Bisphosphonate therapy in CKD: the current state of affairs

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Purpose of review
Chronic kidney disease (CKD) is associated with the development of mineral and bone disorders (MBD), including renal osteodystrophy (ROD). ROD is a global disorder of bone strength that is associated with an increased fracture risk. The use of bisphosphonates for fracture risk reduction in CKD remains controversial. This review provides a synopsis of the state-of-the literature regarding the safety and potential antifracture benefits of bisphosphonates in CKD patients.

Recent findings
In preclinical studies of animals with CKD 3–4 and evidence of CKD-MBD, bisphosphonates resulted in changes in bone quality that improve bone strength. Bone turnover was generally reduced to a similar extent in animals with and without CKD. Post hoc analyses of randomized trials in patients with CKD 3–4 reported increases in bone mineral density (BMD) and fracture reduction that were similar in patients with and without CKD. There are no primary clinical trial data in patients with CKD-MBD.

Summary
In patients with CKD without evidence of CKD-MBD, the use of bisphosphonates should follow general population guidelines. The lack of data for patients with CKD 4–5D and evidence of CKD-MBD makes treatment decisions challenging. Clinical studies are urgently needed to provide data on the safety and antifracture benefits of bisphosphonates in these cohorts.

Keywords
bisphosphonates, chronic kidney disease, chronic kidney disease- mineral and bone disorders, end-stage kidney disease, fractures, osteoporosis

INTRODUCTION

Bisphosphonates are antiresorptive agents used to prevent fractures in postmenopausal and steroid-induced osteoporosis. The management of kidney-associated bone disease for fracture risk reduction remains controversial. Bisphosphonates are commonly used in patients with CKD 1–3 without evidence of abnormalities of CKD-MBD; however, evidence for fracture reduction in patients with CKD 4–5D and CKD-MBD is lacking. Bisphosphonates may be helpful in preventing bone loss and fractures in CKD patients with normal or high turnover bone disease but should be avoided in those with low-turnover bone disease. The 2017 update to the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines on the management of CKD-MBD and the known burden of morbidity and mortality associated with fractures in CKD 4–5D has led to increased bone mineral density (BMD) measurements and off-label use of bisphosphonates in these patients [1]. Along with preclinical studies and subgroup analyses of clinical trials (mostly patients with CKD 3–4 without CKD-MBD), this practice has provided important insights into bisphosphonate use in CKD. However, the lack of clinical and safety data in patients with CKD 4–5D presents an ongoing challenge in clinical practice. Below, we review the pharmacology, clinical use, and safety of bisphosphonates in non-CKD cohorts and focus on the pressing question facing clinicians today: Are bisphosphonates a well tolerated and effective therapy to improve bone strength and reduce fractures in patients with kidney disease?

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Curr Opin Nephrol Hypertens 2019, 28:000–000
DOI:10.1097/MNH.0000000000000585

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KEY POINTS

- Identification of patients with CKD at risk for fractures includes evaluation of BMD, past history of fragility fractures and screening for abnormalities of CKD-MBD.
- In patients with CKD without evidence of CKD-MBD, the use of bisphosphonates for fracture risk reduction should not differ from general population guidelines.
- The results of preclinical studies and analysis of registration trials in CKD 3–4, suggest that bisphosphonates have beneficial effects on bone strength and fracture outcomes.
- The lack of data for patients with CKD 4–5D and evidence of CKD-MBD makes widespread bisphosphonate use challenging and at present treatment needs to occur on a case-by-case basis.
- Clinical studies are needed to provide data on the safety and antifracture benefits of bisphosphonates in patients with CKD 4–5D and evidence of CKD-MBD.

