

Bisphosphonates in Chronic Kidney Disease; Balancing Potential Benefits and Adverse Effects on Bone and Soft Tissue

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Cardiovascular disease is highly prevalent in chronic kidney disease (CKD) and is often associated with increased vascular stiffness and calcification. Recent studies have suggested a complex interaction between vascular calcification and abnormalities of bone and mineral metabolism, with an inverse relationship between arterial calcification and bone mineral density (BMD). Although osteoporosis is recognized and treated in CKD 1 to 3, the interpretation of BMD levels in the osteoporotic range is controversial in CKD 4, 5, and 5D when renal osteodystrophy is generally present. In addition, there is a paucity of data for patients with CKD mineral and bone disorder (MBD), because studies using bisphosphonates in postmenopausal and glucocorticoid-induced osteoporosis have generally excluded patients with significant CKD. For these patients, treatment of low BMD using standard therapies for osteoporosis is not without potential for harm due to the possibility of worsening low bone turnover, osteomalacia, mixed uraemic osteodystrophy, and of exacerbated hyperparathyroidism; and bisphosphonates should only be used selectively and with caution. Some experimental and clinical studies have also suggested that bisphosphonates may reduce progression of extra-osseous calcification and inhibit the development of atherosclerosis. The authors review the potential benefits and risks associated with bisphosphonate use for bone protection in CKD, and assess their effect on vascular calcification and atherosclerosis.

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Cardiovascular disease (CVD) represents the leading cause of mortality for patients with chronic kidney disease (CKD) and, depending on the age group examined, patients on dialysis have a three- to 30-fold increase in mortality compared with the general population (1). Vascular calcification and increased arterial stiffness are major contributors to CVD, and both are independent predictors of cardiovascular mortality (2–4). In the general population, a strong inverse relationship has been reported between cardiovascular morbidity or mortality and bone mineral density (BMD) (5,6), and a similar relationship exists between BMD levels and vascular calcification (7,8). This relationship has also been reported in some, but not all, studies of patients with CKD (9–11). Calcium apatite forms the crystal component of bone and has been found to accumulate in calcified blood vessels of many patients with CKD. The discovery that similar factors mediate both vascular calcification and bone mineralization supports an important interaction of bone disorders and calcification of soft tissues (12).

Bisphosphonates are bone antiresorptive agents widely used to treat postmenopausal or glucocorticoid-induced osteoporosis

and other conditions characterized by excessive osteoclastic bone resorption, such as Paget's disease, multiple myeloma, osteolytic bone metastases, and humoral hypercalcemia of malignancy. Bisphosphonates closely resemble pyrophosphate compounds in binding to hydroxyapatite in bone. Upon osteoclastic bone resorption, bisphosphonate release causes osteoclast death and a consequent reduction in bone resorption, without an equivalent decrease in bone formation. This leads to a shift toward an initial net increase in bone mass, although after a delay there is a decrease in bone formation. Because bone remodeling and vascular calcification appear closely linked in patients with CKD, there has been interest in applying therapeutic strategies that influence this interaction. In experimental and clinical studies, bisphosphonate administration has been reported to reduce the progression of extraosseous calcification, and recent reviews have suggested bisphosphonates as potential therapies to reduce progression of vascular calcification (13,14). This review examines the status of bisphosphonate use in CKD as prophylaxis against reduction in BMD, in fracture prevention, and as a means to reduce vascular calcification and atherosclerosis. Possible adverse effects that may limit the widespread application of this therapy are also addressed.

Bisphosphonate Actions

Bisphosphonates can be classified into two groups with different molecular modes of action: the simpler, non-nitrogen-

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containing bisphosphonates (clodronate and etidronate) and the more potent, nitrogen-containing bisphosphonates (alendronate, ibandronate, pamidronate, risedronate, and zoledronate). The relative potency of these agents varies as shown in Table 1. Intestinal absorption of bisphosphonates is low (<1% for alendronate, ibandronate, and risedronate, 3% to 7% for etidronate (15)) and can be reduced further if they are not taken as prescribed: with a glass of tap water and at least 30 min before food or other fluids (15,16). Once absorbed, bisphosphonates have a high affinity for bone mineral, binding to calcium in the hydroxyapatite crystal with a variable half-life in the skeleton that may be as long as 10 yr (17,18). The remainder of the absorbed bisphosphonate not bound to bone (40% to 60%) is not metabolized and is eliminated unchanged by renal excretion (19). During osteoclastic bone resorption, at acid pH beneath the osteoclast, the negative charge on bisphosphonates is neutralized and the bisphosphonate goes into solution, whereupon it can be incorporated into osteoclast vesicles, passing through the osteoclast and into the circulation, where it again undergoes either renal excretion or recirculation back to bone. This bisphosphonate recycling to bone surfaces may explain some differences between compounds. After cessation of treatment, small quantities of bisphosphonates can be detected in the urine for weeks to months (20), and even up to 8 yr (21), due to gradual release from bone.

