Renal complications from bisphosphonate treatment

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Purpose of review
More than 10 years ago evidence emerged that bisphosphonate therapy especially in malignant bone diseases is associated with renal complications. The nature of renal injury from bisphosphonates has become clearer in recent years.

Recent findings
Pamidronate can rarely cause (collapsing) focal segmental glomerular sclerosis with the nephrotic syndrome and renal insufficiency. This renal complication has also been observed with other bisphosphonates but only in isolated cases. Other types of renal injury include transient but self-limited rises in creatinine, and, very rarely, acute tubular necrosis causing acute renal failure. The frequency of the latter two complications appears to follow the potency of different bisphosphonates. Although thus far no tubular transport for bisphosphonates has been identified (renal excretion appears to be only by glomerular ultrafiltration), the occurrence of tubular cell injury gives rise for the possibility that these cells can take up bisphosphonates. In patients receiving bisphosphonates monitoring of serum creatinine before and after intravenous (i.v.) dosing or periodically with oral bisphosphonates is advised.

Summary
Renal complications with bisphosphonates are rare but creatinine monitoring, especially with i.v. bisphosphonates is strongly advised. The mechanisms by which bisphosphonates can cause renal insufficiency are still elusive and opportunities for research include the discovery of potential mechanisms of tubular cell uptake of bisphosphonates.

Keywords
acute kidney injury, nephrotic syndrome, renal handling of bisphosphonates

INTRODUCTION

Bisphosphonates are chemically related to pyrophosphate but contain a carbon with two side chains. The phosphonate group provides affinity to bone and binding to hydroxyapatite. In most bisphosphonates, one of the side chains is an OH (except clodronate) and the second side chain is more variable between different bisphosphonates [1].

MECHANISMS OF ACTIONS OF BISPHOSPHONATES

After i.v. administration or after oral ingestion and uptake into the blood stream bisphosphonates are rapidly taken up by bone minerals to which they bind with high affinity. Hydroxyapatite-bound bisphosphonates are then slowly taken up by osteoclasts by endocytosis. Nonnitrogen bisphosphonates, that is, those that do not contain nitrogen (N) in the R_2-side chain act primarily by intracellular incorporation into nonhydrolysable ATP-analogues, which inhibit osteoclast function and cause apoptosis (Table 1) [1]. Nitrogenic bisphosphonates have additional actions once internalized into osteoclasts (Table 1). These latter compounds inhibit the mevalonic acid pathway by inhibiting farnesyldiphosphate synthase and, hence, reduce protein farnesylation and geranyl-geranylation. These posttranslational protein modifications are important for the normal function of some cellular proteins and the lack of these modifications inhibits osteoclast function and also causes apoptosis [1]. It is thought that osteoclasts are the only cells that take up bisphosphonates. However, there is a moderate amount of evidence that other cells including perhaps tubular cells may take up bisphosphonates,

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KEY POINTS

- Bisphosphonates can cause the nephrotic syndrome but this is a very rare complication.
- In randomized controlled trials in bone lesions from solid tumors or multiple myeloma, the incidence of renal insufficiency was only moderately greater with zoledronic acid compared with placebo or pamidronate.
- Renal complications appear to be more common in patients with baseline renal diseases or renal insufficiency. It is recommended that bisphosphonates are avoided when the estimated creatinine clearance less than 30–35 ml/min.
- The mechanisms of renal injury by bisphosphonates remain elusive but there may be some uptake by renal epithelial cells albeit the transport mechanisms are not known. If uptake into cells does occur it is possible that cell injury results from the same mode of action of bisphosphonates in osteoclasts.
- There is insufficient data to recommend any dosing of intravenous (i.v.) bisphosphonates in chronic hemodialysis patients and use of bisphosphonates in patients is not recommended by regulatory agencies. One consideration might be to use one-half of the normal dose followed by a hemodialysis session 12–24 h later.

too. This finding could explain renal cell injury by bisphosphonates.

