

# Use of Bisphosphonates in Chronic Kidney Disease

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## Abstract

The primary goal of treatment for post-menopausal osteoporosis (PMO) is reduction in fracture risk. Therefore, bisphosphonates (BF) are the most commonly used drugs for the treatment of osteoporosis. Because of their urinary elimination, bisphosphonates must be carefully administered in chronic kidney disease (CKD) patients. Renal toxicity seems different among these compounds, and it is basically due to their protein binding and the average lifespan of renal tissues. In practice, renal toxicity has been associated with infusion speed and excessive dosage. Treatment decisions are more difficult with stage 4 and especially stage 5 CKD who had fragility fractures. In spite of this, bisphosphonates can safely be used at stage to 1 - 3 CKD stages, haemodialysis and after the kidney transplant. When bisphosphonates are given stage 4 CKD patients it seems reasonable to reduce the dose to 50%. There are few data on the efficacy (reduction in fracture risk) or safety of any BF in patients with stage 5 CKD.

**Keywords:** Chronic kidney disease; Osteoporosis; Bisphosphonates

## Introduction

The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease (CKD) as either kidney damage or a de-

creased kidney glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m<sup>2</sup> for 3 or more months. Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR [1].

CKD is a worldwide public health problem and is now recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF). CKD affects 5 - 10% of the world population [1] and is associated with many adverse outcomes including bone disorders and fractures [2]. A population-based survey of Chronic Renal Disease In Turkey-the CREDIT study stated that the prevalence of CKD in Turkey is 15.7% [3].

CKD is divided into five stages of increasing severity. K/DOQI published a classification of the stages of chronic kidney disease, as Table 1[1].

CKD is associated with an increased risk of fracture. Decreased bone mass and disruption of microarchitecture occur early in the course of CKD and worsens with the progressive decline in renal function so that at the time of initiation of dialysis at least 50% of patients have had a fracture. Despite the excess fracture risk, and the associated increases in morbidity and mortality, little is known about the factors that are associated with an increase in fracture risk [4]. The prevalence of osteoporotic hip and vertebral fractures among dialysis patients exceeds that of the general population, with profound effects on morbidity and mortality [5].

Investigators have reported a number of factors that predispose to low bone mineral density (BMD) in patients with CKD. These factors include advancing age, gender, the onset of menopause, sedentary life style, low calcium intake, vitamin-D deficiency and hyperparathyroidism. In addition to these factors, renal function as measured by creatinine clearance (CCr), has been identified as a potential predictive factor that may causally be related to BMD, with higher CCr being associated with higher BMD [6, 7].

In evaluating the diagnosis of osteoporosis and effectiveness of the treatment of osteoporosis bone mineral density (BMD) have an important place. It is known that BMD only partly explains bone strength [8]. As CKD progresses, ensuing abnormalities in mineral metabolism result in distortions in trabecular microarchitecture, thinning of the cor-

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**Table 1.** Stages of Chronic Kidney Disease

Stage	Description	GFR* mL/min/1.73m <sup>2</sup>
1	Slight kidney damage with normal or increased filtration	More than 90
2	Mild decrease in kidney function	60 - 89
3	Moderate decrease in kidney function	30 - 59
4	Severe decrease in kidney function	15 - 29
5	Kidney failure	Less than 15 (or dialysis)

\*GFR, glomerular filtration rate.

tical shell, and increased cortical porosity. Recent studies have shown significantly increased hip fracture rates in CKD stages 3 and 4, in dialysis patients, and in transplant recipients. The majority of studies of bone loss in CKD relied on dual-energy x-ray absorptiometry (DXA) measures of BMD. However, DXA summarizes the total bone mass within the projected bone area, concealing distinct structural alterations in trabecular and cortical bone [7, 9].

Quantitative assessment of macrostructure can be achieved using (DXA) and quantitative computed tomography (pQCT), particularly volumetric quantitative CT (vQCT) [8].

Recent data have confirmed that pQCT measures of cortical density and thickness provide substantially better fracture discrimination in dialysis patients, compared with hip or spine DXA. The growing evidence for bone fragility in CKD stages 3 through 5, considers the effects of CKD on trabecular and cortical bone structure as it relates to fracture risk, and details the potential advantages and disadvantages of DXA and alternative measures of bone density, geome-

try, and microarchitecture, including pQCT, high-resolution pQCT, high-resolution magnetic resonance and micro-magnetic resonance imaging for fracture risk assessment in CKD [8-10].

Ito [8] stated that further progress in bone imaging technology is promising to bring new aspects of bone structure in relation to bone strength to light, and to establish a means for analyzing bone structural properties in the everyday clinical setting.