During passage through the osteoclast, some bisphosphonate is released from transcytotic vesicles. In the case of nitrogen-containing bisphosphonates, this causes inhibition of the enzyme farnesyl pyrophosphate (FPP) synthase (22), a key enzyme in the mevalonate pathway, which is necessary for the production of FPP and geranylgeranyl diphosphate (23) (Figure 1). Inhibition of FPP prevents prenylation of small GTPase signaling proteins required for normal cellular function and survival of osteoclasts (24). These compounds provide the lipid tails for signaling proteins that influence essential osteoclast functions of terminal differentiation, attachment, endocytosis, cell shape, and apoptosis. As opposed to the nitrogen-containing bisphosphonates, etidronate and clodronate do not inhibit FPP synthase but are incorporated into nonhydrolyzable analogues of adenosine triphosphate that accumulate intracellu-

Table 1. Relative potencies of bisphosphonates for inhibiting bone resorption and IC₅₀ values for inhibiting FPP synthase

Bisphosphonate	Potency ^a	IC ₅₀ (nmol/L) ^b
Etidronate	~1×	–
Clodronate	~10×	–
Pamidronate	~100×	200
Alendronate	>100 to <1000×	50
Ibandronate	>1000 to <10,000×	20
Risedronate	>1000 to <10,000×	10
Zoledronate	>10,000×	3

^aAdapted from Fleisch (18). These rat data correspond well with those from human studies. ^bAdapted from Dunford *et al.* (147), using partially purified recombinant enzyme.

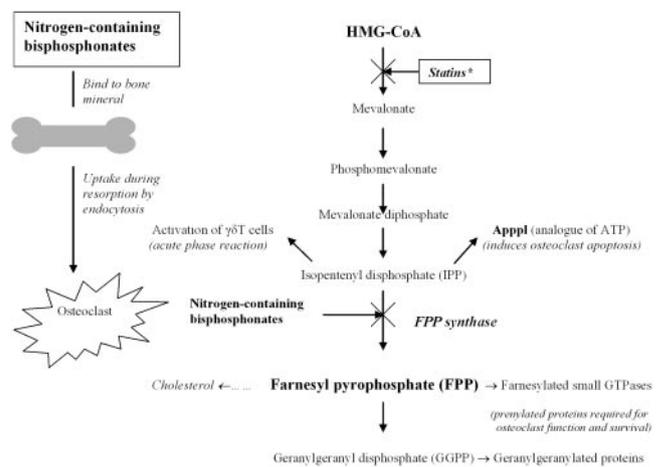


Figure 1. Diagram showing the action of nitrogen-containing bisphosphonates on inhibiting FPP synthase, preventing the synthesis of FPP and GGPP (both required for protein prenylation) and leading to accumulation of IPP. * Statin therapy (HMG CoA reductase inhibitors) act in the same pathway but are targeted to liver, not bone. HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; ATP, adenosine triphosphate; GTP, guanosine triphosphate.

larly in osteoclasts, where they inhibit mitochondrial energy production and induce osteoclast apoptosis (25). Because etidronate is less potent at osteoclast killing, very high doses are required, yet it binds avidly to calcium crystals in bone. This can lead to crystal coating, may inhibit further crystal formation and aggregation and may be associated with osteomalacia. Very high doses of other bisphosphonates can have similar effects, but due to the greater potency of nitrogen-containing bisphosphonates, these drugs are used at lower doses and are less likely to cause crystal coating.

Because FPP synthase is found in all cells, high-dose bisphosphonates may directly influence cellular targets distinct from osteoclasts, including cells of the osteoblastic lineage (osteoblasts and osteocytes) (26). Beyond bone, intravenous (IV) bisphosphonates can block FPP production in monocytes, resulting in an accumulation of isopentenyl diphosphate (IPP) (Figure 1). Because IPP is also a bacterial antigen, peripheral blood $\gamma\delta$ T cells recognize this as a bacterial infection, releasing TNF- α and IFN- γ , increasing levels of IL-6 and CRP, and causing the flu-like symptoms that may be associated with first bisphosphonate doses (27–29). Subsequent anergy of $\gamma\delta$ T cells results in these symptoms seldom recurring on subsequent exposure. Before absorption, bisphosphonates taken orally can bind to gastric cells, where inhibition of FPP synthase rapidly leads to cell death. This may explain the ability of orally administered nitrogen-containing bisphosphonates to cause esophagitis and ulceration (15).

Bone Disorders Associated with CKD

On bone biopsy, the most commonly reported form of renal osteodystrophy is high-turnover hyperparathyroid bone disease (osteitis fibrosa), often with abnormal mineralization

(mixed uraemic osteodystrophy) (30). With increased bone turnover and a mismatch between coupling of bone formation to resorption, calcium and phosphate are released from bone and may cause an increase in levels of serum calcium and phosphate. Low bone turnover, or adynamic bone disease, is generally associated with inappropriately low levels of parathyroid hormone (PTH) and was previously associated with aluminum deposition in bone. It too may be associated with increased serum calcium and phosphate levels because when turnover is low, bone ceases to buffer dietary calcium or phosphate loads. Both conditions are associated with increased vascular calcification (9,31) and with calciphylaxis (32). Metabolic bone disorders associated with CKD influence bone quality and contribute to high rates of hip and vertebral fracture (33–35). Reflecting an increased recognition of the close relationship of mineral metabolism to bone abnormalities; vascular calcification; and the patient-level consequences of fracture, CVD, and increased mortality, the term “chronic kidney disease-mineral and bone disorder” (CKD-MBD) was recently introduced to encompass one or more combinations of these abnormalities (36).