The efficiency of bisphosphonates to reduce bone reabsorption appears to reside in their avidity to bind to bone mineral as well as their intracellular activity in osteoclasts. As a rule, nitrogenic bisphosphonates are more efficacious compared with nonnitrogenic bisphosphonates. Bisphosphonates that are 'buried' in bone mineral are believed to be inactive for long periods (many months to few years). This situation has clinical importance as it allows for long dosing intervals of monthly (ibandronate) to annually (zoledronic acid) in some indications. However, there is a slow 'leak' of bone bisphosphonates back into the blood stream during interdosing intervals.

Table 1. Nonnitrogenic and nitrogenic bisphosphonates

Nonnitrogenic bisphosphonates	Nitrogenic bisphosphonates
Etidronate	Pamidronate
Clodronate	Alendronate
Tiludronate	Risedronate
	Ibandronate
	Zoledronic Acid

Bone-bound bisphosphonates become active when resolved from the bone matrix and endocytosed by osteoclasts. These cells express electrogenic Proton-(V-)-ATPase in the bone exposed membrane and secrete protons (and Cl^- through Cl-channels) as well as cathepsin K into the neighboring bone. The acidification (pH $\leq$ 5) dissolves minerals and cathepsin digests the organic bone matrix. During this process, bisphosphonates are endocytosed and exert intracellular effects that reduce osteoclast activity.

Bisphosphonates are clinically used to treat hypercalcemia of malignancy, for the treatment of Paget's disease and to prevent skeletal-related-events (SREs) in malignant bone disease (multiple myeloma and bone metastases from solid cancers) and in osteoporosis. In the latter setting, bisphosphonates have been shown to increase bone mineral density (BMD). In osteoporosis, bisphosphonates may be given for long periods of time and side effects and complications are perhaps more likely to develop. On the contrary, treatment regimen of some bisphosphonates with long-dosing intervals up to 1 year are efficacious and reduce drug exposure to other organs such as kidney [2,3]. Another approach to minimize exposure to bisphosphonates is based on biomarker-directed dosing, using urinary levels of N-telopeptide of collagen type I (NTx) or procollagen 1 c-terminal extension peptide (P1NP) to direct dosing and dosing intervals [4,5]. Such approaches may help to reduce complications of bisphosphonate therapy. One of the most serious complications of treatments with bisphosphonates may be renal toxicity.

HANDLING OF BISPHOSPHONATES BY THE KIDNEY

Oral bisphosphonates are poorly absorbed by the gastro-intestinal tract ($\leq$3%) and nitrogenic bisphosphonates tend to have even lower absorption rates after oral administration [6]. After i.v. administration bisphosphonates are largely and quickly taken up by bone but the proportion of bone-bound drug varies more so between patients than between bone diseases and individual bisphosphonates. For example the bone retention for zoledronic acid in patients with bone metastases ranged between 25% and 93% [7]. Bisphosphonates that are not taken up in bone are rapidly excreted by the kidney in their unchanged, native form. Thus, the variation in the proportion of a fixed administered dose that is rapidly taken up by bone defines renal exposure to the drug and, as a result, may help to define patients at greater risk for renal toxicity.

As indicated earlier, nonnitrogenous bisphosphonates are metabolized to ATP-analogues in

osteoclasts, which are part of their mode of action. Nitrogenic bisphosphonates are not recognized by metabolizing enzymes or transporters: Bisphosphonates that are not taken up in bone are rapidly excreted in urine after glomerular ultrafiltration in their native, un-metabolized form. There is no evidence for active tubular secretory transport in humans albeit this has been shown for some first generation bisphosphonates in rodents [8]. In humans all renal excretion of bisphosphonates results from glomerular ultrafiltration and correlates closely with glomerular filtration rate (GFR) for all of the second and later generation compounds and the renal drug clearance is less than GFR [9]. The lower drug clearance compared with the GFR is well explained by the substantial protein binding of bisphosphonates. Most of the drug that is not taken up by bone is excreted renally, quickly within less than 24 h. Bone-bound bisphosphonates are very slowly liberated and there are very low levels of renal exposure and excretion in urine for long period after a single dose. Thus, the kidney is exposed to high levels of bisphosphonates shortly and transiently after a single (i.v.) dose and is chronically exposed to very low drug levels. To the extent that bisphosphonates do not undergo tubular absorption, their tubular concentration increases several-fold during downstream tubular travel. Thus, the kidneys have transient but high exposure to bisphosphonates, especially after intravenous administration. There appears to also be some renal accumulation and perhaps retention in the renal cortex and medulla as has been shown for zoledronic acid [10]. This situation could be explained by adhesion to cell surfaces, intercellular matrix or cellular uptake, in fact, does occur. Indeed, uptake into cells within noncalcified tissues, namely plasmocytoma cells as well as monocytes, has recently been demonstrated [1,11].