BONE DISEASE AND FRACTURE EPIDEMIOLOGY IN CHRONIC KIDNEY DISEASE

Osteoporosis is a disorder of compromised bone strength that predisposes to increased fracture risk. Bone strength is a composite measure of bone density [commonly areal BMD as measured by dual-energy X-ray absorptiometry (DXA)] and bone quality, which refers to bone material properties (e.g. cortical and trabecular microarchitecture). Renal osteodystrophy (ROD) is the skeletal component of CKD-MBD and is a disorder of bone strength. ROD begins in the earliest phases of CKD and is associated with global impairments in bone quality and may be associated with abnormalities in BMD. Bone biopsy studies suggest that high-turnover is the dominant lesion in early CKD and continues to persist in CKD-5D, although recent studies suggest low-turnover to be the dominant lesion [2]. Microarchitectural abnormalities are common and the prevalence of osteomalacia is low, reported in large bone biopsy cohorts as approximately 3% [3]. Compared with postmenopausal osteoporosis, ROD results in a profound, global impairment of bone strength and increased fracture rates, and by definition is a sub-type of osteoporosis.

Patients with end-stage kidney disease (ESKD) have significantly higher fracture rates compared with age-matched general population cohorts. Hip fracture rates in CKD 5D patients increased by 43% between 1990 and the mid-2000s, and in 2010, these remained 27% higher (as compared with 1996) in individuals 66 years and older with ESKD [4,5]. Peripheral fractures rates also more than doubled over the corresponding time-period [6]. Patients with CKD 4–5D have both traditional and CKD-specific risk factors for bone disease and fractures (Table 1).

Table 1. General and chronic kidney disease-specific risk factors for bone loss and fractures

General risk factors	CKD-specific
Patient-related (nonmodifiable)	Hyperparathyroidism
Age	Low nutritional and activated vitamin D
Gender	Disordered mineral metabolism
Ethnicity	Chronic inflammation
Past history of fracture	Metabolic acidosis
	Premature hypogonadism
General (modifiable)	Medications
Low physical activity	Steroids
Smoking	Phosphate binders (e.g. aluminium)
Alcohol	Calcineurin inhibitors
Medications (e.g. steroids)	Dietary restriction
Diabetes	Dialysis-related amyloidosis
Sarcopenia	Higher prevalence of general risk factors for osteoporosis
Chronic inflammatory disorders	

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BISPHOSPHONATE STRUCTURE AND MECHANISM OF ACTION

Bisphosphonates are structural analogues of pyrophosphate (Table 2). Older, nonnitrogen bisphosphonates are inert analogues of ATP that inhibit bone resorption and mineralization to a similar extent. Newer, nitrogen-containing bisphosphonates differ in their mechanism of action to early bisphosphonates by inhibiting the enzyme farnesyl pyrophosphate (FPP) synthase, which is necessary for osteoclast function and attachment and normal bone remodelling [10]. The antiresorptive potency of the various bisphosphonates are directly related to their degree of FPP synthase inhibition (Table 2) [11]. The newer bisphosphonates bind this enzyme more tightly, with lower circulating concentrations needed to achieve an antiresorptive effect and no inhibition of mineralization at doses used in routine clinical practice [9].

Pharmacokinetics and effects on bone

Bisphosphonates have poor oral bioavailability (1–5%) [12]. In non-CKD patients, around half of the

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Table 2. Properties and antiresorptive potency of bisphosphonates

Drug	Route of administration	Relative antiresorptive potency	HAP affinity constants K_L/106 l mol^{-1}	Comments
Nonnitrogen-containing				Inhibit mineralization and resorption at similar concentrations
Clodronate	o/i.v.	1	0.72	Osteomalacia with prolonged use
Etidronate	o/i.v.	10	1.19	Rarely used in modern clinical practice
				More potent inhibitors of resorption
Nitrogen-containing				Gastrointestinal side effects common with oral preparations
Alendronate	o	100 < 1000	2.94	Renal injury uncommon at conventional dosing and frequency intervals
Ibandronate	i.v.	1000 < 10 000	2.36	ONJ is a rare but serious complication associated with more potent bisphosphonates
Risedronate	O	1000 < 10 000	2.19	AFF associated with long-term (median 7-years) use.
Zolendronic acid	i.v.	10 000 < 100 000	3.47	Positive effects on BMD and bone quality in CKD (preclinical and clinical studies)

