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REVIEW ARTICLE

Bisphosphonate nephropathy: A case series and review of the literature

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From rat studies, human case reports and cohort studies, bisphosphonates seem to impair renal function. However, when critically reviewing the literature, zoledronate and pamidronate are more frequently involved in renal deterioration than other bisphosphonates. When bisphosphonate nephropathy occurs, zoledronate more frequently induces tubular toxicity whereas pamidronate typically induces focal segmental glomerulosclerosis. Thus, although bisphosphonates are highly effective in preventing complications for patients with osseous metastases and are highly effective in preventing fractures for patients with osteoporosis, renal function should be monitored closely after initiation of these drugs.

KEYWORDS
bisphosphonate, focal segmental glomerulosclerosis, mevalonate pathway, nephropathy, pamidronate, tubular toxicity, zoledronate

1 | INTRODUCTION

Bisphosphonates are a class of drugs inhibiting bone resorption through several mechanisms, which are used in various skeletal disorders, such as osteoporosis, malignancy-associated bone disease and Paget's disease.[1,2] In 2018 in the Netherlands, bisphosphonates were prescribed for 197.765 users, thus including >1% of the Dutch population.[3] Generally, treatment with bisphosphonates is considered effective and safe.[4,5] However, in some cases, bisphosphonates may induce renal impairment. Here, we report on 3 cases of **zoledronate**-induced renal toxicity in a single Dutch health centre and provide a review of the available literature on bisphosphonate nephropathy. All patients alive provided informed consent to use their information for educational purposes. Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[6]

2 | CASE DESCRIPTIONS

2.1 | Case 1

A 71-year-old male was referred to the emergency department of our hospital for a severe acute kidney injury. Two years before this event, hypertension and chronic kidney disease (CKD) stage 3b were diagnosed, with serum creatinine at approximately 100 μmol/L. The CKD was ascribed to previously undiagnosed hypertension. One year before admittance to the emergency room, prostate carcinoma was diagnosed with hydronephrosis of the right kidney. No clinically relevant deterioration of renal function was observed. Despite the initiation of hormonal therapy, osseous metastases were found a few months later. Treatment with **docetaxel** and **prednisone** was started, which resulted in remission 6 months later. Again, no clinically relevant deterioration of CKD was present at that time. Hereafter, hypercalcaemia developed, for which monthly zoledronate was initiated

(3 doses had been administered at the time of admission). Three weeks before admittance to the emergency room, the patient noticed a decline in general well-being and reduced exercise tolerance. On admission, serum creatinine was 2000 μmol/L, potassium 5.4 mmol/L, bicarbonate 12 mmol/L and phosphate 4.1 mmol/L. Urinary analysis showed proteinuria and erythrocyturia. Kidney ultrasound showed a small right kidney of 9 cm (similar to earlier findings) and a normal-sized left kidney with a dilatation of the pyelocalyceal system of 8–9 mm. Serum anti-GBM and ANCA autoantibodies were negative. Fluid resuscitation did not improve renal function. Dialysis was initiated and a renal biopsy was performed (Figure 1). The biopsy included 15 glomeruli, of which 2 were globally sclerosed. No segmental glomeruloscelerosis was found. Tubular damage was observed, consisting of vacuolization of the tubular epithelial cells, dilatation of tubules and desquamation of the tubular epithelial cells, compatible with drug toxicity. In addition, the biopsy showed a mild interstitial nephritis with presence of eosinophil granulocytes. Routine immune fluorescence (IF) showed no deposits. Unfortunately, despite cessation of zoledronate, renal function did not improve, which necessitated chronic haemodialysis. A few months later, the patient decided to discontinue dialysis treatment. He died shortly after.