It is difficult to accept that renal toxicity of bisphosphonates could develop without uptake into renal cells. Evidence for uptake of nitrogenic bisphosphonates and intracellular inhibition of farnesyl diphosphonate synthase in tubular cells has been shown *in vitro* but in-vivo proof is thus far missing [12]. Similarly, the transport proteins or mechanisms that may facilitate entry into tubular cells are also unknown. Possibly, uptake of bisphosphonates occurs by endocytosis similar to the process in osteoclasts.

PATTERNS OF RENAL INJURY BY BISPHOSPHONATES

Essentially, three different patterns of bisphosphonate renal toxicity have been observed: The nephrotic syndrome and (collapsing) focal segmental glomerular sclerosis (FSGS); acute kidney injury (AKI) with acute renal failure and tubular necrosis; 'creeping creatinine', that is, slowly progressing or nonprogressing renal insufficiency. More common is a transient rise in serum creatinine with subsequent return to baseline.

Renal complications have been mostly but not exclusively reported with i.v. bisphosphonates, which is consistent with the greater albeit transient exposure of the kidneys to drug. AKI has been reported with intravenous etidronate [13], oral clodronate [14], pamidronate [15], oral alendronate [16], risedronate [17], ibandronate [18], and zoledronic acid [19,20]. There is very little published data detailing the type of renal injury with bisphosphonate-associated AKI. Loss of tubular cell polarization, loss of brush border and apoptosis of proximal tubular cells and increased proliferation, all hallmarks of acute tubular necrosis, have been described in some cases wherein kidney biopsies were available [21].

The nephrotic syndrome has been described in patients receiving intravenous pamidronate, in several cases at high doses [22,23], oral alendronate [24▪] and zoledronic acid [25]. The biopsy histology in all of these cases showed FSGS or collapsing FSGS, sometimes with renal insufficiency. This glomerular lesion is caused by injury to glomerular visceral epithelial cells and is typically progressive and not well responsive to therapy. However, this renal complication of bisphosphonates is exceedingly rare and is limited to very few and isolated cases. The nephrotic syndrome has also not been noted during any of the pivotal clinical trials of bisphosphonates.

Chronic kidney disease (CKD), which is marked clinically by a slowly progressing or nonprogressing rise in serum creatinine levels ('creeping creatinine') has been observed in major clinical trials with bisphosphonates. In most cases urinalysis findings are unrevealing and biopsy histology is not available. The mechanisms of injury to nephrons in these cases remain unknown but may include transient acute tubular necrosis that does not completely recover. More commonly, there is a small rise in serum creatinine within about 10 days of i.v. administration of bisphosphonates that tends to normalize thereafter.

INCIDENCE AND OUTCOMES OF RENAL IMPAIRMENT WITH BISPHOSPHONATES

Until the conduct of phase III clinical trials with zoledronic acid in patients with lytic bone lesions from solid cancers (breast and prostate) and

Table 2. Incidence of increases in serum creatinine[a] in three phase III clinical trials of zoledronic acid versus placebo or pamidronate

Malignancy	Reference	Zoledronic acid (4 mg/15 min)	Placebo	Pamidronate (90 mg/2 h)
Breast cancer	[26]	7.7%	–	6.0%
MM and breast	[27]	10.7%	–	9.3%
Prostate cancer	[25]	15.2%	11.5%	–

[a]Defined as an increase by at least 0.5 mg/dl in patients with serum creatinine less than 1.4 mg/dl at baseline; or by at least 1.0 mg/dl in patients with 1.4 mg/dl or more at baseline or doubling of the baseline value.