Data from Fleisch *et al.* [8] and Nancollas *et al.* [9]. AFF, atypical femoral fractures; BMD, bone mineral density; CKD, chronic kidney disease; HAP, hydroxyapatite; i.v., intravenous; o, oral; ONJ, osteonecrosis of the jaw.

absorbed drug is bound to bone and the remainder is cleared unaltered by the kidney [13]. Serum concentrations of bisphosphonates are inversely related to estimated glomerular filtration rate (eGFR) and in CKD 4–5D the half-life is significantly prolonged, along with the time required to reach steady state concentration [14]. The prolonged half-life of bisphosphonates in CKD 4–5D may also promote their accumulation in soft-tissue; however, any clinical consequence of this is unclear. The bone half-life of bisphosphonates is in the magnitude of years; therefore, markedly higher than the serum half-life. This is related to the ability of each bisphosphonate to bind hydroxyapatite (Table 2), with zoledronic acid having the highest affinity amongst the bisphosphonates routinely used in clinical practice [15]. The role of bone turnover on skeletal accumulation of bisphosphonates remains unclear; however, recent preclinical data suggested little or no effect of turnover on skeletal accumulation [16▪].

Randomized trials of bisphosphonates in osteoporosis achieved a fracture reduction rate of around 40% [17]. Bone mass was generally increased (mostly because of increased mineralization), with no significant change in bone volume [18]. The inhibition of osteoclasts results in a marked reduction in bone resorption, with a rise in PTH that is more pronounced in CKD [19]. Bone formation continues unabated for a period of months before the absence of resorption causes a secondary reduction in bone formation, which has been shown to be in excess of 90% in some studies [20]. The concern pertaining to bisphosphonate use and adynamic bone disease remains one of the biggest challenges with the use of these drugs in CKD 4–5D.

Adverse effects

The safety data for bisphosphonate therapy is available from randomized controlled trials (RCTs) for postmenopausal osteoporosis. Gastrointestinal upset, such as reflux and oesophagitis are common with oral agents [21,22]. Intravenous administration can commonly cause bone pain and an acute phase reaction [23,24]. Less common and more serious side-effects have become apparent with increasing use and include uveitis, atrial fibrillation, atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ) [23,25–27]. ONJ is a rare but serious complication and has been reported with all bisphosphonates. Risk factors include intravenous administration, higher dose and administration frequency, existing dental disease, smoking, glucocorticoid therapy and diabetes [28]. There is no reported increase in patients with kidney disease; however, many of the predisposing factors are common in CKD 4–5D. AFF occurs in the

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subtrochanteric region and diaphysis of the femur and is considered to be a type of stress fracture. AFFs are associated with long-term bisphosphonate use (median 7 years). Although the absolute risk of AFF is low (3.2 to 50 per 10000 person-years), risk increases with long-term use (~100 per 100000 person-years) [25].

Kidney injury associated with bisphosphonate use

Acute kidney injury (AKI) has been described with the use of bisphosphonates, mostly with intravenous administration. Early case reports described the association of intravenous pamidronate with AKI and nephrotic syndrome, with biopsy showing collapsing FSGS and marked tubular injury. Subsequent reports revealed a spectrum of change from noncollapsing FSGS to minimal change disease [29]. In contrast, zoledronic acid appears to be predominantly associated with acute tubular injury. These reports were almost universally in patients with multiple myeloma or metastatic solid organ tumours, who received high-dose, frequent and rapid bisphosphonate infusions. Subsequent protocols were developed to reduce nephrotoxicity with dose, infusion rate and administration frequency adjustment. A more recent study of 201 multiple myeloma patients (16% had a CrCl of <60 ml/min) undergoing stem-cell transplantation and treatment with bisphosphonates found no significant decline in kidney function [30]. Treatment of postmenopausal osteoporosis with intravenous bisphosphonates generally utilizes lower doses and greater intervals between treatments. The renal safety of zoledronic acid in this cohort was established in three large trials, where an annual infusion of 4 or 5 mg of zoledronic acid demonstrated no significant difference in kidney function at 3 years [23,31,32]. For oral bisphosphonates, there is no clinical evidence demonstrating an increased risk of AKI. For example, in a large Canadian population-based study of 122272 oral bisphosphonate users, there was no statistically significant difference in the risk of AKI or long-term reduction in eGFR among bisphosphonate users compared with nonusers [33].