2.2 | Case 2

An 82-year-old man was referred to the outpatient nephrology clinic for evaluation of a slowly declining renal function. His medical history included prostate carcinoma with osseous metastases diagnosed 2 years before admittance, for which he was treated with **goserelin** and monthly zoledronate. In the first 8 months of treatment with these drugs, his serum creatinine increased from 95 to 120 μmol/L. In the 4 months thereafter, a further decline in his renal function was noticed with an increase of serum creatinine to 160 μmol/L. Other serum tests were unremarkable. Urinary analysis showed a mild proteinuria of 0.8 g/L. Renal biopsy (Figure 2) showed 23 glomeruli, of which 8 were globally sclerosed. No segmental glomerulosclerosis was observed. Furthermore, acute tubular injury, comprising loss of tubular epithelial cells and presence of apoptotic tubular epithelial

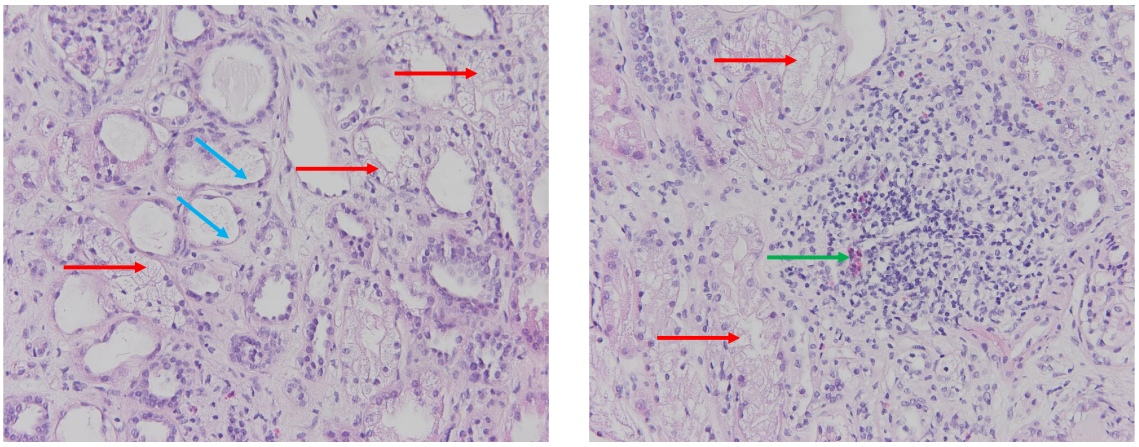

FIGURE 1 Renal biopsy of patient 1. Red arrows: vacuolization of tubular epithelial cells. Blue arrows: flattening and simplification of tubular epithelial cells. Green arrows: interstitial inflammation with presence of eosinophils

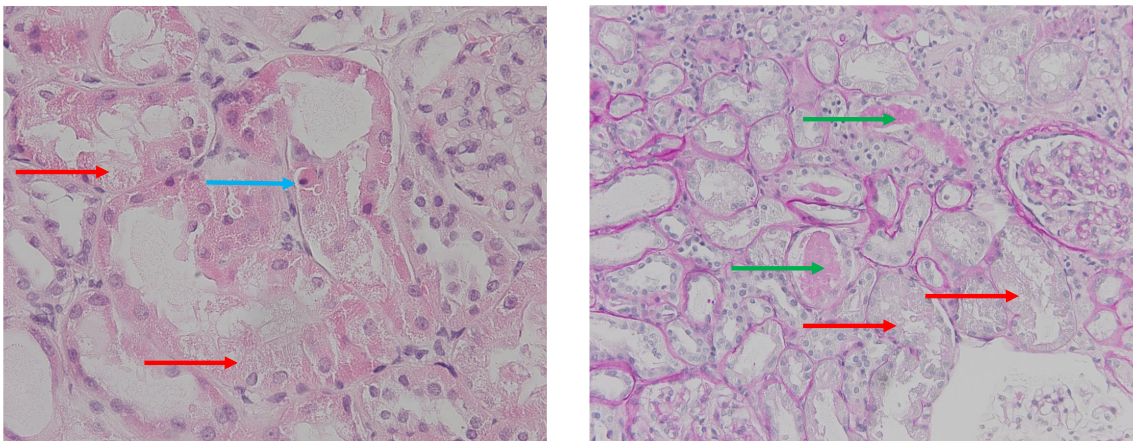

FIGURE 2 Renal biopsy of patient 2. Red arrows: vacuolization and necrosis of tubular epithelial cells. Blue arrow: apoptotic tubular epithelial cells. Green arrows: stasis of periodic acid–Schiff-positive Tamm–Horsfall protein (sign of obstruction)

cells were found. Routine IF showed no deposits. In addition, there were signs of tubular obstruction, consisting of tubular casts of Tamm–Horsfall protein. Cessation of zoledronate resulted in normalization of renal function.

