/mL)
Hyperparathyroidism	
Mild	200–400
Moderate	350–800
Severe	> 700
Aluminum bone disease	10–500 (mostly < 100)
Aplastic or adynamic bone disease	< 100–150
Disorder	**Serum BSAP levels**
Hyperparathyroidism	Elevated
Adynamic bone disease	Low
Aluminum bone disease	Low
Osteomalacia	Elevated
Osteoporosis	Normal

BSAP—bone specific alkaline phosphatase; PTH—parathyroid hormone.
(*Adapted from* Miller and Shane [18••].)

Table 4. Causes of adynamic renal osteodystrophy

Sustained causes
Parathyroidectomy
Steroid-induced osteoporosis
Diabetes mellitus
Reversible causes
Calcitriol therapy
Exogenous calcium loading
Immobilization
Aluminium toxicity

(*Adapted from* Salusky and Goodman [39].)

start a bisphosphonate to prevent steroid-induced bone loss or fractures, the potential presence of adynamic bone disease should not be a concern, unless the patient has ESRD and there is unexplained low BSAP or PTH values. The more likely renal bone disease(s) in CKD that might mitigate a bisphosphonate therapeutic response is severe hyperparathyroidism. Severe hyperparathyroidism or osteomalacia should be resolved first, since progressive osteitis fibrosa cystica might mitigate the effect of bisphosphonates to prevent bone loss and osteomalacia is a contraindication to bisphosphonates. Severe hyperparathyroidism and osteomalacia can first be treated and then the bisphosphonate provided later, if necessary.

Recently, the National Kidney Foundation published their guidelines, Kidney Disease Outcomes Quality Initiative (KD/OQI) for the management of bone metabolism and disease in CKD [1••]. The KD/OQI provides evidence-based or opinions on management of calcium/phosphorus/vitamin D/PTH during the different stages of CKD as well as ESRD and postrenal transplantation. These guidelines do suggest bone biopsy in stage 5 CKD (GFR < 15 mL/min or dialysis patients) who are having fragility fractures, or have intact 1-84 PTH levels between 100–500 pg/mL and unexplained hypercalcemia (where adynamic bone disease presence may be high), elevated bone specific alkaline phosphatase, or severe bone pain (where osteomalacia is a probable diagnosis). Any suspicion for aluminum bone disease should also be followed-up by documentation of bone aluminum by biopsy. It is important to point out that hypercalcemia in patients with CKD may be related to hyperparathyroidism, adynamic, or aluminum bone disease, once hypercalcemia of other etiologies has been excluded (*eg*, myeloma, excess vitamin D usage).

What Are the Considerations in Bisphosphonate Utilization in CKD in the Patient with Osteoporosis?

The pharmacokinetics of bisphosphonates, for the intent of this discussion, will generalize among the amino-bisphosphonates, recognizing that the bone pharmacokinetics (surface affinity, binding, off-set of effects, and so on) of bisphosphonates may differ, and future suggestions on the application of dosing schedules may be different than offered in this paper [41–44]. There may be differences between the renal effects of oral bisphosphonates as opposed to the intravenous bisphosphonates and these possible distinctions will be made.

What was the basis of the FDAs product-labeling cautions about the use of oral bisphosphonates in patients with GFR values less than 35 mL/min? This cautionary language was based on renal "toxicity" observed with high dose exposure in rat models, assessed by declines in GFR and abnormal renal histology and the knowledge that bisphosphonates are filtered by the glomerulus as well as secreted by renal tubules [45]. In this regard, therefore, the clearance of bisphosphonates exceeds insulin clearance, supporting the data that bisphosphonates are excreted by filtration and tubular secretion.

Oral bisphosphonates are generally poorly absorbed by the gastrointestinal tract, but what does get absorbed usually has potent bone effects to inhibit bone resorption. Of the amount absorbed, 50% attaches to bone and 50% is excreted by the kidney. Obviously, there will be differences in this generalization depending upon the baseline remodeling space of the patient. In theory, patients with a smaller remodeling space will have less of the absorbed dose adhering to the bone surfaces and more excreted than a patient with a larger basal remodeling space. Nevertheless, in patients that have been randomized in the oral bisphosphonate clinical trials

where efficacy has been demonstrated to reduce incident vertebral, nonvertebral, and hip fractures, basal remodeling space was assumed not to be a factor in choosing the dosing strength or dosing frequency, which has largely been chosen by dose-ranging studies using BMD changes and/or resorption marker changes between daily and weekly bisphosphonate formulations [8,9,46,47].