So, in patients with CKD stages 3-5D with evidence of CKD-MBD, KDIGO recommended that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (ROD) [1].

On the other hand, according to KDIGO bone biopsy is a gold standard in patients with CKD stages 3-5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to ther-

**Table 2.** Bisphosphonate Prescribing Advice for Persons With Reduced Renal Function

Bisphosphonate	Recommendation
Alendronat	GFR < 35 ml/min
Pamidronat	CrCl < 30 ml/min
Risedronat	CrCl < 30 ml/min
Ibandronik asid	CrCl < 30 ml/min
Zoledronik asid	CrCl < 40 ml/min
Etidronat	Mild and moderate renal disease

GFR: glomerular filtration rate; CrCl: creatinine clearance; min: minute.

apy with bisphosphonates in patients with CKD-MBD [1]. Bone histology is important for assessment of bone turnover and an iliac crest biopsy with double tetracycline labelling is recommended before embarking on the treatment of bone disease in patients with CKD [11].

BF are bone antiresorptive agents widely used to treat postmenopausal or glucocorticoid-induced osteoporosis, and they are effective in the prevention and treatment of osteoporosis but current recommendations limit their use in patients with renal impairment because of concern regarding the safety profile of these agents in the setting of reduced renal function [11, 12].

Bisphosphonates can be classified into two groups with different molecular modes of action: the simpler, non-nitrogen-containing bisphosphonates (clodronate and etidronate) and the more potent, nitrogen-containing bisphosphonates (alendronate, ibandronate, pamidronate, risedronate, and zoledronate). Intestinal absorption of bisphosphonates is low (1% for alendronate, ibandronate, and risedronate, 3% to 7% for etidronate 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 [11].

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. The remainder of the absorbed bisphosphonates not bound to bone (40% to 60%) is not metabolized and is eliminated unchanged by renal excretion [12].

The appropriateness of BF treatment for patients with CKD is also in question since CKD is independently associated with a variety of skeletal abnormalities, collectively termed renal osteodystrophy (ROD), including pre-existing low bone turnover. The evidence to support the current prescribing restrictions is not robust and there are some data to suggest both that BF treatment reduces fracture risk without an increase in adverse events in patients with CKD, and that in clinical practice there is under utilisation of this treatment in early CKD [11].

In developed countries prescribing of BF treatment is likely to increase. Nevertheless, there are persisting concerns regarding the safety of this group of drugs in persons with renal impairment. CKD is also more common in the elderly population; hence the issue of BF prescribing in CKD is important and relevant. Although the current guidelines are specific for

each drug, most manufacturers suggest avoidance of BF treatment if the CrCl is low (Table 2) [11].

In patients with stage 1 to 3 CKD, pharmacologic management of osteoporosis does not differ from that used in postmenopausal women with a normal GFR. In these patients, the bisphosphonates alendronate, ibandronate, risedronate, and zoledronic acid, as well as raloxifene, calcitonin, teriparatide, and denosumab, can be used to manage osteoporosis [13]. Clinical trial data have demonstrated ef-

ficacy with the use of these agents in patients with a serum creatinine concentration < 2.0 mg/dL or creatinine clearance > 30 mL/min (eGFR by Cockcroft-Gault equation) [13]. In a post-hoc study of patients with mild, moderate, and severe (eGFR down to 15 mL/min using the Cockcroft-Gault equation) renal impairment, risedronate reduced the incidence of vertebral fractures and effectively preserved BMD. Likewise, in a post-hoc analysis, alendronate was similarly effective in reducing the risk of vertebral and all clinical fractures in patients with eGFR down to 15 mL/min using the Cockcroft-Gault equation [14].

However, not all bisphosphonates behave the same. Because used as peroral and parenteral bisphosphonates nephrotoxic effects vary [15]. Oral bisphosphonates are not associated with significant nephrotoxicity, although there have been exceptions to this rule. Renal failure has been reported after the use of intravenous bisphosphonates and therefore intravenous bisphosphonates should be used with caution for the treatment of patients with osteoporosis, who have compromised renal function [15].

Miller [16] showed that, a daily 5 mg dose of risedronate over an average of 2 years did not significantly change serum creatinine concentration. No difference in renal function was observed between patients receiving risedronate or placebo in any of the renal impairment subgroups at any point during this study. In the pooled analysis of risedronate treatment the incidence of new vertebral fractures in the placebo groups was significantly correlated with the severity of renal function; however, BF treatment significantly reduced this incidence compared to placebo within each category of renal impairment [16].

The efficacy and safety of intravenous bisphosphonates (intravenous ibandronate and zoledronic acid) have been shown in patients with stage 1 to 3 CKD.