Many patients with CKD have low bone mass. Although age-related osteoporosis would be a common cause in the general population, the etiology may be complex when CKD is present. Osteoporosis is a systemic disease of impaired bone strength and increased fragility that predisposes to an increased risk of low-trauma fracture. World Health Organization criteria define osteoporosis as a BMD measured by dual-energy x-ray absorptiometry (DXA) ≥ 2.5 SD below the mean BMD of a young normal Caucasian female population, whereas osteopenia is defined as a value between -1 and -2.5 SD below this mean. A limitation of this definition is that bone microarchitecture is a major contributor to bone strength and is not adequately assessed by DXA.

Patients with CKD 1 to 3 may have few identifiable abnormalities of mineral metabolism and share traditional risk factors of age, gender, and hypogonadism with the general community. If CKD-related abnormalities of vitamin D metabolism and PTH can be excluded, these people may be diagnosed with osteoporosis and offered standard treatments. With worsening CKD, the prevalence of osteoporotic-range BMD values increases (37–39). However, particularly in patients with CKD 4–5D, metabolic acidosis, inadequate levels of 25-hydroxyvitamin D, calcitriol deficiency, and the almost universal presence of renal osteodystrophy complicate a BMD-based diagnosis of osteoporosis (39,40). Because DXA is a two-dimensional “areal” rather than a volumetric measure, artifactual increases in BMD due to calcified soft tissue in the path of the x-ray beam may further complicate the interpretation of BMD (41–43). Abnormalities in levels of serum PTH, alkaline phosphatase (ALP), or bone-specific alkaline phosphatase (BALP) may assist in alerting the clinician to complicating renal osteodystrophy, but often lack sensitivity or specificity except toward the extremes. Given these limitations, quantitative double tetracycline-labeled bone histomorphometry remains the only means of confidently excluding other pathologies in severe CKD. For a diagnosis of osteoporosis, biopsy would be expected to reveal

low trabecular bone volume and disrupted microarchitecture, without significant abnormalities in mineralization or bone turnover.

Bisphosphonate Use in Patients with CKD and Low BMD

Used appropriately, bisphosphonates clearly provide fracture protection for patients with osteoporosis in the general community, and many patients with CKD are treated with bisphosphonates in the hope of similar efficacy (44,45). The presence of renal disease has been a general exclusion criterion in studies of bisphosphonate efficacy, but on the basis of calculated levels of estimated GFR (eGFR), considerable numbers of patients with CKD 1 to 3 participated in these studies. One pooled analysis of nine clinical trials (8996 postmenopausal women) suggested that when secondary causes of low BMD are excluded and blood levels of calcium, phosphate, PTH, ALP, and vitamin D are normal (laboratory features of CKD-MBD), bisphosphonate use in CKD 1 to 3 is safe and results in fracture reduction (46).

The value of bisphosphonate treatment in more severe forms of CKD is unknown because there are virtually no data for CKD 4 to 5D. Nevertheless, patients with CKD 3 who are being treated with bisphosphonates may progress to CKD 4 to 5D, and a number of patients with CKD 4 to 5D who fracture will be found to have BMD levels in the osteoporotic range. More data are required so that informed treatment decisions can be made in these groups. The analysis described above did report that bisphosphonates may reduce fracture risk in those with severe CKD and median GFR 27 ml/min (46). However, women in this analysis were elderly (average age, 83 ± 5 yr) and, unlike many patients seen by nephrologists with CKD 4 or 5, did not have elevated PTH levels nor symptoms or signs of CKD. In fact, as a result of differences in the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) calculations, the average MDRD eGFR was 42 ml/min, placing most subjects in CKD 3 (47). Secondary analysis of another study, the Fracture Intervention Trial (FIT), in which women were randomly assigned to placebo or alendronate, showed significant increases in total hip BMD and reduced risk of clinical fractures with alendronate, irrespective of baseline renal function (48). This finding was more pronounced in those with creatinine clearance (CrCl) <45 ml/min, and adverse events were similar between alendronate and placebo irrespective of baseline kidney function. However women with a serum creatinine level >1.6 mg/dl were excluded from the study.

Although data on bisphosphonate use in CKD 5 is limited, one randomized placebo-controlled trial of 31 hemodialysis (HD) patients demonstrated that hip BMD remained stable after 6 mo in patients treated with alendronate, compared with a reduction in those treated with placebo (49). However, despite being significant, the difference was minimal, and the treatment time was short. Therefore, in CKD 4 and certainly in CKD 5, bone biopsy should be considered before commencing bisphosphonates, and therapy should be individualized for specific indications. Because bisphosphonates have not been shown to prevent fractures in people with normal BMD or with

low baseline markers of bone formation, the subset of patients with severe CKD who might receive therapy would be those with low BMD but high bone resorption. Even in this group, bisphosphonate should be used with caution, because by reducing bone resorption and causing incremental reductions in levels of serum ionized calcium, bisphosphonates may stimulate glandular release of PTH and induce parathyroid hyperplasia over time.