As previously stated, none of the clinical trials that led to the FDA registration of alendronate, risedronate, or ibandronate required baseline GFR determinations for inclusion/exclusion criteria. Clinical trial exclusion was based on the baseline serum creatinine concentration, that generally excluded patients with serum creatinine concentrations of 2.0 mg/dL and higher. During the course of these clinical trials, that lasted at least 3 years with a placebo group being maintained (based on the FDA requirement to demonstrate fracture reduction through 3 years for a "treatment" indication), changes in serum creatinine concentration were not different within groups (placebo or bisphosphonate) or between groups (placebo vs bisphosphonate) over the 3 year interval suggesting no adverse effects over the 3 years of the clinical trial. Yet, these observations were not specific endpoints of the clinical trials and baseline GFRs or changes in GFR over the time-course of the clinical study were examined. Certainly the age range in the clinical trials included many individuals who on the basis of the known reductions in GFR seen with aging had GFRs that were low, including the risedronate hip trial that randomized one group 70 years of age and older and a second group 80 years of age and older and no renal impairment over time was reported in these patients, at least captured as adverse events [6]. Nevertheless, the clinical trials did not systematically study renal functional changes as an endpoint.

Just recently published is a post hoc analysis of over 9000 patients in the risedronate clinical trial dataset where baseline GFRs were assessable by the Cockcroft-Gault equation [48••]. Cockcroft-Gault estimates the GFR from a formula that incorporates the baseline serum creatinine and the body mass index into the equation. The correlation between the Cockcroft-Gault estimation of GFR and GFR determination by creatinine clearance is very high. In the cited risderonate dataset, there were three separate groups of patients classified at randomization as severe renal insufficiency (GFR < 30 mL/min), mild renal insufficiency (GFR 30–60 mL/min), or moderate renal insufficiency (GFR 60–80 mL/min), and these groups were equally divided between the placebo and risedronate-treated groups. Over the course of the clinical trial (mean observation follow-up time period 2.4 years) there were no changes in serum creatinine between or within these groups, and incident vertebral fracture reduction was also not different within or between groups at the FDA approved doses of 5 mg/day [48••]. Therefore, even in patients with GFR's less than 30 mL/min (the lowest GFR was 15 mL/min) at baseline, approved doses of risedronate did not alter GFR or effectiveness of risedronate to reduce incident fracture risk. It is important to stress that patients in the clinical trials did not have systemic medical illnesses or specific renal diseases responsible for their lower GFR. The lower GFR was related only to age-related decline in GFR. Hence, the safety and efficacy observed in this risedronate dataset may not apply to patients whose GFR is low because of a specific renal disease (*eg*, lupus nephritis) or to patients with stage 5 CKD (GFR < 15 mL/min or ESRD). Nevertheless, in patients selected for bisphosphonate treatment based on postmenopausal osteoporosis (PMO) or GIOP it appears that oral bisphosphonates at approved doses do not alter GFR even down to GFR levels of 15 mL/min over 2 years of use and are effective to reduce incident fractures. This nonrenal toxicity of oral bisphosphonates in patients with PMO or GIOP may not apply to patients given intravenous bisphosphonates or in patients with ESRD. Patients with ESRD or with stage 5 CKD have a greater probability of having a different metabolic bone disease causing fracture(s) than patients with CKD at stages 2–4. While osteoporosis may occur in patients with ESRD and bisphosphonates could be efficacious in this specific population, the specific diagnosis of the type of metabolic bone disease in patients with ESRD or stage 5 CKD is far more important to establish before bisphosphonates are initiated, because of the greater probability that in these patients with more severe renal failure may have adynamic or osteomalacic bone disease.

Bisphosphonates are not dialyzed. Therefore, in the patient with ESRD, on dialysis and with an established diagnosis of osteoporosis, what should the bisphosphonate dosage be? There is no data to support this question— my opinion would suggest that since 50% of an oral dosage of bisphosphonates is eliminated from human beings by renal excretion, and bisphosphonates are not dialyzed, that in those ESRD patients with osteoporosis and are having fragility fractures or who are receiving chronic glucocorticoids, that they should receive 50% of the FDA approved dosing. We certainly need data to support this opinion, but based on the pharmacokinetics of oral bisphosphonates and known renal function, the opinion seems reasonable. The length of use of bisphosphonates is unclear even for postmenopausal women but for patients with osteoporosis and ESRD who do receive bisphosphonates where the skeletal retention may differ than in patients with normal GFR, perhaps a shorter duration of use would be a cautious consideration [49].

