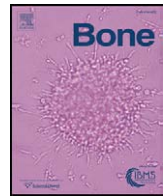




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## Review

## The kidney and bisphosphonates

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## ABSTRACT

Bisphosphonates are eliminated from the human body by the kidney. Renal clearance is both by glomerular filtration and proximal tubular secretion. Bisphosphonates given rapidly in high doses in animal models have induced a variety of adverse renal effects, from glomerular sclerosis to acute tubular necrosis. Nevertheless in the doses that are registered for the management of postmenopausal osteoporosis (PMO), oral bisphosphonates have never been shown to adversely affect the kidney, even (in post-hoc analysis of clinical trial data) down to estimated glomerular filtration rates of 15 ml/min. In addition fracture risk reduction has also been observed in these populations with stage 4 chronic kidney disease (CKD) with age-related reductions in glomerular filtration rate (GFR). Intravenous zoledronic acid is safe when the infusion rate is no faster than 15 min though there have been short-term (days 9–11 post-infusion) increases in serum creatinine concentrations in a small sub-set of patients from the postmenopausal registration trials. For these reasons intravenous zoledronic acid should be avoided in patients with GFR levels <35 ml/min; and the patients should be well hydrated and have avoided the concomitant use of any agent that may impair renal function. Intravenous ibandronate has not to date been reported to induce acute changes in serum creatinine concentrations in the PMO clinical trial data, but the lack of head-to-head comparative data between ibandronate and zoledronic acid precludes knowing if one intravenous bisphosphonate is safer than the other. In patients with GFR levels <30–35 ml/min, the correct diagnosis of osteoporosis becomes more complex since other forms of renal bone disease, which require different management strategies than osteoporosis, need to be excluded before the assumption can be made that fractures and/or low bone mass are due to osteoporosis. In addition, in patients who may have pre-existing adynamic renal bone disease, there is a lack of evidence of any beneficial effect or harm by reducing bone turnover by any pharmacological agent, including bisphosphonates on bone strength or vascular calcification. Bisphosphonates are safe and effective for the management of osteoporosis when used in the right dose and in the right patient population for the right duration.

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## Introduction

Bisphosphonates are widely used in the treatment of postmenopausal osteoporosis, and increasingly used in male osteoporosis and glucocorticoid-induced osteoporosis. They have been shown to

increase bone mineral density, reduce bone turnover, and reduce the risk of fragility fractures [1,2]. As a class of agents, they are generally well tolerated. Due to the mechanism of excretion of bisphosphonates via the renal system, and the lack of clinical trial data in patients with osteoporosis and severe renal impairment (glomerular filtration rate {GFR}<30 ml/min), the oral bisphosphonates: alendronate, risedronate and ibandronate and the intravenous (IV) bisphosphonates ibandronate and zoledronic acid all carry governmental registration warnings

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regarding their use in patients with creatinine clearance (CrCl) <30 ml/min (risedronate, oral and IV ibandronate) or <35 ml/min (alendronate and zoledronic acid) [3]. In general, bisphosphonates, which are excreted by the kidneys, have the potential for causing adverse renal effects when present at sufficiently large plasma concentrations. As both osteoporosis and renal insufficiency are known to become more prevalent with age [4,5], and bisphosphonates are the most widely prescribed treatment for osteoporosis, this section will examine the available data regarding renal safety in patients with osteoporosis treated with bisphosphonates, in order to provide clinicians with information on which patients may be suitable for such treatment with respect to renal function.

### Pharmacokinetics

Bisphosphonates are not metabolized, and are retained and re-cycled back into the circulation in the same molecular structure as in the parent formulation [6,7]. Oral bisphosphonate absorption is poor (<1% of the formulated dose). Due to their avid affinity for the bone (calcium-phosphorus surface) between 27% and 62% of the drug in the blood rapidly binds to bone mineral. Any remaining bisphosphonate is excreted via the kidneys, predominantly within the first few hours after administration [8,9]. Renal excretion occurs by both passive glomerular filtration and active transportation in renal proximal tubular cells [10,11]. These excretion pathways are common to many drugs. A number of these drugs are known to cause changes in kidney function and structure which may result in reversible or permanent renal dysfunction. Permanent renal damage has been reported in case reports using the 1st generation IV bisphosphonates, data not validated by randomized, controlled clinical trials [12–14].