2.3 | Case 3

A 60-year-old female was diagnosed with breast carcinoma with osseous metastases, for which zoledronate once a month was started 6 months before referral to our outpatient clinic. At presentation, serum creatinine was 142 μmol/L. Renal biopsy included 19 glomeruli of which 4 were globally sclerosed. No segmental glomerulosclerosis was observed. Furthermore, a mild interstitial nephritis with subtle signs of tubular injury and accumulation of Tamm–Horsfall protein were observed. Routine IF showed no deposits. After cessation of zoledronate, her renal function normalized.

In the 3 renal biopsies, nonsclerosed glomeruli were without histological abnormalities and immunostainings for IgA, IgG, IgM, κ and λ light chains, C3c, and C1q showed no specific deposits.

3 | DISCUSSION

The basic structure of all bisphosphonates is P-C-P with 2 side chains (R1 and R2), as shown in Figure 3 and described in Table 1. Most bisphosphonates have an OH-molecule at R1, which enhances bone affinity. The R2 chain may contain a nitrogen (N) atom, which highly increases the potency of the bisphosphonate when compared to bisphosphonates with a non-nitrogen containing chain. Non-nitrogen containing bisphosphonates inhibit **adenosine triphosphate** (ATP)-dependent enzymes that are necessary for activity of osteoclasts. Nitrogen-containing bisphosphonates bind and stabilize calcium phosphate in bone matrix and thus prevent dissolution.[1] Furthermore, these agents inhibit the **mevalonate** pathway, essential in post-translational lipid modification and anchoring of **guanosine triphosphates** in the cell membrane, which plays a role in various cell functions, such as apoptosis and ATP-dependent metabolic pathways.[7,8] Lastly, bisphosphonates disrupt the cytoskeleton of cells by inhibition of actin assembly.[9]

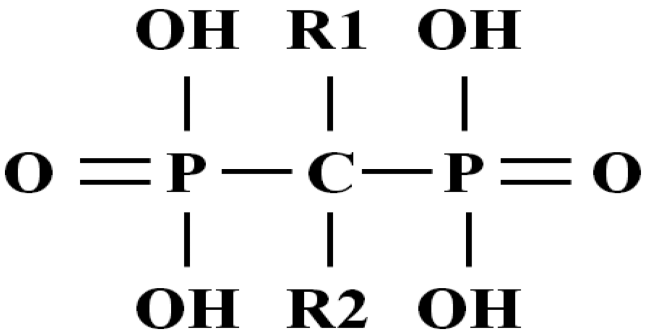

FIGURE 3 Basic structure of bisphosphonates

3.1 | Bisphosphonate nephropathy

Bisphosphonate nephropathy has been described since the 1980s[10,11] and the presence of limited renal tolerability of this class of agents has been further explored in the 1990s.[12,13] In 2008, the available literature on the nephrotoxic effects of **pamidronate**, zoledronate and **ibandronate** was extensively reviewed.[2] However, since then, additional information has become available. Furthermore, more bisphosphonates, such as **alendronate**, **risedronate** and **clodronate**, are presently available. Therefore, we provide an updated and more extensive review of the literature on bisphosphonate nephropathy of these 6 drugs.