The issues of renal safety and dosing schedules might be different for intravenous bisphosphonates and there could be differences between the available intravenous bisphosphonates: pamidronate, zoledronate, and ibandronate.

While intravenous bisphosphonates are not FDA approved for the management of any form of osteoporosis, they are FDA approved for other nonosteoporotic indications (reduction of fractures in patients with metastatic

bone lesions, multiple myeloma, and in Paget's disease). In addition, intravenous bisphosphonates are widely used to reduce fractures in children and adolescents with osteogenesis imperfecta [50]. In that regard, they are often used "off-label" for the treatment of osteoporosis, especially when oral bisphosphonates cannot be tolerated from a gastrointestinal side-effect aspect, or where the clinician does not want to attempt to use an oral bisphosphonate. The latter situation may be present when the clinician is faced with a patient who has severe pre-existing gastroesophageal disease (scleroderma esophagus, achalasia, severe gastroesophageal reflux disease) and may not want to put a patient at-risk to any oral bisphosphonate. Furthermore, there are many clinical scenarios where the fastidiously absorbed oral bisphosphonates may not be absorbed such as celiac disease. Therefore, the off-label use of intravenous bisphosphonates is quite prevalent and it should not be too long before intravenous bisphosphonates are FDA approved for the treatment of osteoporosis. Hence, their safety in patients with CKD will become an increasingly important issue.

Intravenous pamidronate has been associated with the development of a chronic renal lesion: focal glomerular sclerosis [51]. Intravenous zolendronate has been associated with the induction of acute renal failure, most likely because of the renal-cell lesion of acute tubular necrosis [52,53]. To date, intravenous ibandronate has not been associated with the development of any renal disease. It does appear that the induction of acute tubular necrosis is "rate-of-infusion" dependent, not dose-dependent. In the zolendronic acid clinical trials when the rate of infusion was reduced from 5 minutes to 15 minutes, there was no longer observed any rise in serum creatinine concentrations, though the dose of zolendronic acid was the same. In addition, it seems that the exacerbation of renal failure may be predicated on the pre-existing level of renal function. Thus, patients with CKD may be more likely to have an exacerbation of their reduced kidney function than patients with pre-existing normal renal function. Here we also need more data. Until we have better data, my opinion at this time would be to slow the infusion rate down to half of the recommended infusion rates for patients with GFR less than 30 mL/min or baseline serum creatinine concentration greater than 2.0 mg/dL.

Conclusions

Oral bisphosphonates are safe agents for the treatment of osteoporosis. They can be used in patients with CKD because of age-related declines in GFR in usual dosage formulations down to GFRs of 15 mL/min and are equally effective in these patients and to improve bone strength. In patients with National Kidney Foundation defined stage 5 level of renal failure (GFR < 15 mL/min and ESRD), the diagnosis of osteoporosis is more complex to establish and there is little evidence of efficacy of bisphosphonate efficacy in this population, though there are intuitive reasons to utilize bisphosphonates even in this population that are experiencing fragility fractures or on chronic glucocorticoids. It is, however, important to stress that in this group with stage 5 CKD, that adynamic bone disease and osteomalacia must first be excluded since bisphosphonates are potentially harmful in the first group and contraindicated in the second group. The dosage of bisphosphonates in patients with ESRD and established osteoporosis should be reduced to half of the prescribed formulations for PMO and GIOP, since bisphosphonates are cleared by the kidney and are not dialyzable. If intravenous bisphosphonates need to be used, the rate of infusion should be slowed to double the infusion time in patients with CKD. It should be kept in mind that patients may well have CKD, even though their serum creatinine concentrations may not reflect the magnitude of their CKD, because of increased age and/or reduced muscle mass. Measuring baseline GFR by creatinine clearance calculations best defines the level of renal function.

It is also abundantly clear from the foregoing discussions that we sorely need evidence-based data to guide clinicians on the proper use of bisphosphonates in patients with CKD and ESRD and more specific noninvasive means of diagnosing osteoporosis and excluding the other nonosteoporotic forms of renal bone disease that can mimic osteoporosis in these populations.

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