On review of the studies published so far on intravenous, BF administration, a slight deterioration of renal function is seen in 6 - 10% of all patients, except in the case of ibandronate in which the percentage is only 2 - 3% [11].

For instance, higher and repeated administration of zoledronic acid yielded renal histological abnormalities with the presence of degeneration and tubular atrophy, findings that were evident only with repeated doses of ibandronate [15, 17-21].

The renal toxicity of the intravenous bisphosphonates used in patients with malignant diseases involving bone is probably enhanced by risk factors for kidney function which may be present in these patients: pre-existing CKD, multiple myeloma, hypercalcaemia, hypertension, diabetes mellitus, advanced age, chemotherapy or previous treatment with a BF [15-22]. Important factors which may increase renal toxicity of the intravenous bisphosphonates are higher dose, shorter infusion times (< 15 ml/minute) or dose interval lower than recommended [15, 23, 24]. The total dose of the drug which has been administered during a long-term treatment may also

play a role because of its probable cumulative effect [25].

According to FDA zoledronic acid is not recommended for use in patients with severe renal impairment ( $\text{CrCl} \leq 40$  mL/min) [11, 26]. Physicians should monitor serum creatinine in patients with pre-existing renal compromise or other risk factors, including concomitant nephrotoxic medications (such as nonsteroidal anti-inflammatory drugs) or diuretic therapy, or severe dehydration, before and after each infusion [26-28].

Although reports of acute renal failure have not been reported with intravenous ibandronate, it may be wise to follow safety precautions with the use of this agent in patients with renal insufficiency [29].

It is well known that bisphosphonates treatment clearly provide fracture protection for patients with osteoporosis in the general community, and many patients with CKD [30].

## **Bisphosphonate Use in Patients with CKD and Low BMD**

### **Utility of bisphosphonates in patients with CKD [31]**

1) Prevention and treatment of decreased bone mass after kidney; 2) Transplantation; 3) Treatment of decreased bone mass in advanced CKD or dialysis; 4) Treatment of hypercalcaemia; 5) Treatment of calciphylaxis; 6) Prevention and treatment of vascular calcifications.

### **Treatment of decreased bone mass in chronic kidney disease stages 3 - 5 and dialysis**

The efficacy and safety of bisphosphonates have been shown in patients with stage 1 to 3 CKD [29]. The value of BF 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. Although data on BF use in CKD 5 is limited [12]. 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 [12].

There have been no prospective trials in patients with impaired renal function, although it has been observed that, in general, at recommended doses, these drugs do not cause impairment of renal function. No dose adjustment is neces-

sary in patients with mild or moderate renal failure ( $\text{ClCr}$  greater than or equal to 30 mL/min), although there may be increased risk of renal toxicity in elderly patients or in patients simultaneously receiving other nephrotoxic drugs [31, 32].

But in patients with  $\text{CrCl} < 30$  mL/min renal elimination is decreased, the concentration being approximately two times higher than in patients with normal renal function, so it is advisable to reduce the dose by half [31-34].

Although a recent study with ibandronate did not show any differences when comparing an infusion period of 60 minutes with a period of 15 minutes [35], in general, the infusion rate may also determine renal toxicity, with less observed toxicity when the infusion is slower [36, 37].

Bisphosphonates could potentially be beneficial to those with a low bone density and a high bone turnover, with well-controlled serum PTH and minerals. An RCT is needed for this population.

### **KDIGO recommendations [1]**

In patients with CKD stage 3 with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (Graded 2-D).

In patients with CKD stages 4-5D, having biochemical abnormalities of CKD - MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (Graded 2-C).

BF dose reduction is mandatory in persons with advanced CKD stage 4D. Today, with or without fragile fracture in patients with CKD stages 4-5D how to do osteoporosis treatment is controversial.

### **Can we use raloxifene in CKD stages 4-5D?**

A post hoc study used data from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial [38] to evaluate the efficacy of raloxifene in patients with reduced kidney function. The original trial included 7705 postmenopausal women aged 31 - 80 year. Women were randomly assigned to receive placebo, raloxifene 60 mg/d, or raloxifene 120 mg/d, in addition to daily calcium supplements of 500 mg and 400 - 600 IU of vitamin D. The trial included women at least 2 years postmenopausal, with osteoporosis defined by low BMD or radiographical evidence of vertebral fractures. Women with a serum creatinine level  $> 2.6$  mg/dL, with elevations in serum PTH, or with vitamin D deficiency, at baseline were excluded. For the post hoc analysis, some sites that did not use the central lab for creatinine were excluded, with a total of 7316 postmenopausal women being included. CKD was



defined using the Cockcroft-Gault formula, and divided by kidney function into CrCl: > 60 ml/min (n = 2343), CrCl 45 - 59 ml/min (n = 3293), or CrCl 45 ml/min (n = 1480). In the latter group, the median CrCl was 40.6 (range 20 - 44.9) and only 55 individuals had CrCl < 30 ml/min; thus, this group represents CKD stage 3 patients. The femoral neck BMD increase was greatest in patients with lower CrCl compared with those in other kidney disease groups and there was a significant reduction in vertebral fractures in the overall cohort of raloxifene-treated patients, with no difference in the three (CrCl) group.