3.1.1 | Pamidronate

Four case-series including a total of 22 patients with multiple myeloma (n = 17) or breast cancer (n = 5) describe the development of acute kidney failure and severe proteinuria after administration of pamidronate. Seventeen renal biopsies were available that showed collapsing focal segmental glomerulosclerosis (FSGS) in 11, non-collapsing FSGS in 2, undefined FSGS in 2 and minimal change disease in 2. Cessation of the drug induced a reduction in proteinuria in 14 out of 22 patients.[14–17] A retrospective study found an impaired renal function in 7 out of 57 (12%) of treated cancer patients,

TABLE 1 Properties and pharmacokinetics of available bisphosphonates[60,61]

Drug	R1	R2	Administration route	Protein binding (%)	T_{max} (h)	$T_{1/2}$ (h)	V_d (L/kg)
Alendronate	OH	$(CH_2)_3$-NH_2	Oral	78	n/a	1.87	0.4
Clodronate	Cl	Cl	Oral	36	0.5	15	0.3–0.7
Ibandronate	OH	$(CH_2)_2N(CH_3)(CH_2)_4CH_3$	Oral/i.v.	85–87	0.5–2	10–72	1.3
Pamidronate	OH	$(CH_2)_2$-NH_2	i.v.	54	2	27	n/a
Risedronate	OH	3-pyridylmethyl	Oral	24	1	480	6.3
Zoledronate	OH	1*H*-imidazol-1-ylmethyl	i.v.	43–55	0.25	146	n/a

R1 and R2 are the side chains as shown in Figure 3.
i.v. = intravenous; $T_{1/2}$ = half-life; T_{max} = time to maximum concentration; V_d = distribution volume

although this study encompassed a heterogeneous population.[18] However, in 2 randomized trials, no differences in renal function were found between: (i) treatment with 9 cycles of pamidronate 90 mg intravenously (i.v.; *n* = 196) and placebo (*n* = 181) on patients with multiple myeloma[19]; and (ii) between treatment with monthly pamidronate 90 mg i.v. (*n* = 367) and placebo (*n* = 384) on patients with advanced breast cancer.[20] In patients with osteoporosis, 3 studies were found that showed no renal safety issues for treatment with pamidronate, administered either orally[21] or i.v.[22,23]

3.1.2 | Zoledronate

The adverse renal effect of zoledronate was demonstrated in a recent study on Wistar rats with normal or impaired renal function treated with placebo, ibandronate or zoledronate. All rats treated with a bisphosphonate showed significant tubular toxicity, but only the rats with impaired renal function at baseline treated with a high cumulative dose of zoledronate showed permanent damage.[24] In humans, the first case series on zoledronate nephropathy included 5 patients with multiple myeloma and 1 with Paget's disease. Acute kidney failure and subnephrotic proteinuria developed after a mean of 4.7 administrations of monthly 4 mg zoledronate i.v. Biopsies showed toxic acute tubular necrosis (ATN) in all patients. After zoledronate was discontinued, all patients had a subsequent improvement in renal function.[25] Notably, a case of collapsing FSGS and nephrotic syndrome after the administration of zoledronate has also been described.[26] In 2003, the Food and Drug Administration Adverse Event Reporting System identified 72 cases (42 with multiple myeloma, 22 with solid tumours, 2 with benign diseases and 6 with unknown diagnoses) of renal failure related to zoledronate after an average of 56 days. In total, 27 required dialysis and 18 died.[27] A repeated analysis in the same database found 481 acute kidney injuries in cancer patients that were attributed to bisphosphonate use. In 411 cases (87.5%), zoledronate was considered the responsible agent.[28] A French database similarly identified 7 patients who developed acute kidney injury (4 de novo and 3 as acute on chronic renal insufficiency) related to zoledronate. For 6 patients in whom follow-up was available, 3 were left with permanent (additional) kidney damage or death.[29] An observational study on 122 patients with metastatic prostate cancer found a prevalence of zoledronate nephrotoxicity of 23%.[30] In a randomized phase 3 trial on 1648 patients with multiple myeloma or advanced breast cancer treated with pamidronate or zoledronate, 2 protocol amendments were needed (an increase in infusion time and a reduction in maximum dosage) because of acute kidney injury in patients treated with zoledronate. Hereafter, the rate of renal injury was similar in the 2 groups (8.1 and 9.3%, respectively).[31] Another placebo-controlled trial in patients with solid cancer other than breast or prostate showed more renal insufficiency in those treated with zoledronate (10.9%) *vs.* those treated with placebo (6.7%), although this difference did not reach statistical significance.[32] Compared to ibandronate, treatment with zoledronate is associated with a 1.5-fold relative risk of renal impairment despite a better baseline kidney function in a retrospective study including 333 cancer patients.[33] For osteoporosis, zoledronate has been investigated in 4 trials. In a 1-year study evaluating zoledronate 4 mg i.v., no nephrotoxicity was observed.[34] Two randomized, placebo-controlled trials including a total of 9892 patients found a similar long-term renal safety,[35,36] although 1 study found more transient increases in serum creatinine in patients treated with zoledronate.[35] The latter finding was confirmed in a randomized, placebo-controlled trial in 5035 postmenopausal osteoporotic women.[37]