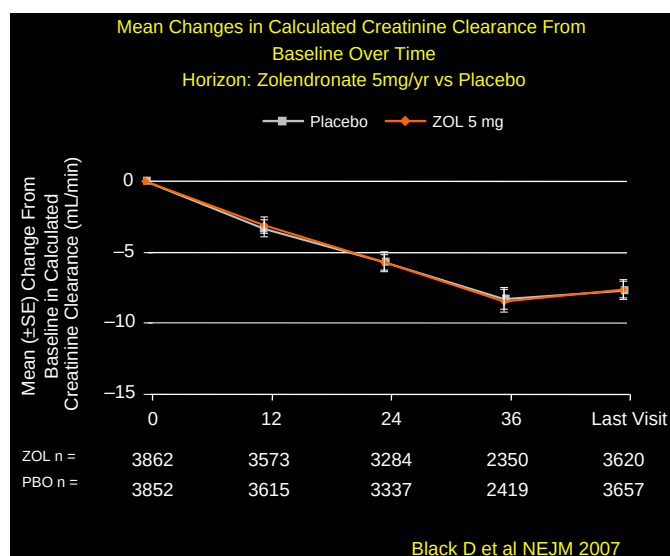
Following IV administration of bisphosphonates, approximately 50% of the dose is incorporated into the bone. Apart from a negligible amount of drug transiently exposed to other tissues, most of the remainder is also excreted unchanged in urine via the same filtration and proximal tubular secretion pathways as oral bisphosphonates. Bisphosphonates persist in bone for long durations, are slowly released during cycles of bone remodeling, and can reenter the systemic circulation, and also the kidney, with no change observed in their molecular structure or metabolic activity. In general bisphosphonates do not undergo any detectable metabolism, do not induce or inhibit cytochrome P450 activity, and do not use the anionic or cationic renal transport systems involved in the excretion of many other drugs [15–22].

### Risk of renal adverse effects

Early studies showed that rapid IV (200 mg/h) infusions of bisphosphonates such as etidronate, tiludronate, and clodronate were associated with acute renal failure and other adverse renal effects. These events were likely due to nephrotoxic effects of the high systemic drug concentrations on tubular cells. [17–22]. Data regarding rapid infusions of IV pamidronate and zoledronate provided additional evidence of direct renal effects and suggest that any renal adverse effect may be related to the C<sub>max</sub>, rather than the area under the curve (AUC). Rapid (<5 min) infusion of monthly pamidronate and/or monthly zoledronate in metastatic prostate and breast cancer or multiple myeloma trials was shown to induce acute increases in serum creatinine concentrations in some patients; while a slower infusion rate of the same dose/dosing interval was not associated with acute increases in serum creatinine concentrations [21–23]. Thus, in patients with oncologic conditions, the FDA label advises that the zoledronic acid dose is adjusted based on the pre-dose serum creatinine clearance levels and the infusion is given over 15 min. While anecdotal cases showing the development of a chronic glomerular lesion have been reported during the administration of IV pamidronate, these patients also had many other co-morbidities that have been associated with glomerulosclerosis [24,25]. For treatment of osteoporosis, oral bispho-