BISPHOSPHONATES IN THE TREATMENT OF RENAL OSTEODYSTROPHY AND FRACTURE PREVENTION

Preclinical studies

Although animal studies on bisphosphonates in CKD 3–4 with CKD-MBD are limited, those that have been conducted provide important insights into their skeletal effects.

In a study of rats with CKD 3 and biochemical abnormalities of CKD-MBD, high-turnover was the predominant ROD lesion [34]. Pamidronate increased mineral content to endocortical and trabecular bone and decreased bone turnover to below average levels without a significant effect on markers of mineral metabolism (calcitriol, phosphate and PTH). The effects of low-dose and high-dose zoledronic acid were compared in normal rats and those with CKD and evidence of CKD-MBD [35]. Animals with CKD had significantly higher bone remodelling – zoledronic acid-suppressed remodelling rates to a similar extent in both normal and CKD rats, without evidence of inducing adynamic bone disease. There was a modest suppression in the PTH levels in the high-dose zoledronic acid group compared with the CKD vehicle (558 versus 853 pg/ml). An extension of this study compared the skeletal effects of zoledronic acid with and without calcium in animals with more advanced CKD and CKD-MBD, specifically high and low-PTH levels [36]. Individually, zoledronic acid and calcium each improved trabecular bone volume and suppressed bone formation and mineralization to a similar extent. Calcium alone and with zoledronic acid improved cortical porosity and mechanical properties and lowered PTH levels. However only the calcium-alone group was reported to have a significant increase in circulating FGF-23 levels and aortic arch calcium content compared with the CKD controls. In another study of rats with stage 4 CKD and CKD-MBD, alendronate reduced bone turnover and increased cortical bone mineralization with an improvement in cortical mechanical properties [37]. There were no adverse effects of kidney function and markers of mineral metabolism (calcium, phosphate, PTH and FGF-23).

These studies provide important insights for clinical practice. In animals with CKD 3–4 and evidence of CKD-MBD, bisphosphonates resulted in changes in bone quality that improve bone strength: lowering bone turnover, increasing bone volume and mineralization, and improving cortical mechanical properties. Bone turnover was generally reduced to a similar extent as in non-CKD animals without any clear evidence of an increased risk in adynamic bone disease in the CKD animals. It is noteworthy that there were no obvious adverse effects on kidney function.

Clinical studies

The available clinical data is largely from secondary analysis of fracture intervention trials that included patients with CKD 3–4 without evidence of CKD-MBD and smaller, investigator initiated clinical studies.

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A post hoc analysis of nine double-blind, randomized trials comparing risedronate to placebo identified 8996 female individuals as having CKD, with 4071 having CKD stage 3 and 572 CKD stage 4, as calculated by the Cockcroft–Gault method (the mean eGFR using CKD-EPI in the CKD 4 group was 38 ml/min/1.73 m^2) [38]. The analysis showed an improvement in BMD and vertebral fractures and adverse event rates that were similar in patients with and without CKD. Paired bone biopsy data from 57 patients (29 with mild or moderate renal impairment – Cockcroft–Gault CrCl 30–80 ml/min) demonstrated that patients with and without CKD had a reduction in the mineralizing surface, which was greater in the risedronate group. A similar analysis was performed using data from the Fracture Intervention Trial, where 581 women (9.9%) had a GFR less than 45 ml/min calculated using Cockcroft—Gault method (mean eGFR using CKD-EPI was 44 ml/min/1.73 m^2) [39]. Women with reduced GFR had a 5.6% increase in total hip BMD, and fractures were reduced to a similar extent in those with and without renal impairment.