multiple myeloma, it was thought that renal complications with bisphosphonates including intravenous bisphosphonates, albeit known, were reasonably rare. In two of these three trials zoledronic acid was initially administered as 4 or 8 mg in 50 ml of isotonic saline over 5 min every 3–4 weeks. In one study the comparator was placebo [26]; in two other studies zoledronic acid at the same schedule or pamidronate (90 mg in 250 ml over 2 h) were given [27,28]. These trials were amended twice because of an increased incidence of rises in serum creatinine (Table 2). In these amendments the dose of 8 mg of zoledronic acid was discontinued (patients were switched to the 4 mg dose), the time of infusion was increased to 15 min and the volume of infusion was raised to 100 ml. Data in Table 2 reflect incidences of increases in serum creatinine after the amendments and does not include patients, who received an initial zoledronic acid dose of 8 mg. This data requires some critical evaluation. First, a relatively high incidence of rises in serum creatinine has to be viewed with regard to the patient population, namely advanced malignancies. The high incidence of renal insufficiency in placebo treated prostate cancer patients indicates important contributions of the underlying disease and perhaps concomitant therapies (Table 2). Moreover, the incidence of renal impairment in the breast carcinoma and multiple myeloma patients in these studies was similar between pamidronate and zoledronic acid despite the latter is more efficacious in reducing skeletal related events, SREs [28] (Table 2). This observation caused the United States Food and Drug Administration (FDA) to amend the labeling to include measurements of serum creatinine prior to each dose and abstain from administration of a scheduled dose if serum creatinine has increased by 0.5 mg/dl from baseline in patients with normal baseline creatinine or by 1.0 mg/dl in patients with abnormal baseline serum creatinine. Whether this regulatory dosing recommendation successfully reduces renal complications with zoledronic acid remains elusive as it has never been tested in clinical trials. As clinical trials of all bisphosphonates have largely excluded patients with renal insufficiency (serum creatinine >3.0 mg/dl or estimated creatinine clearance <30 ml/min) the labeling warns for the use of i.v. bisphosphonates in general in such patients.

Regulatory recommendations also include graded dose adjustments for zoledronic acid based on patients' estimated creatinine clearance (eCrCl) at time of a scheduled dose: eCrCl greater than 60 ml/min: 4 mg/15 min; eCrCl = 50–60 ml/min: 3.5 mg/15 min; eCrCl = 40–49 ml/min: 3.3 mg/15 min; eCrCl = 30–39 ml/min: 3.0 mg/15 min; eCrCl less than 30 ml/min: dosing not recommended. These renal function-based dose adjustments for zoledronic acid in malignant bone disease were based on the assumption that the total drug exposure [area-under-the-curve, (AUC)] rather than peak concentrations are causative for renal impairment. Peak drug concentrations would be reduced by increasing the infusion time. This question was only recently addressed by Berenson *et al.*, who randomized patients with multiple myeloma to receive zoledronic acid intravenously in 250 ml over 15 or 30 min every 3–4 weeks for up to 2 years ($n = 88$ each arm). The end-of-infusion serum levels were 249 ng/ml and 172 ng/ml, respectively, in the short and long infusion time groups [29▪▪]. There was no significant difference in the incidence of rises in serum creatinine in the two groups. Thus, extension of the infusion time may not provide substantial renal benefit. This study retrospectively validates the FDA's dose adjustment schedule.

Using the above renal function-based dose adjustment Shah *et al.* evaluated 220 patients (184 with normal renal function and 36 with renal impairment at baseline [19]. A (transient) decrease in the estimated creatinine clearance occurred in 20.7% of normal renal function patients and 19.4% of patients with impaired renal function. One patient in each group required dialysis therapy for acute renal failure (0.5 and 2.8%, respectively). This study did not analyze any causality and it is possible and perhaps likely that underlying diseases and concomitant medicinal drugs may have played important roles.