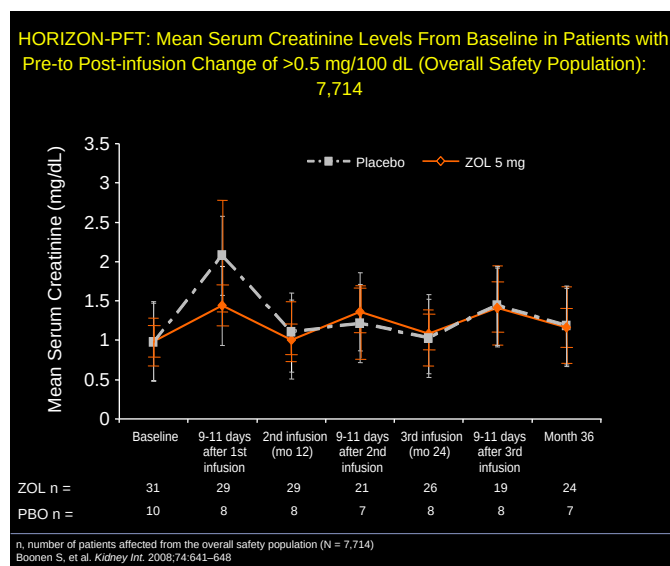
phonates have not been associated with adverse effects on renal function in populations treated in the guidelines of the registration labels. It is important to point out that most of the osteoporosis clinical trials did not enroll patients based on a pre-specified creatinine clearance, but a serum creatinine cut-off of <2.0 mg/dl. Hence, it is probable that many elderly patients with a low body mass index (BMI and/or body surface area {BSA}) which are major determinants of kidney size, glomerular filtration rate (GFR) and serum creatinine concentration had a creatinine clearance below 30 ml/min that were, nevertheless, randomized in the oral bisphosphonate trials [26–28]. In 2 post hoc studies of the pivotal risedronate and alendronate registration trials, approved doses of risedronate and alendronate reduced fracture risk and also did not alter renal function in postmenopausal women with Cockcroft–Gault estimated GFR determinations as low as 15 ml/min for a 2- to 3-year period of use. [29,30]. This post-hoc data has not been validated prospectively nor in patients with known intrinsic renal disease as opposed to the clinical trial populations where the reduction in GFR was felt to be “age-related” reductions in renal function [31–34]. Additionally, none of the patients randomized in any of the postmenopausal pharmacological clinical trials had elevated pre-treatment intact parathyroid hormone levels (PTH). Hence, results seen with any pharmacological agent registered for the treatment of postmenopausal osteoporosis (PMO) may not result in the same outcome in patients with elevated endogenous PTH values. The only bisphosphonate clinical trial that excluded and randomized patients based on an eGFR by the Cockcroft–Gault equation was the intravenous zoledronic acid trials: “HORIZON” (Reclast™; Novartis Pharmaceuticals Corporation, East Hanover, NJ) and IV ibandronate (Boniva; Roche Therapeutics Inc., Nutley, NJ) [35–37]. There is no standard of care in clinical practice in any nation that requires clinicians to perform a creatinine clearance for pre-treatment management of patients considered for bisphosphonate therapy despite the FDA labeling advising clinicians to avoid use of oral bisphosphonates in patients with a creatinine clearance <30–35 ml/min. The automatic reporting on commercial clinical laboratory printouts of the estimated glomerular filtration rate (eGFR) will provide clinicians with a fairly accurate estimation of glomerular filtration rate [24–27]. In those cases where the eGFR, which by either the Cockcroft–Gault (CG) or Modification of Diet in Renal Disease (MDRD) equations, both of which are highly correlated with the most accurate methods for determining GFR, falls below the lower level of GFR cut-off recommended by registration agencies for bisphosphonates, a well hydrated 24 hour urine for creatinine clearance will often be higher than the eGFR [38–41].

At registered doses for osteoporosis both IV bisphosphonates (zoledronic acid and ibandronate) show little risk of renal adverse events in patients with creatinine clearances >30 ml/min. Intravenous zoledronic acid has induced transient short term increases in serum creatinine concentrations in osteoporosis trials in a small but significant number of subjects. In the phase 3 Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)—Pivotal Fracture Trial in 7500 women with postmenopausal osteoporosis (mean age, 73 years), a 15-minute infusion of zoledronate 5 mg once yearly was associated with no increased risk of renal side effects over the course of 3 years compared with placebo (Fig. 1) [35]. Assessment of changes in serum creatinine concentrations at 9 to 11 days after the infusion in a subset (5500 patients) of the total randomized population showed that a small, though significant, percentage of patients receiving zoledronate had an increase in serum creatinine concentration of 0.5 mg/dl or more compared with patients given placebo (1.2% vs. 0.4%,  $P<0.05$ ) only after the second infusion (Fig. 2) [42]. In all of these patients increases in serum creatinine returned to baseline levels before the next annual infusion. In the HORIZON—Recurrent Fracture Trial, which included 2000 older male and female patients (mean age, 75.5 years) with recent low-trauma hip fracture, there were no significant differences between zoledronate 5 mg once yearly and placebo with regard to proportion of patients with a 0.5-mg/dl increase in serum creatinine (6.2% vs. 5.6%) or a reduction in eGFR to less than



**Fig. 1.** The change in estimated glomerular filtration rate (eGFR) over 3 years between the placebo vs. the treated groups in the HORIZON pivotal registration trial for postmenopausal osteoporosis. Ref. [35].