### **Can we use teriparatide in postmenopausal women with osteoporosis and with or moderate renal impairment?**

The safety and efficacy of teriparatide have been demonstrated in patients with mild to moderate renal impairment (GFR > 30 mL/min), but there are no data on the use of this agent in patients with GFR < 30 mL/min. Since PTH is a vasodilator and increases renal function, an increase in the GFR level may occur with the use of teriparatide. Teriparatide is contraindicated in patients with mild to moderate CKD who have hypercalcemia or an elevated PTH [39].

Conclusion, there are no data on teriparatide in patients with CKD stage 3 who have biochemical abnormalities (high serum PTH, abnormal serum ALPs or 25(OH)D), and also no data in patients with CKD stages 4 - 5. Moreover, patients with CKD-MBD show resistance to skeletal actions of PTH, hence they may not respond to intermittent injections of usual 1-34 PTH doses [29].

The KDIGO clinical guidelines emphasize the importance of bone turnover in the development of renal osteodystrophy with high bone turnover strongly associated with uncontrolled secondary hyperparathyroidism, and adynamic bone disease (ABD) defined as a very low bone turnover state associated with functional hypoparathyroidism [1, 29].

### **Can we use denosumab in CKD stages 4-5D?**

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density [40]. Given its unique actions, denosumab may be useful in the treatment of osteoporosis. It was stated that denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis [40].

It is not cleared by the kidney and may be useful in patients with CKD. There are no FDA restrictions on the use of denosumab according to baseline renal function. This agent is metabolized by the reticuloendothelial system and has a fast on-set, off-set mechanism of action on bone tissue [41].

Post-hoc analysis of the registration clinical trial demonstrated the efficacy and safety of denosumab over 3 years in patients with eGFR down to 15 mL/min [42].

## **Conclusions**

Renal insufficiency, as a result of an age-related decline in kidney function or in patients diagnosed with CKD, can increase an individual's risk of fracture and is a risk factor for osteoporosis. In patients with CKD, accurate diagnosis of osteoporosis or CKD-MBD is important for determining the most appropriate treatment. Additionally, a patient's renal function status can help guide therapeutic decisions, so renal function should be assessed prior to initiating therapy for osteoporosis. According to the KDIGO working group, fractures that occur in patients with early-stage CKD (stages 1 through 3) are far more likely to be caused by osteoporosis than CKD-MBD.

Measuring bone mineral density (BMD) using DXA is of limited benefit for predicting fracture risk or diagnosing osteoporosis in patients with moderate to severe CKD (stages 4 and 5). In these patients, bone strength may be affected by a process that leads to CKD-MBD but is not captured by two-dimensional DXA imaging. Additionally, a diagnosis of osteoporosis cannot be made based on the presence of a fragility fracture since all forms of severe CKD-MBD may cause fracture. In patients with stage 4-5 CKD, a bone biopsy may be necessary to differentiate between the various types of bone disease that can occur in these patients.

The efficacy and safety of peroral and intravenous bisphosphonates have been shown in patients with stage 1 to 3 CKD. However, temporary elevation of the creatinine level may occur with intravenous BF use, and acute renal failure has been reported with zoledronic acid. To prevent renal damage, zoledronic acid should be infused no faster than 15 minutes, patients should be well hydrated, and, if possible, concomitant use of medications that might reduce renal function (eg, nonsteroidal anti-inflammatory drugs) should be avoided. Although reports of acute renal failure have not been reported with intravenous ibandronate, it may be wise to follow safety precautions with the use of this agent in patients with renal insufficiency. Stage 4-5 CKD (GFR < 30 ml/min or < 15 ml/min) may be considered for off-label use of bisphosphonates for a limited period of time (2 - 3 years) only if they have fractured and have a secure diagnosis of osteoporosis [43].

In patients with osteoporosis and CKD, calcium and vitamin D supplementation is recommended at the same dose used for individuals with postmenopausal osteoporosis - 1,200 to 1,500 mg/day of calcium and adequate vitamin D replacement to maintain the serum 25 (OH) D concentration at the recommended level of  $\geq 30$  ng/mL [44].

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