Morgan *et al.* compared the efficacy and safety of intravenous Zoledronic acid with daily oral clodronate in patients with multiple myeloma [14]. Renal failure causing death during the first 4 months of treatment was observed only in the clodronate group. This outcome suggests that at least some of the renal complications, especially severe renal failure causing death were quite likely not caused by the bisphosphonates rather than renal involvements of the underlying multiple myeloma or other medical events. The overall rate of renal impairment was low (about 1%) and very similar between the two groups. In a retrospective study, in myeloma patients ibandronate was found to be associated with a (transient) rise in serum creatinine in 10.5% of patients (which was less than with zoledronic acid) [30]. Overall, most or all i.v. and at least some oral bisphosphonates have been associated with renal impairment in patients with underlying malignancies with bone lesions.

Bisphosphonates are also widely used for increasing BMD and reducing the risk of bone fractures in patients with osteoporosis or steroid-induced osteoporosis. Renal complications in this indication are far less compared with the use in bone malignancies because of the less frequent dosing and, hence, reduced kidney exposure. For the treatment of osteoporosis zoledronic acid (5 mg i.v. once a year) should not be given if the estimated creatinine clearance (eCrCl) is less than 35 ml/min but no eCrCl-based dose adjustment is recommended for the treatment of osteoporosis. Moreover, serum creatinine levels should be monitored before and at about 10 days after each infusion. Transient increase in serum creatinine and, very rarely, acute renal failure have been reported. In placebo-controlled trials the incidence of renal insufficiency was reported in 1.0% of patients receiving zoledronic acid and in 0.8% of placebo patients. Transient and subsequently resolving rises in serum creatinine were reported in two large placebo-controlled clinical trials in 2.0–2.1% of patients on zoledronic acid and 1.7–2.4% of placebo patients [31]. There is no renal function-based dose adjustment. Oral risedronate should not be given to patients with eCrCl less than 30 ml/min. Similarly, oral ibandronate is also not recommended in patients with eCrCl less than 30 ml/min.

BISPHOSPHONATES IN CHRONIC MAINTENANCE DIALYSIS

The use of bisphosphonates in patients with chronic kidney disease (CKD) on chronic maintenance hemodialysis or peritoneal dialysis (CKD stage 5D) has been studied as a treatment for secondary hyperparathyroidism and accelerated calcifying arteriopathy both of which occur commonly in this population; or for the reduction in bone fracture risk and to improve BMD. This area has been reviewed elsewhere [32]. Given the context of this narrative, the author will limit his remarks to the use of bisphosphonates for malignant complications in patients on chronic dialysis.

The FDA and the European Medicines Agency (EMA) discourage the use of bisphosphonates in patients with an eCrCl less than 30 ml/min, which includes dialysis patients. There is very limited data on the dialysis clearance of bisphosphonates, and their removal during one dialysis session depends on the dialysis settings and the type of dialyzer used. Of 300 mg of clodronate that were infused prior to hemodialysis 53% (159 mg) were removed into the dialysate within 4 h accounting for 84% of total serum clearance with the remainder being mainly taken up by bone [33]. On average, 36% of a 1 mg i.v. infusion of ibandronate was removed during a single 4-h hemodialysis session in 12 chronic hemodialysis patients. In these latter patients, one dialysis session reduced plasma levels by 78% [34]. The dialysis clearance of clodronate and ibandronate were about 88 ml/min and 92 ml/min, respectively. About 32% of ^{99m}Tc-Pamidronate, 1 mg i.v., was removed during one dialysis session in 23 patients with an average clearance of about 70% [35]. It is difficult to derive generalized recommendations from such limited data but one consideration might be to administer i.v. bisphosphonates at 50% of their normal dose followed by a regular hemodialysis session 12–24 h later.

There is essentially no peritoneal clearance data available in patients on chronic peritoneal dialysis (about 10% of dialysis patients in the US) but values may be lower than with hemodialysis [36]).

CONCLUSION

Renal complications with bisphosphonates are rather rare. They appear to be more common with i.v. bisphosphonates and the most potent bisphosphonate, zoledronic acid, may have a somewhat higher incidence compared with less potent ones. A substantial proportion of renal impairments that are observed in patients with bone malignancies may, in fact, be complications of the underlying disease. In patients with osteoporosis renal impairment is a rare complication of bisphosphonate therapy.

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Conflicts of interest

The author has been a consultant and advisor to Novartis Pharmaceuticals during the clinical development of zoledronic acid.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 410).

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