Bisphosphonate Use in CKD for Hyperparathyroidism

The hypothesis that bisphosphonates may be useful in renal osteodystrophy was tested initially in animal models, and potential benefits for CKD-induced hyperparathyroidism were demonstrated. In nephrectomized rats, ibandronate prevented increases in erosion depth and bone turnover (50), and olpadronate lessened decreases in BMD associated with high-turnover bone disease (51). Clinically, the affinity of bisphosphonates to bone in dialysis patients is related to the degree of hyperparathyroidism, although bisphosphonates' effects in CKD 5D have been examined only in a limited number of studies. Administration of clodronate in 9 HD patients with severe hyperparathyroidism produced inhibition of osteoclast-mediated bone resorption, with decreased calcium, phosphate, and hydroxyproline (52); in other studies, skeletal deposition of clodronate correlated positively with PTH levels (53,54).

Bisphosphonate Use for Hypercalcemia and Multiple Myeloma in CKD

Successful use of bisphosphonates in the treatment of hypercalcemia has been documented for many years in case reports and case series in CKD (55). One case study reported pamidronate to be safe and effective in 10 patients with CKD 5D (56). Hypercalcemia is common in multiple myeloma, and approximately 30% of patients with myeloma have renal impairment at the time of diagnosis; approximately 50% are affected during the course of the disease. Many develop end-stage kidney disease, but limited case series have reported on bisphosphonate administration in this group. Ibandronate was effective in reducing hypercalcemia and improving renal function in seven patients with myeloma hospitalized for acute renal failure (57), and in a study of 6 HD patients with myeloma, ibandronate was well tolerated, with effective clearance of ibandronate levels by HD (58).

Dose Adjustments in CKD

Most of the safety data on bisphosphonates in CKD come from the management of hypercalcemia in patients with renal insufficiency (56,58). Because bisphosphonates are renally cleared, slower infusion rates and lower doses than those of standard osteoporosis management are generally used in patients with severe CKD. However, because of the lack of clinical trials in this population, clear recommendations on dose, schedule, and duration of infusion are lacking. Several case series have described pamidronate use in CKD to be safe at doses of 60 to 90 mg administered every 1 to 2 mo (59–61). The phar-

macokinetics of pamidronate, zoledronate, and ibandronate in different stages of CKD has been studied in cancer patients with varying evidence of drug accumulation (62–64). In one study, elimination of pamidronate was slower in patients with CrCl < 30ml/min, although the plasma accumulation may not have been clinically relevant because successive doses of pamidronate were separated by weeks (62). Administration of zoledronate showed no evidence of drug accumulation or worsening of renal function in 19 patients with bony metastases, despite varying degrees of renal insufficiency (63). In another study, the area under the curve for ibandronate was significantly different for CrCl < 30ml/min compared with CrCl > 80ml/min in 40 patients with multiple myeloma, but with no deterioration in renal function after administration (64).

The effect of dialysis on bisphosphonate pharmacokinetics has also been studied, although with smaller patient numbers. For peritoneal dialysis, one study reported equal peritoneal and renal clearance of technetium-labeled bisphosphonate compared with clearance of plasma chromium-EDTA (65). When given immediately before HD, clodronate was effectively removed, with 35% to 53% of the injected dose measured in dialysate (52,66). Ibandronate and pamidronate are also effectively removed by HD (67,68). One study in 16 HD dialysis patients assessed the pharmacokinetics and bone uptake of IV ibandronate, administered directly after dialysis thrice weekly (69). In this study there was high bone binding of ibandronate, but no correlation of bone binding with parameters of osteoclast activity or PTH. It was suggested that as a result of high bone binding in these patients, a 2-mg dose of IV ibandronate was equivalent to a 4- to 5-mg dose in patients with normal renal function. Thus many clinicians halve the dose or reduce the frequency of administration of bisphosphonates in CKD. When severe CKD is present, the suggested treatment duration may be limited to 2 yr (70).

Bisphosphonates During Glucocorticoid Treatment and After Transplantation

In glucocorticoid-treated patients without renal impairment, bisphosphonates prevent or attenuate bone loss and reduce fractures (71–73). However in patients with CKD who begin glucocorticoid treatment, calcium and cholecalciferol or ergocalciferol should be first-line prophylaxis against loss of BMD, unless contraindicated by hypercalcemia. This combination may improve BMD and provide fracture protection for patients with few risk factors who are likely to be exposed to glucocorticoids for up to 3 mo (74). Calcitriol has proven efficacy against glucocorticoid-induced loss of BMD in nonrenal settings (75) and may also be of benefit to glucocorticoid-exposed patients with CKD, especially when hyperparathyroidism is present. The role of bisphosphonates for patients with severe CKD who are treated with glucocorticoids remains unclear. As discussed earlier, interpretation of BMD data is complex, and for patients with low bone turnover, there is concern that a further reduction in bone remodeling caused by bisphosphonates may contribute to a deterioration of microarchitecture and increase fracture risk. With these limitations in mind, a recent randomized study in 114 CKD patients (CrCl > 30 ml/min) who

received glucocorticoid therapy for more than 6 mo before enrolment showed significant 1-yr increases in lumbar BMD after risedronate, with or without vitamin D, compared with patients treated with vitamin D alone (76). Another study assessed the effect of bisphosphonates on change in BMD in patients with CKD (baseline GFR between 73 and 81 ml/min) who were receiving high-dose corticosteroids (77). This small study involving 38 subjects randomly assigned treatment groups to alfacalcidol, risedronate, or both and reported that combined therapy was more effective in reducing loss of BMD.