3.1.3 | Ibandronate

Ibandronate was investigated in 4 trials, in which no renal safety issues were found: (i) 25 patients with metastatic prostate cancer treated with ibandronate 6 mg i.v. for 3 days followed by 6 mg every 4 weeks; (ii) 466 patients with metastatic breast cancer treated with placebo (*n* = 158), ibandronate 2 mg i.v. (*n* = 154) or ibandronate 6 mg i.v. (*n* = 154); (iii) patients with advanced neoplasms (*n* = 18) treated with ibandronate 2 mg i.v.; and (iv) a placebo-controlled trial on 309 patients with breast cancer.[38–41] Furthermore, ibandronate 6 mg was administered i.v. for 30 minutes to 21 patients with multiple myeloma in an open-label trial, of whom 17 had chronic kidney disease. Nevertheless, no increase in serum creatinine or urinary markers was observed.[42] Lastly, a study evaluating i.v. ibandronate in 7 patients (6 mg in 6 patients, 2 mg in 1 and all followed by 4–6 mg every 3–4 weeks) with acute kidney injury caused by nephrocalcinosis or hypercalcaemia showed an improvement in renal function and correction of hypercalcaemia for all patients.[43] For osteoporosis, 2 trials investigated ibandronate as therapeutic agent. In a double blind, randomized noninferiority trial on 1395 postmenopausal women with osteoporosis comparing i.v. with oral pamidronate showed equal efficacy and no bisphosphonate-related toxicity.[44] Another trial on over 1609 postmenopausal osteoporotic patients treated with oral ibandronate also showed no pamidronate-related nephrotoxicity.[45]

3.1.4 | Alendronate

For alendronate, a case report described a 74-year-old man with chronic lymphatic leukaemia who developed acute renal failure within 2 weeks after initiation of alendronate. Kidney biopsy showed acute granulomatous interstitial nephritis. Cessation of the drug induced partial recovery of renal function.[46] In another case report, a 48-year-old man who was treated with immunosuppressant therapy after a liver transplantation developed acute renal failure and nephrotic proteinuria after initiation of alendronate. Renal biopsy showed collapsing FSGS. Withdrawal of alendronate did not result in improvement of renal function or reduction of proteinuria. It should be noted, however, that the time-course of events is not clear from this case.[47] A third case report describes acute renal failure and

aggravation of proteinuria in a 61-year-old patient with FSGS after initiation of alendronate. Cessation induced reversal of renal failure and proteinuria within 40 days.[48] Lastly, a 36-year-old man developed nephrotic syndrome within 4 months after alendronate initiation. Renal biopsy showed a mild increase of mesangial cells and matrix, but no tubular or interstitial abnormalities. Proteinuria had completely disappeared within 40 days after cessation of alendronate.[49] In a cohort of 5227 elderly patients, treatment with alendronate or risedronate was not associated with more adverse renal effects when compared to no treatment.[50] Lastly, a randomized trial in 127 osteoporotic or osteopenic patients comparing alendronate with risedronate or raloxifene showed no deterioration in renal parameters in any of these drugs during 12 months of follow-up.[51]

3.1.5 | Risedronate

A 54-year-old woman with osteoporosis who was prescribed risedronate developed intravascular haemolysis, complicated by ATN within 7 hours after the first administration.[52] However, in general, risedronate is considered safe regarding renal function, even in the presence of chronic kidney disease.[53,54]