30 ml/min (8.2% vs. 7.3%) [36]. In the Dosing Intravenous Administration (DIVA) trial of IV and ibandronate, which involved 1395 postmenopausal women, the incidence of renal adverse events was low among groups receiving IV ibandronate by injection (2 mg every 2 months or 3 mg every 3 months) and no cases of acute renal failure reported or decreases in creatinine clearance were seen at any time point [37]. A pooled database including >3000 women with postmenopausal osteoporosis exposed to IV ibandronate at 2 to 12 mg annually also indicated no cases of acute renal failure or other significant adverse renal effects. [43]. Since there have been no head-to-head clinical trials comparing effects of intravenous zoledronic acid to intravenous ibandronate, there is no data on comparative renal safety between these 2 intravenous bisphosphonates. Recently the FDA sent out a newsletter to physicians reporting on 24 cases of acute renal failure reported post marketing with intravenous zoledronic acid in the osteoporosis population (Reclast™) [44]. Many of these patients had other (including renal) co-morbidities that might have put them at increased risk for acute renal failure. The clinical point is that



**Fig. 2.** The change in the short term serum creatinine concentration (days 9–11 post-infusion) between the placebo vs. the treated group in the renal safety sub-groups from the HORIZON pivotal registration trial for postmenopausal osteoporosis. Ref. [42].

### Bisphosphonate (BP) Use Across CKD Glomerular Filtration Rate (GFR) by Creatinine Clearance or estimated GFR (eGFR)

- 1. GFR < 90–30 (35)\* ml/min (stage 1–3 CKD)
- 2. Manage as one would for treatment indications for PMO with usual bisphosphonate dose
- 3. If biochemical tests suggest CKD-MBD\*\* consider strategies as recommended by KDIGO (Moe S et al KI 2009)
- 1. GFR < 30–15 ml/min (stage 4 CKD). Treat (off-label) patients at high risk for fracture with established\*\*\* osteoporosis; oral: usual doses for 2–3 yrs. IV: usual dose given slowly (>30 min).
- 2. GFR < 15 ml/min (stage 5 CKD). Only consider in fractured patients with established osteoporosis.
- Oral: ½ formulation for 2–3 yrs. IV: ½ formulation given very slow (> 60 minutes)

\* FDA label differs among BP's

\*\* Chronic kidney disease-mineral and bone disorder

\*\*\* Established osteoporosis has excluded CKD-MBD (Miller PD *Clev Clin Med J* 2009)

**Fig. 3.** A basic algorithm suggesting management strategies for groups of patients with low bone mineral density or low trauma fractures across the stages of normal to reduced glomerular filtration rate. Ref. [52].

before patients receive intravenous Reclast™ they should be well hydrated and not receiving agents that are known to possibly adversely affect kidney function. On balance, it appears that the risk of kidney damage in patients receiving IV bisphosphonates for osteoporosis is very small and can be further reduced by ensuring adequate hydration and use of appropriate infusion times (Fig. 3) [52].

### Treatment of osteoporosis in patients with impaired kidney function

The automatic reporting of eGFR on commercial laboratory reports will increase the challenges in making decisions about management of skeletal health in patients with reduced GFR. The National Kidney Foundation classifies chronic kidney disease into 5 stages based on calculations of GFR [39,41].

Patients who are suffering low-trauma fragility fractures with stage 1 through 3 CKD (GFR < 80–30 ml/min) are more likely to have osteoporosis than chronic kidney disease-mineral and bone disorder (CKD-MBD) as the cause of their impaired bone strength [44–46]. CKD-MBD is the acronym given by the National Kidney Foundation's Kidney Disease Improving Global Outcome to describe the abnormalities in bone turnover, mineralization and volume that accompany chronic kidney disease [47]. Although several articles have described a higher fragility fracture risk associated with age-related reduction in renal function compared with age-matched and bone mineral density matched patients with normal renal function, the specific metabolic bone disease other than osteoporosis accounting for this bone fragility has not been well defined. Hence, in patients with osteoporosis and who are in stage 1 through 3 CKD ranges of glomerular filtration rate who do not have a known biochemical abnormality (especially hyperphosphatemia or unexplained secondary hyperparathyroidism) that might suggest some form of CKD-MBD, can and should be considered for treatment with Food and Drug Administration-registered pharmacologic agents that reduce the risk for fractures in postmenopausal, male, or glucocorticoid-induced osteoporosis. [47–51]. It is important to emphasize that in the assessment of all patients with fragility fractures or low BMD secondary etiologies for bone fragility are excluded; and that all patients receive the recommended doses of calcium (1500 mg/day total intake) and vitamin D. Serum levels of 25 hydroxyvitamin D should be kept at least at 30 ng/ml or higher and replacement of vitamin D should be adjusted accordingly to achieve this end point [53]. Although those patients in stage 1 through 3 CKD as well as in stage 4 through 5D CKD who already have suffered fragility fractures are at high risk for future fractures and merit consideration for intervention with an