After renal transplantation, fracture rates in CKD are higher than for patients on dialysis (78). Bisphosphonates have been shown in numerous studies to prevent BMD loss after renal transplantation (79,80), but there has generally been no evidence of fracture reduction (81,82). The latter may reflect a lack of statistical power in these studies or may result from a true absence of effect of bisphosphonates on improving bone strength after transplantation, despite attenuating BMD losses (83). A Cochrane review on the treatment of bone disease after renal transplantation examined the use of bisphosphonates, as well as vitamin D and calcitonin, and reported that no individual intervention was associated with a reduction in fracture risk compared with placebo (84). In this analysis, all interventions had a beneficial effect on BMD at the lumbar spine, and bisphosphonates and vitamin D improved BMD at the femoral neck, although bisphosphonates were more effective at preventing BMD loss compared with vitamin D.

A significant concern with regard to bisphosphonate use after transplantation is the potential to prolong or induce adynamic bone. Few studies include bone biopsy data, but in the study by Coco *et al.* (82), which included baseline and 6-mo bone biopsies after pamidronate therapy, six of the six patients treated with pamidronate and having bone biopsies developed adynamic bone, compared with three of eight control patients. However, only 14 of 72 patients in this study underwent bone biopsies, so it is difficult to extrapolate these results. Nevertheless, if bisphosphonates are to be used after transplantation, treatment should be individually targeted to patients deemed at most risk of fracture, in the knowledge that many will have persisting abnormalities of PTH, vitamin D metabolism, phosphate and calcium homeostasis, and reductions in eGFR.

Bisphosphonates and Atherosclerosis

Bisphosphonates have been shown to accumulate in atherosclerotic aortas, in femoral vessels (85), and in healthy aortas without atheroma (86). Although they may bind with high affinity to calcium in atherosclerotic deposits, bisphosphonates may also be taken up into arteries by macrophage phagocytosis (87). Once phagocytosed, bisphosphonates have been reported to affect the ability of macrophages to internalize atherogenic LDL cholesterol and subsequent transformation into foam cells (88). Bisphosphonates can also induce macrophage apoptosis by inhibiting intracellular enzymes, and they may inhibit sterol biosynthesis (89). Etidronate was the first bisphosphonate reported to suppress the formation of atherosclerotic lesions in the arteries of rabbits fed on high-cholesterol diets and vitamin D, without any change in serum calcium (90). Experimental

studies of etidronate, pamidronate, and clodronate have shown inhibition of development of atherosclerosis without any effect on cholesterol or lipid profiles (89,91–93).

Despite experimental studies supporting an anti-atherogenic action of bisphosphonates, effects on the atherogenic process in humans had not been reported until Koshiuama *et al.* studied the effect of etidronate treatment on carotid arterial intima-media thickness in 57 patients with type 2 diabetes associated with osteopenia (94). After 12 mo of cyclical etidronate therapy (200 mg daily for 2 wk every 3 mo), there was a significant decrease in intima-media thickness in the 57 participants treated with etidronate compared with 57 control participants ($P < 0.005$). However, the selection criteria for those treated with etidronate (on the basis of low BMD) differed from those treated with placebo (no BMD criteria). In addition, 32% of those in the etidronate group had nephropathy compared with 19% of controls, although this difference was reported to be nonsignificant. As recent experiences with statin therapy and hemoglobin targets have emphasized, even if confirmed in the general population, these data may not be applicable to patients with CKD.

Bisphosphonates and Vascular Calcification

Vascular calcification in CKD is a highly regulated active process, involving a complex interaction of calcification inducers and inhibitors similar to osteogenesis and distinct from passive mineral precipitation (14). Structures resembling bone, as well as diffuse matrix calcification, have been found in calcified vessels (95). Increased serum levels of both calcium and phosphate have been reported to increase activity of vascular smooth muscle cell (VSMC) sodium phosphate (NaPi) cotransporters, resulting in increased intracellular levels of phosphate (96,97). This influences Cbfa-1, a master regulator of cellular differentiation that can induce VSMCs to transdifferentiate to cells with an osteoblast phenotype. Levels of phosphate required for these changes are equivalent to those commonly seen in patients with CKD (98). In an *in vitro* model, prolonged exposure of VSMCs to levels of calcium and phosphate induced the release of membrane-bound matrix vesicles and apoptotic bodies that contained preformed calcium phosphate (99). These vesicles calcified extensively, and the process was inhibited by normal serum.

The first report of the effects of bisphosphonates on vascular calcification was in the 1970s, with experiments showing inhibition of soft tissue calcification in both animals and humans (100,101). These data have been confirmed by more recent animal studies using a number of bisphosphonates at varying doses (Table 2). The ability of etidronate to inhibit (bone) mineralization is supported by a rat model in which etidronate injection caused a rapid accumulation in serum of a fetuin-matrix Gla protein-mineral complex (102). It is hypothesized that this complex is generated as a consequence of etidronate inhibiting bone mineralization, rather than as a consequence of inhibiting bone resorption. Bisphosphonates have also been shown to inhibit the expression of TNF- α , which may promote osteoblastic differentiation, as well as calcium deposition in atheromatous lesions of rabbit aorta (93).