3.1.6 | Clodronate

Clodronate is a non-nitrogen containing bisphosphonate. Nevertheless, renal issues have been described. In 1983, a 49-year-old woman with metastatic breast cancer was administered a high cumulative dose of clodronate i.v. for hypercalcaemia as a result of osseous metastases over 30 days. Although her renal function improved initially, progressive renal failure was noted shortly thereafter. She died 34 days after the first administration. Necropsy showed interstitial oedema, tubular atrophy and nephrocalcinosis. There were no signs of inflammation.[10] A 1985 cohort study on 31 patients with Paget's disease found no permanent adverse renal effects of clodronate 300 mg i.v. once daily for 5 days, although transient proteinuria was observed in 13% of all patients.[11] Another cohort study on 30 patients with cancer-related hypercalcaemia (which persisted after rehydration) who were administered a single dose of 1.5 g clodronate i.v. showed no adverse renal effects.[55] Finally, a randomized trial compared zoledronate i.v. 4 mg every 3–4 weeks to clodronate 1600 mg once daily in 1970 patients with multiple myeloma. Although the primary goal of the study was to evaluate overall and progression free survival, similar rates of adverse renal effects were observed in both groups (5–7%).[56]

In short, although all bisphosphonates may impair renal function, predominantly pamidronate and zoledronate are potentially nephrotoxic. Most literature on bisphosphonate nephropathy describes patients with neoplasms who may be more susceptible to the nephrotoxic effects of a high cumulative dose of bisphosphonates administered in a shorter time interval as well as the co-administration of other nephrotoxic drugs, such as cytostatic therapy. The negative renal effects of bisphosphonates appear reversible in most patients, but not all. Pamidronate has been associated with nephropathy based on FSGS, whereas zoledronate mostly has been associated with direct tubular toxic effects. Nevertheless, the case of FSGS in a patient treated with zoledronate[26] suggests that postulating strictly different pathogenesis of the renal impairment of these agents is probably an oversimplification of reality. Moreover, the analyses on databases and large trials lack information on renal pathology, which is essential to clarify possible differences or similarities in the toxic effects of the various bisphosphonates.

As yet, our understanding of the pathogenesis of bisphosphonate nephropathy is not complete. In cases with collapsing FSGS, pathological findings implicate a direct toxic effect on podocytes as indicated by an increased Ki-67 expression. In those specimens, an increased Ki-67 expression was found in tubular cells, which implies tubular damage as well.[14] Toxicity directed at tubular epithelium (toxic ATN) is pathologically characterized by an increased Ki-67 expression in tubular cells as well as loss and/or alteration of tubular Na^+/K^+-ATPase.[2] These effects may be the result of inhibition of the mevalonate pathway by inhibition of the enzyme farnesyl diphosphate synthase,[8] which affects multiple cellular processes including apoptosis. As stated previously, these effects are also mechanisms through which bisphosphonates exert its therapeutic effect. Furthermore, bisphosphonates may disrupt cytoskeleton assembly and impair cellular energy.[2,9] Lastly, activation of the immune system may play a role.[57] The possible different pathogenesis and prevalence of nephrotoxicity between the various bisphosphonates may be the result of different pharmacokinetic properties due to different side chains on R1 and R2, which are shown in Table 1.[58] Additional research is warranted to further investigate the abovementioned findings. For example, the determinants of patients at high risk of bisphosphonate nephropathy should be identified.

4 | CONCLUSION

In conclusion, predominantly zoledronate and pamidronate may induce a deterioration in renal function. The recent finding that 40% of cancer patients continue nephrotoxic drugs after an impairment of renal function[59] highlights the importance of being aware of the potential nephrotoxic effects of bisphosphonates, and the importance of assessing and monitoring renal function when prescribing these drugs.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

C.d.R.v.Z. was the primary investigator and responsible for the draft of the manuscript. J.R. and S.F. provided information on the pathology. W.v.D. and C.V. provided clinical information. J.R., S.F., W.v.D. and C.V. critically revised the manuscript. All authors approved the final manuscript for publication.

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