osteoporosis pharmacologic agent, intervention decisions in patients who have not suffered a fragility fracture are not defined as clearly. The recent publication of the WHO-validated 10-year fracture risk in untreated postmenopausal women and elderly men (FRAX™, WHO, Geneva, Switzerland) helps define levels of risk that facilitate intervention decisions. FRAX™, however, did not validate CKD in their model [54]. The US implementation guidelines for practical application of FRAX in the health care system also should make it easier for clinicians to decide who to treat based on absolute risk calculations [55].

Although all of the osteoporosis pharmacological registered agents have evidence of risk reduction for vertebral fractures, patients at higher fracture risk or who already have suffered a nonvertebral fracture are more often considered candidates for bisphosphonates which have evidence for global fracture risk reduction. Though this section deals with bisphosphonate use in patients with impaired GFR, comments about 2 other registered agents are appropriate. The recently approved fully human monoclonal antibody to RANKL, an osteoblast-derived glycoprotein, denosumab (Prolia™) merits comment. Denosumab, which also reduces global fracture risk in the postmenopausal population, is not cleared by the kidney and in a post-hoc analysis of the pivotal registration trial for PMO was safe and effective down to eGFR of 15 ml/min [56,57]. Likewise the anabolic agent, teriparatide both at 20 µg/day and 40 µg/day had a positive bone effect as measured by increases in osteoblast activity markers and BMD down to eGFR of 30 ml/min and without any adverse renal effects [58]. It is important to emphasize that in all of the teriparatide clinical trials, all patients, even those with an eGFR down to 30 ml/min, had normal baseline serum intact PTH levels. It is possible that the bone biological response could differ between patients with CKD who have an increased as compared with a normal serum PTH level.

Treatment decisions become more difficult to make in fracturing patients with stage 4 and especially stage 5 and 5D CKD, where the mortality rate is exceptionally high [59–61]. This is even the case when the clinician has determined to the best of his/her ability that the patient with stage 4 through 5D CKD has suffered a fragility fracture and has osteoporosis rather than CKD-MBD. There are no prospective data showing efficacy of any of the approved pharmacologic agents to treat osteoporosis at these levels of GFR. There are no data on the efficacy or safety of bisphosphonates of any formulation on fracture risk reduction in patients with a GFR less than 15 ml/min (stage 5 or 5D CKD). Nevertheless, the question often arises on opinions regarding the management of fragility fractures in this population. Here only opinion exists and is controversial, and leads us to appeal for good science and randomized prospective data in these groups. In my opinion, patients without fractures with stage 4, 5, or 5D CKD should not be given bisphosphonates or teriparatide off-label [52]. That is, treating only on the basis of low BMD and other risk factors would seem possibly to be associated with greater risk than benefit. In those 4 through 5D CKD patients suffering fragility fractures, a bisphosphonate may be considered but only after a thorough elimination of CKD-MBD. While the renal metabolic bone diseases (severe secondary hyperparathyroidism) are highly probable with intact parathyroid hormone levels (PTH) >400 pg/ml, or, (osteomalacia) with elevated bone specific alkaline phosphatase, the disease where reducing bone turnover is intuitively undesirable would be renal adynamic bone disease. An intact PTH under 150 pg/ml has a high sensitivity for adynamic bone disease [59]. In cases where the cause of fractures cannot be discriminated between osteoporosis and CKD-MBD, a quantitative bone histomorphometry can be diagnostic [62]. A transiliac bone biopsy is a safe procedure with little morbidity when performed in skilled hands. Once a diagnosis of osteoporosis appears to be the cause of fractures, then if one chooses to use a bisphosphonate after open informed consent by the patient, then in my opinion the formulation dose should be half of the registered dose, and restrict the use to no more than 3 years [52,63]. For the intravenous formulation, zoledronic acid, the infusion rate should be slower—e.g. 60 min or longer. This approach is based on the known pharmacokinetics of bisphosphonates in human beings with normal renal