A recent systematic review compared bisphosphonates with placebo in six studies ($n = 1013$) of CKD patients and reported on BMD, fractures and safety [40]. Four of these studies were conducted in renal transplant recipients (RTR) and two in CKD 3 and 4. In RTRs, three of the studies showed that alendronate or pamidronate attenuated bone loss posttransplantation (average 6% reduction in lumbar BMD over a 12-month period in controls) [41–43], whereas the other study (using ibandronate) demonstrated no benefit on lumbar BMD, but a small 1.3% increase in total femur BMD [44]. The CKD studies included the Fracture Intervention Trial highlighted above [39] and a small study comparing alendronate versus placebo in 51 patients [45]. Over 18-months follow-up treatment with alendronate resulted in an increase in the lumbar spine T score of 0.3, $P < 0.05$.

A post hoc analysis of three Japanese RCTs included 852 patients with an eGFR from 30 to more than 90 ml/min/1.73 m^2 (with 228 having an eGFR <60) and compared the effects of risedronate to placebo on lumbar BMD and bone turnover markers (BTM), urine CTX and serum BSAP [46]. There was a significant increase in lumbar BMD and inhibition of BTMs ($P < 0.001$) with the use of risedronate, which remained consistent across eGFR categories. Similarly, in a post hoc analysis of a separate Japanese trial that compared risedronate to placebo in 420 patients (42 with an eGFR 30–60 ml/min/1.73 m^2, mean eGFR 54) reported that BTMs were significantly suppressed and BMD significantly increased from baseline, with a similar magnitude of change in eGFR subgroups [47]. Finally, a recent open-label study of 32 patients examined the effect of a single dose of zoledronic acid on bone loss posttransplantation: zoledronic acid partially attenuated peripheral bone loss and did not induce a greater decrease in bone turnover compared with controls [48▪].

CONCLUSION

Fracture prevention is the primary goal of osteoporosis treatment, therefore, the identification of patients at risk for fractures remains paramount. In CKD cohorts, this includes evaluation of BMD, past history of fragility fractures and the presence or absence of abnormalities of CKD-MBD. In general, in patients with CKD 1–3 without abnormalities of CKD-MBD management is similar to general population guidelines, although this largely remains an assumption based on post hoc analyses of large osteoporosis trials, rather than dedicated studies in early CKD. In patients with CKD and evidence of CKD-MBD, treatment is indicated in the presence of fragility fractures and/or BMD in the osteoporotic range; however, determination of ROD type needs to occur prior to treatment. Given the inherent difficulties in obtaining bone biopsy in most centres, the combination of PTH and BSAP can improve our ability to exclude low turnover.

The results of the preclinical studies along with analysis of registration trials in CKD 3–4, suggest that bisphosphonates have beneficial effects on bone strength, and therefore, fracture outcomes. Furthermore, the use of bisphosphonates was not associated with an increase in adverse outcomes. Given the lack of specific antifracture therapies and growing anecdotal experience suggesting safety for patients with CKD 4–5D and evidence of CKD-MBD, bisphosphonates (along with other agents for osteoporosis) will continue to be used in these patients. However, clinical trials are urgently needed to provide data on the safety and antifracture benefits of bisphosphonates in CKD 4–5D. For these to occur, there is a need for stronger advocacy from kidney societies and support from drug companies worldwide. At present, the use of bisphosphonates in these patients needs to occur on a case-by-case basis, where the increased fracture risk, morbidity and mortality need to be balanced against the potential antifracture benefits and skeletal and systemic effects of bisphosphonates.

Acknowledgements

None.

Financial support and sponsorship

T.N. – is supported by NIH R01DK119266 and R01DK110871, M.D. – none.

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Conflicts of interest

T.N. – Amgen: grant support and scientific advisory board, M.D. – none.

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A recent clinical trial in patients pretransplantation.

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