Table 2. Recent experimental studies directly assessing bisphosphonate effect on vascular calcification

Author and reference number	Year	Animal or in vitro	Bisphosphonate	Comment
Price <i>et al.</i> (103)	2001	Uremic rats (adenine induced) treated with warfarin +/- vitamin D	Ibandronate and alendronate	Both bisphosphonates, in doses that inhibit bone resorption, inhibited calcification in arteries and heart valves
Tamura <i>et al.</i> (105)	2005	Uremic rats (5/6 nephrectomised) treated with calcitriol	Etidronate	Vascular calcification was inhibited by bisphosphonate (only at 10 mg/kg, not 2 mg/kg)
Li <i>et al.</i> (148)	2006	Rats treated with warfarin and vitamin D	Alendronate	Bisphosphonate inhibited arterial calcification
Price <i>et al.</i> (149)	2006	Uremic rats (adenine induced)	Ibandronate	Bisphosphonate inhibited bone resorption in aorta and carotid arteries; lowering dietary protein increased calcification
Tamura <i>et al.</i> (106)	2007	Uremic rats (5/6 nephrectomised)	Etidronate	Aortic calcification reduced (with no changes in serum calcium and phosphate) at low doses of bisphosphonate
Saito <i>et al.</i> (107)	2007	Bovine aortic VSMCs in high phosphate	Pamidronate	Vascular calcification inhibited by vitamin K +/- bisphosphonate

VSMCs, vascular smooth muscle cells.

Alendronate and ibandronate are reported to inhibit calcification of arteries and cardiac valves in rat models of warfarin-related calcification, without affecting serum calcium and phosphate levels (103). This study provided experimental evidence implicating bone resorption in the pathogenesis of uremia-related vascular calcification. In another study by Price *et al.*, doses of vitamin D that were lethal to rats caused excessive calcification of arteries, lungs, kidneys, and cartilage (104). However, when subjects were given vitamin D plus the bisphosphonate ibandronate at doses capable of reducing bone turnover, soft tissue calcification was inhibited in all organs and death was prevented. It should be noted that in these studies, methods to induce vascular calcification involved extreme conditions that are rarely, if ever, seen in clinical practice.

Tamura *et al.* used 5/6 nephrectomized rats to show that aortic calcification induced by calcitriol could be reduced by etidronate. Initially, they demonstrated that low-dose etidronate (2 mg/kg) was ineffective, but a dose of 10 mg/kg inhibited calcification; the latter dose suppresses bone metabolism (105). The same group subsequently demonstrated that etidronate at an intermediate dose (5 mg/kg) that did not affect bone metabolism or BMD also inhibited aortic calcification, with associated reversal of the reduction in expression of matrix Gla protein seen in the nephrectomized rats (106). In another study using bovine aortic smooth muscle cells, pamidronate and vitamin K were reported to synergistically inhibit arterial calcification induced by high phosphate levels (107).

The exact mechanism by which these bisphosphonates inhibit vascular calcification is not clear. It may be by inhibition of bone resorption, with reduced efflux of calcium and phosphate limiting their availability for deposition in the vasculature (108) or their ability to influence the activity of the VSMC NaPi co-transporter. Alternatively, bisphosphonates may have direct effects on the vessel wall and, like pyrophosphate, on crystal formation. Patients receiving HD are reported to have low levels of pyrophosphate, perhaps related to dialysis clearance, and this may contribute to vascular calcifications (109).

Vascular Effects of Bisphosphonate Therapy in Clinical Studies

Similar to animal experiments that reveal conflicting results for bisphosphonate treatment of atherosclerosis and related vascular calcification, there have been varying responses in clinical studies (Table 3). Two prospective well-conducted studies in the general population have reported no difference in vascular calcification with bisphosphonate administration compared with control. One study assessed coronary artery calcification (CAC), measured by spiral computed tomography scans in 56 alendronate-treated osteoporotic patients, compared with 56 matched controls and 213 subjects from a reference cohort (110). This was a pilot study to determine whether alendronate (administered orally 10 mg daily for 24 mo) would actually accelerate calcification. Results showed significant progression of CAC over 24 mo, with no between-group differences. Another non-CKD study analyzed aortic calcification assessed by lateral plain abdominal x-rays in 474 elderly women (aged 55 to 80 yr) participating in two 3-yr randomized,

Table 3. Clinical studies assessing bisphosphonate effect on vascular calcification

Author and reference number	Year	Subjects	Study type	Duration	Bisphosphonate	Outcome
Hill <i>et al.</i> (110)	2002	56 osteoporotic pts vs 56 controls vs 213 reference cohort	Prospective, controlled	24 mo	Alendronate	CAC progressed over duration of the study, but no difference in the treated group compared to the matched controls
Hashiba <i>et al.</i> (113)	2004	18 HD pts	RCT	6 mo	Etidronate	Increase in aortic calcification in control group compared to no increase with treatment
Nitta <i>et al.</i> (112)	2004	35 HD pts	Prospective, observational	24 mo	Etidronate	CAC increased 12 mo before treatment; then reduced with 12 mo of treatment
Tanko <i>et al.</i> (111)	2005	474 women (postmenopausal)	Sub-analysis of two RCTs	36 mo	Ibandronate	Increase in aortic calcification (lateral X-ray) with bisphosphonate similar to control
Ariyoshi <i>et al.</i> (115)	2006	14 HD pts	RCT	12 mo	Etidronate (6 mo)	Improvement in CAC and aortic calcification in bisphosphonate treated group compared to increase in calcification in controls
Hashiba <i>et al.</i> (114)	2006	21 HD pts	Prospective, observational	23 mo	Etidronate	Aortic calcification increased 12 mo before bisphosphonate; no change in following 11 mo with treatment

pts, patients; mo, months; RCT, randomized clinical trial; CAC, coronary artery calcification; HD, hemodialysis.