function: 50% of an administered dose goes to bone and 50% gets excreted by the kidney. Thus, with severe impairment of renal function, and because the ability of bisphosphonates to be dialyzed has not been well studied, it seems reasonable to give half the usual dose. The limitation of administration to no more than 3 years is based on the unknown, but probable, greater bone retention of bisphosphonates when excretion is impaired. It should be stressed that these approaches are based on no evidence for efficacy but are considered in extreme cases of often recurrent fragility fractures in which the fractures per se pose a great risk for morbidity and mortality. These approaches should be clearly discussed with the patient, be undertaken by specialists knowledgeable in complex metabolic bone disease management, and be initiated only after the disease leading to fractures is well characterized.

One final comment is justified in considerations for using any agent that reduces bone turnover in patients with CKD, especially more severe stage 3 to stage 5 CKD. There is experimental data that suggests that there may be a link between low bone turnover and an increased risk of cardiovascular disease. The hypothesis is that in situations where absorbed phosphorus cannot either be adequately eliminated by the kidney or taken up into bone tissue that has low bone remodeling, a depository tissue for phosphorus (and calcium) is the vasculature [64]. These intriguing links between bone and vasculature merit validation in prospective human being investigations but should be made aware by the medical community considering any agent that reduces bone turnover in more severe CKD.

## Conclusions

Although there is no consensus regarding the criteria for the diagnosis of osteoporosis in stage 4, 5, and 5D CKD, there seems to be wider agreement that the WHO criteria and/or low-trauma fractures can be used for the diagnosis of osteoporosis in stage 1 through 3 CKD because many of the patients randomized in the prospective registration trials for osteoporosis pharmacologic agents had these levels of GFR.

This agreement also is predicated on the absence of biochemical abnormalities that might suggest CKD-MBD, and here the recent KDIGO (2008) guidelines provide excellent leadership in these areas [58]. In patients with stage 1 through 3 CKD (prospective data with all formulations) and stage 4 CKD (post-hoc data with oral formulations) bisphosphonates are effective and safe. Intravenous zoledronic acid should not be given under a 15 minute infusion time and the patients should be well hydrated and, if possible, not have concomitant presence of other agents that may increase the risk for renal damage (intravenous contrast dye, and non-steroidal anti-inflammatory drugs). If there are any concerns for renal safety, slowing the infusion rate to 30 min or longer appears to reduce risk in clinical experience. The use of bisphosphonates in stage 5 CKD should only be considered off-label, in patients whose mortality, as a consequence of their fractures alone is high, and other forms of CKD-MBD have been excluded. It is unknown if bisphosphonates, by reducing bone turnover in a pre-existing low bone turnover state, would help or harm bone or lead to more or less cardiovascular disease, which in CKD may often be associated with low bone turnover. These questions must be addressed by better science and prospective data. In clinical practice, at the current time and with current limited knowledge, treatment of osteoporosis in stage 4, 5, and 5D CKD is opinion based.

After 40 years of bisphosphonate use in many metabolic bone diseases, including the most prevalent, osteoporosis, bisphosphonates are safe and effective and their benefit to risk ratio exceedingly favors a benefit used in the right populations and in the right formulations for the right duration. Bisphosphonates are not nephrotoxic drugs though intravenous zoledronic acid administration must follow labeled guidelines.



## References

- [1] Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008;19:733–59.
- [2] Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin North Am* 1998;27:419–39.
- [3] Food and Drug Administration, U.S. Department of Health and Human Services. Guidance for industry. Pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. Available at: <http://www.fda.gov/cder/guidance/1449fnl.pdf> 1998 Accessed 3/29/2010.
- [4] Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: a growing concern. *Kidney Int* 2008;2:1–11.
- [5] Coresh J, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Examination Survey. *Am J Kidney Dis* 2003;41(1):1–12.
- [6] Papapoulos SE. Pharmacodynamics of bisphosphonates in man: implications for treatment. In: Bijvoet OLM, Fleisch H, Canfield RE, Russell RGG, editors. Bisphosphonate therapy in acute and chronic bone loss. Amsterdam: Elsevier Science; 1995. p. 231–45.
- [7] Russell RGG, Rogers M. Bisphosphonates: from the laboratory to the clinic and back again. *Bone* 1999;25:97–106.
- [8] Mitchell DY, Barr WH, Eusebio RA, Stevens KA, Duke FP, Russell DA, et al. Risedronate pharmacokinetics and intra- and inter-subject variability upon single dose intravenous and oral administration. *Pharm Res* 2001;18:166–70.
- [9] Kahn SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. *J Bone Miner Res* 1997;12:1700–7.
- [10] Luhe A, Kunkle KP, Haiker M, Schad K, Zihlmann C, Baus F, et al. Preclinical evidence for nitrogen-containing bisphosphonate inhibition of farnesyl diphosphate (FPP) synthase in the kidney: implications for renal safety. *Toxicol In Vitro* 2008;22:899–909.
- [11] Troehler U, Bonjour JP, Fleisch H. Renal secretion of diphosphonates in rats. *Kidney Int* 1975;8:6–13.
- [12] Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. *Nat Clin Pract Nephrol* 2006;2:80–91.
- [13] Chen T, Berenson J, Vescio R, Swift R, Gilchick A, Goodin S, et al. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002;42:1228–36.
- [14] Phipps R, Christiansen C, Burgio D, Sun L, Russell D, Keck B, et al. Comparison of risedronate and alendronate pharmacokinetics at clinical doses. *Osteoporos Int* 2003(suppl 17):38.
- [15] Lassetter KC, Porras AG, Denker A, Santhanagopal A, Daifotis A. Pharmacokinetic considerations in determining the terminal elimination half-lives of bisphosphonates. *Clin Drug Investig* 2005;25(2):107–14.
- [16] Mitchell DY, Eusebio RA, Sacco-Gibson NA, Pallone KA, Kelly SC, Nesbitt JD, et al. Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. *J Clin Pharmacol* 2000;40:258–65.
- [17] Body JJ, Pfister T, Baus F. Preclinical perspectives on bisphosphonate renal safety. *Oncologist* 2005;19(suppl 1):3–7.
- [18] Dumon JC, Magritte A, Body JJ. Efficacy and safety of the bisphosphonate tiludronate for the treatment of tumor-associated hypercalcemia. *Bone Miner* 1991;15:257–66.
- [19] O'Sullivan TL, Akbari A, Cadnapahornchai P. Acute renal failure associated with the administration of parenteral etidronate. *Ren Fail* 1994;16:767–73.
- [20] Kanis JA, Preston CJ, Yates AJ, Percival RC, Mundy KI, Russell RG. Effects of intravenous diphosphonates on renal function. *Lancet* 1983;1:1328.
- [21] Adams S, Zamberlan N. Adverse effects of bisphosphonates: a comparative review. *Drug Saf* 1996;14(3):158–70.
- [22] Aredia (pamidronate) [injection prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2007.
- [23] Zometa (zoledronic acid) [injection prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2007.
- [24] Markowitz GS, Appel GB, Fine PL, Fennes AZ, Loon NR, Jagannath S, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol* 2001;12:1164–72.
- [25] Markowitz GS, Fine PL, Stack JL, Kunis CL, Radhakrishnan J, Palecki W, et al. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 2003;64:281–9.
- [26] Lindeman RD. Assessment of renal function in the old. Special considerations. *Clin Lab Med* 1993;13:269–77.
- [27] Lafayette RA, Perrone RD, Levey AS. Laboratory evaluation of renal function. In: Schrier RW, Gottschalk CW, editors. *Diseases of the kidney*. 5th ed. Boston/Toronto/London: Little, Brown, and company; 1993. p. 333–70.
- [28] Lin J, Knight EL, Hogan ML, et al. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. *J Am Soc Nephrol* 2003;14:2573–80.
- [29] Miller PD, Roux C, Boonen S, Barton I, Dunlap L, Burgio D. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005;20(12):2015–115.
- [30] Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res* 2007;22(4):503–8.