placebo-controlled studies involving oral or IV ibandronate (111). All women were receiving calcium and vitamin D supplements, and despite increases in BMD at the hip measured by DXA, there were no differences in the rate of aortic calcification change after 3 yr.

For patients with CKD, there is a paucity of clinical data. Several Japanese studies that assessed the use of bisphosphonates in HD patients showed beneficial effects on vascular calcification. In one study, 35 HD patients followed for 12 mo demonstrated CAC progression (112). After administration of etidronate (200 mg daily for 14 d, repeated in 3 monthly cycles) there was a reduction in CAC. BMD measured by DXA did not change, but levels of osteoprotegerin, a decoy receptor for RANK-ligand and a regulator of bone resorption, decreased with etidronate treatment. In another randomized study of 18 HD patients, there was inhibition of the progression of calcification with etidronate (200 mg thrice weekly after dialysis for 6 mo) (113). In the control group, aortic calcification increased, compared with suppression in the etidronate group, with no change in serum parameters of mineral metabolism.

Hashiba *et al.* reported on 21 HD patients initially observed to have progression of aortic calcification over 12 mo (114). After initiation of etidronate, there was no change in calcification over the subsequent 11 mo. More recently, 14 HD patients were randomized to etidronate (400 mg daily for 24 wk) or control, with CAC, thoracic, and aortic calcification measured at baseline, 6 mo, and 12 mo (115). In this study there was no significant temporal change in CAC observed in either group; however, the thoracic and aortic calcification in the etidronate-treated group decreased at 12 mo (mean aortic score decrease, -64%) compared with a progression of calcification in the control group (mean increase, + 130%). These studies suggest that etidronate may be useful in reducing vascular calcification in some patients. However, with prolonged use at these doses, etidronate therapy results in crystal coating, inhibition of crystal formation and aggregation, and the development of osteomalacia in most patients. Also, the impact of bisphosphonate therapy on cardiovascular outcomes, as opposed to surrogate markers of CVD such as vascular calcification is unknown.

Calcific uremic arteriolopathy (calciphylaxis) is a rare but life-threatening complication of CKD, manifesting as painful nonhealing eschars in association with panniculitis and dermal necrosis. This condition is increasingly recognized as a contributing factor to death in dialysis patients (116). The pathognomic lesion consists of vascular calcification with intimal arterial hypertrophy and superimposed small vessel thrombosis. Several case reports have documented the potential usefulness of both etidronate (117) and pamidronate (118) in treating calciphylaxis. Case reports have also suggested that bisphosphonate therapy may be useful in reducing calcification in myositis ossificans (101), universal calcinosis (119), idiopathic infantile arterial calcification (120), and cerebral calcinosis (121). In another case report of a woman with glucocorticoid-induced osteoporosis, ectopic calcification completely disappeared after 6 mo of risedronate treatment (122).

Despite some data supporting a role for bisphosphonates in the management of vascular calcification, additional clinical

studies of their use in CKD are required. One randomized placebo-controlled clinical trial assessing the use of alendronate on vascular calcification and arterial stiffness in CKD patients is underway (ClinicalTrials.gov Registration No. NCT00395382). Fifty patients with reduced GFR (between 20 and 60 ml/min) have been enrolled in this 18-mo study with computed tomography assessments of aortic calcification. Results are expected in 2009.

Accumulation of Bisphosphonates and Low Bone Turnover in CKD

Bisphosphonates diffuse into the bone matrix, where they accumulate because of their exceptional affinity to bind to the calcium-phosphorus crystal surface. It is not known whether this accumulation increases with progressive renal impairment (47,70). In patients without CKD, the reduction in bone turnover caused by bisphosphonates contributes to improved mineral apposition and an increase in BMD, but even with regard to this group there is debate regarding effects of long-term bisphosphonate use on brittleness *versus* toughness, and ultimately on bone quality and resistance to fracture. For patients with CKD, clinical studies have reported that higher calcification scores may be associated with *lower* levels of PTH, which are often indicative of low bone turnover or adynamic bone (123). Previous experimental animal studies have demonstrated that bisphosphonates, especially when given in higher doses, can induce osteomalacia (124) or result in accumulated microdamage (125,126). In the later stages of CKD a *potential* problem of bisphosphonate therapy is diminished bone remodeling that could lead to reduced repair of microcracks and impairment of bone strength (108). The frequency of microcracks in clinical studies of patients on long-term bisphosphonates varies from low (127) to high, with an increased accumulation of microdamage (128), although there is as yet no clinical evidence demonstrating that bisphosphonates actually result in impairment of bone strength. Recent long-term bone biopsy data are also conflicting. One study reported marked reduction of bone turnover in postmenopausal osteoporotic women administered alendronate for >3 yr (127), whereas another did not show adynamic bone disease after long-term risedronate (129). Given these data, bisphosphonates cannot be recommended when low bone turnover, adynamic bone disease, or osteomalacia are present or suspected, as they have potential to do harm.

Renal Adverse Effects of Bisphosphonates

Bisphosphonates have been reported to produce direct nephrotoxicity, particularly when used at high dosage in an oncology setting (130). High-dose pamidronate, administered rapidly by the IV route, has been reported to be associated with collapsing focal glomerulosclerosis and resultant nephrotic range proteinuria (131). A case series of patients with multiple myeloma, where pamidronate was given to delay osteolytic lesions, documented bisphosphonate-induced focal glomerulosclerosis (132), but after dose reduction or discontinuation, renal function stabilized in four of five patients in this report. Pamidronate-induced nephrotic syndrome with renal impairment has also been reported (133), and monitoring of protein-

uria is recommended in patients being administered bisphosphonates.

Acute tubular necrosis (ATN) with resultant acute renal impairment is another recognized complication of pamidronate therapy (134). Acute renal failure has also been reported with rapid administration of zoledronate (135). Restoration of renal function was not necessarily complete, with one study reporting a mean serum creatinine of 1.7 mg/dl before and 2.7 mg/dl after the acute renal failure resolved (136). Risk factors for acute renal toxicity include multiple myeloma, advanced age, and a change in prescribed bisphosphonates (from pamidronate to zoledronate) (137). Recently, a retrospective analysis of patients with myeloma and bone metastases from solid tumors who were receiving zoledronate reported that 9.4% experienced deterioration in renal function. Multivariable analysis showed that the cumulative dose of zoledronate was an independent predictive factor for renal impairment (138). Therefore, renal toxicity appears to be associated with both dose and infusion time. In a recent study, reducing bisphosphonate dose and prolonging the IV infusion time were associated with a decreased risk of renal toxicity (139).

The mechanism of bisphosphonate-induced ATN has been described by Markowitz *et al.* in renal biopsy findings of six patients who developed renal failure after treatment with zoledronate (135). The predominant findings were marked tubular atrophy, interstitial fibrosis, interstitial inflammation, and mild-to-moderate vascular disease. Animal experimental studies have also shown renal toxicity with high doses of ibandronate, clodronate, and zoledronate where the target of injury is the proximal tubule, and the resultant problem is ATN (140). One study used minimally nephrotoxic doses of ibandronate and zoledronate to investigate differences on the proximal tubule of rats and revealed a higher risk of nephrotoxicity with zoledronate if used repeatedly, because of its higher accumulation (141). The authors concluded that administration of intermittent ibandronate, as opposed to zoledronate, may provide sufficient time for repair of subclinical renal damage. Despite these reports, nephrotoxicity is uncommon and rarely of clinical significance when lower (osteoporotic range) doses of bisphosphonate are used (83).

Osteonecrosis of the Jaw

Localized osteonecrosis of the jaw (ONJ) is generally associated with tooth extraction and/or local infection with delayed healing. This condition has been reported with bisphosphonates, although rarely with oral bisphosphonates (142). Most reported cases of bisphosphonate-associated ONJ have been in patients treated for cancer with IV bisphosphonates, with reported risk factors including diagnosis of cancer; concomitant therapies (chemotherapy, radiotherapy and corticosteroids); poor oral hygiene; and comorbid disorders such as anemia, coagulopathy, and infection (143,144). Patients with multiple myeloma and metastatic carcinoma involving the bone who have received IV bisphosphonates are at greatest risk and represent 94% of published cases (143).

Although there are no specific associations with CKD and ONJ, studies have also identified type of bisphosphonate, in-

creasing duration of exposure, and older age as risk factors for development of ONJ (145). The latter two factors may be inter-related with CKD, because increasing age leads to increasing renal impairment, and renal insufficiency may lead to prolonged bisphosphonate exposure. Preventative strategies have been recommended before commencement of bisphosphonates, including removal of all foci of dental infection. Routine dental care and regular oral examinations are suggested for patients taking bisphosphonates (146).

Conclusion

Because there is an intimate relationship between atherosclerosis, vascular calcification, and bone disorders in CKD, the possibility of using or developing pharmacologic agents that may effectively treat these processes is attractive. Although there is a paucity of evidence, bisphosphonates may be used for osteoporosis in CKD 1 to 3. A number of other bone pathologies result in low BMD in CKD 4 and 5, which should warn against the common perception that these agents may provide bone protection in all stages of CKD. In severe CKD, bisphosphonates should only be used with caution in carefully selected patients and after consideration of bone biopsy, because of the possibility of worsening low bone turnover, osteomalacia, and mixed uraemic osteodystrophy, and exacerbating hyperparathyroidism. In some experimental and clinical studies, bisphosphonates have been reported to reduce the progression of extraosseous calcification, to inhibit enzymes involved in cholesterol biosynthesis, and to suppress macrophages in atheromatous lesions. Because current evidence is inconclusive, further studies are required to examine the role of bisphosphonates in CKD-MBD. Although their widespread use should be discouraged, selected patients may benefit from carefully targeted bisphosphonate therapy.

Disclosures

None.

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