- [31] Levey AS, Coresh J, Balk E, et al. National Kidney Foundation clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137–47.
- [32] Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005;67:2089–100.
- [33] Bennett WM. Reporting eGFR. *Clin J Am Soc Nephrol* 2008;3:1561–2.
- [34] Glasscock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008;3:1563–8.
- [35] Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–22.
- [36] Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357:1799–809.
- [37] Delmas PD, Adams S, Strigala C, Stakkestad JA, Reginster JY, Felsenberg D, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006;54:1838–46.
- [38] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
- [39] National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2009;39:S1–S266.
- [40] Levey AS, Bosch JP, Coggins CH, Greene T, Mitch WE, Schulchter MD, et al. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. *J Am Soc Nephrol* 1996;7:556–66.
- [41] National Kidney Disease Education Program Laboratory Professionals: Estimating and Reporting GFR. National Kidney Disease Education Program. [http://www.nkdep.nih.gov/labprofessionals/estimate\\_report\\_gfr.htm](http://www.nkdep.nih.gov/labprofessionals/estimate_report_gfr.htm) Accessed 23 June 2010.
- [42] Boonen S, Sellmeyer DE, Lippuner K, Orlov-Morozov A, Abrams K, Mesenbrink P, et al. Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women. *Kidney Int* 2008;74:641–8.
- [43] Lewiecki EM, Miller PD. Renal safety of intravenous bisphosphonates in the treatment of osteoporosis. *Expert Opin Drug Saf* 2007;6(6):1–10.
- [44] US Food and Drug Administration (FDA). Drug Safety Newsletter, Volume 2; 2009. Number 2.
- [45] Dukas LC, Schacht E, Mazor Z, Stähelin HB. A new significant and independent risk factor for falls in elderly men and women: a low creatinine clearance of less than 65 ml/min. *Osteoporos Int* 2005;16(3):332–8.
- [46] Ensrud KE, Lui LY, Taylor BC, et al. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 2007;167(2):133–9.
- [47] Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 2006;17(11):3223–32.
- [48] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009(113):S1–S130.
- [49] Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Curr Osteoporos Rep* 2005;3(1):5–12.
- [50] Gal-Moscovici A, Sprague SM. Osteoporosis and chronic kidney disease. *Semin Dial* 2007;20(5):423–30.
- [51] Miller PD. Diagnosis and treatment of osteoporosis in chronic renal disease. *Semin Nephrol* 2009;29(2):144–55.
- [52] Miller PD. Fragility fractures in chronic kidney disease: an opinion-based approach. *Cleve Clin J Med* 2009;76(12):715–23 Review.
- [53] Gal-Moscovici A, Sprague SM. Use of vitamin D in chronic kidney disease patients. *Kidney Int* 2010;78:146–51.
- [54] Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007;18:1033–46.
- [55] Dawson-Hughes B, Looker AC, Tosteson AN, Johansson H, Kanis JA, Melton III LJ. The potential impact of the new National Osteoporosis Foundation guidance on treatment patterns. *Osteoporos Int* 2010;21:41–52.
- [56] Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756–65.
- [57] Jamal<sup>1</sup> SA, Ljunggren<sup>2</sup> O, Stehman-Breen<sup>3</sup> C, Cummings<sup>4</sup> SR, McClung<sup>5</sup> MR, Goemaere<sup>6</sup> S, Ebeling<sup>7</sup> PR, Franek<sup>8</sup> E, Yang<sup>3</sup> Y, Egbuna<sup>3</sup> OI, Steven Boonen<sup>9</sup>, Miller<sup>10</sup> PD. The effects of denosumab on fracture and bone mineral density (BMD) by level of renal function. *J Bone Miner Res* in press.
- [58] Miller PD, Schwartz EN, Chen P, Misurski DA, Kregg JH. Teriparatide in postmenopausal women with osteoporosis and impaired renal function. *Osteoporos Int* 2007;18:59–68.
- [59] Moe S, Drüeke T, Cunningham J, Goodman W, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69(11):1945–53.
- [60] Dooley AC, Weiss NS, Kestenbaum B. Increased risk of hip fracture among men with CKD. *Am J Kidney Dis* 2008;51(1):38–44.
- [61] Lindberg JS, Moe SM. Osteoporosis in end-stage renal disease. *Semin Nephrol* 1999;19(2):115–22.
- [62] Miller PD. The role of bone biopsy in patients with chronic renal failure. *Clin J Am Soc Nephrol* 2008;3(Suppl 3):S140–50.
- [63] Miller PD. Is there a role for bisphosphonates in chronic kidney disease? *Semin Dial* 2007;20(3):186–90.
- [64] Hruska KA, Mathew S, Lund R, et al. The pathogenesis of vascular calcification in the chronic kidney disease mineral bone disorder: the links between bone and the vasculature. *Semin Nephrol* 2009;29(2):156–65.