Management of osteoporosis in patients with chronic kidney disease

Osteoporosis and chronic kidney disease are common in old age and often occur together. Both diseases lead to increased bone fragility and fractures but with different pathophysiological backgrounds. This article reviews the challenges in diagnosis, evaluation and management of osteoporosis in patients with chronic kidney disease.

Osteoporosis and chronic kidney disease are common conditions among older people and often occur together. Population trends suggest that the older the person, the greater the degree of osteoporosis, the greater the risk of bone fractures and the higher the likelihood of that person having chronic kidney disease.

Osteoporosis

The World Health Organization (1994) has defined osteoporosis as a condition of skeletal fragility characterized by reduced bone mass and microarchitectural deterioration which results in fragility fractures. 'Osteoporosis' means a value of bone mineral density that is 2.5 standard deviations or more below the young adult mean value for women (T score ≤ -2.5 standard deviations). 'Osteopenia' is the higher threshold of bone mass that lies between -1 and -2.5 standard deviations. 'Severe' or 'established' osteoporosis denotes osteoporosis in the presence of one or more fragility fractures. Osteoporosis primarily results from imbalance between factors which promote bone production and those that promote bone resorption, leading to a net increase in bone breakdown. The bone mineral content is normal in osteoporosis.

Chronic kidney disease

Chronic kidney disease is a new term for what was previously called chronic renal failure. Chronic kidney disease is defined as kidney damage or glomerular filtration rate <60 ml/min/1.73 m^2 for 3 months or more, regardless of the cause of renal disease (Levey et al, 2005). Five stages of chronic kidney disease are described based on glomerular filtration rate (*Table 1*) – the lower the glomerular filtration rate the worse the stage of chronic kidney disease. Coresh et al (2007) found that about 39% of people aged 60 years or older had some form of chronic kidney disease, with the greatest proportion having stage 3 disease.

Bone disease in chronic kidney disease

Chronic kidney disease is associated with abnormalities in calcium, phosphate, parathyroid hormone and vitamin D metabolism and all of these can affect bone health (*Figure 1*). Chronic kidney disease is associated with a range of distinctly different metabolic bone diseases, so Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009) created the term chronic kidney disease with mineral and bone disorder. This is manifested by one or more of:

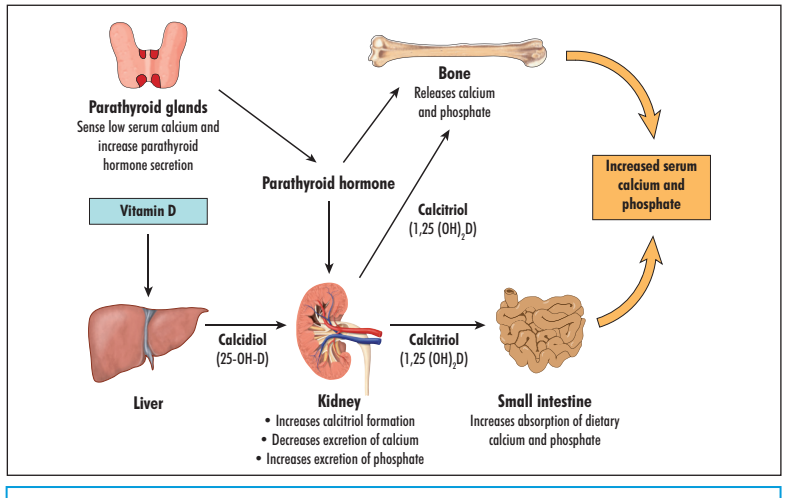
1. Abnormalities of calcium, phosphate, parathyroid hormone or vitamin D metabolism
2. Renal osteodystrophy. This spectrum of abnormalities in bone turnover, mineralization, volume, linear growth and/or strength can be classified into:
   a. Adynamic bone disease: low bone turnover, minimal osteoid accumulation, reduced collagen synthesis by osteoblasts, minimal mineralization of bone collagen, and low bone formation rate associated with low parathyroid hormone levels (Brandenburg et al, 2008)

Table 1. Stages of chronic kidney disease

Stage	GFR (ml/min/1.73 m^2)	Description
1	>90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mildly reduced GFR
3	30–59	Moderate reduced GFR
4	15–29	Severe reduced GFR
5	<15	Kidney failure
5D	<15	Kidney failure with dialysis

GFR = glomerular filtration rate

Figure 1. Role of kidney in calcium and vitamin D metabolism.



Dr Abhaya Gupta *is Consultant Physician in Medicine and Elderly Care, Glangwili Hospital, Carmarthen SA31 2AZ (guptaabhaya@hotmail.com)*

b. High turnover disease – osteitis fibrosa – is increased osteoblast and osteoclast activity with abnormal collagen deposition, marrow fibrosis and high rates of both formation and resorption. It is caused by the effects of high parathyroid hormone levels on bone
c. Mixed disease (high turnover with mineralization defect)
d. Osteomalacia – this is also a low turnover disease but the mineralization defect exceeds the defect in bone formation, resulting in relative osteoid excess.

3. Vascular or other soft tissue calcification.

The term chronic kidney disease-mineral and bone disorder takes a wider view of the role of bone metabolism than its local effects. It is recommended that 'chronic kidney disease-mineral and bone disorder' should replace the terms 'renal osteodystrophy' and 'renal bone disease'.

Role of vitamin D

Vitamin D is essential for musculoskeletal health as it promotes calcium absorption from the bowel and plays an important role in muscle function (National Osteoporosis Society, 2013). There is controversy about the biochemical criteria used to define vitamin D deficiency and insufficiency (National Osteoporosis Society, 2013) and a lack of agreement about optimal levels for prevention and treatment in different population groups (Holick, 2007). For the UK the level recommended for serum 25-hydroxy vitamin D is >50 nmol/litre (sufficiency), with 30–50 nmol/litre considered insufficiency and <30 nmol/litre deficiency (National Osteoporosis Society, 2013).

Chronic kidney disease is an established risk factor for vitamin D deficiency. Increased parathyroid hormone levels and a decrease in serum vitamin D are the earliest mineral metabolism disturbances in chronic kidney disease, while serum phosphate and calcium levels tend to remain in the normal range until late in the disease. Levels of 25-hydroxy vitamin D, the principal storage form of vitamin D and the best index of vitamin D nutrition, are extremely low in most patients with chronic kidney disease (Gonzalez et al, 2004) and the decline in 25-hydroxy vitamin D levels is linear with the decrease in estimated glomerular filtration rate (Levin et al, 2007) because kidneys are the principal site of production of activated vitamin D.

Fracture risk in chronic kidney disease

There are five main causes of fracture in patients with chronic kidney disease:

1. Severe hyperparathyroidism
2. Osteoporosis
3. Osteomalacia
4. Adynamic bone disease
5. Post-transplantation syndrome

The risk of hip and vertebral fractures increases with the severity of chronic kidney disease, especially in end-stage chronic kidney disease (Ensrud et al, 2007). In early stages of chronic kidney disease (stages 1–3) there is some evidence of increased risk of fragility fracture as a result of slight changes in bone turnover (mild hyperparathyroidism) or low bone turnover, but strong evidence exists that late stages of chronic kidney disease (stage 4–5) are associated with fragility fractures from severe hyperparathyroidism, adynamic bone disease and osteomalacia (either very high or low bone turnover) (Moe et al, 2006). The greater risk of falls in this population with sarcopenia (loss of muscle mass and strength with age) and frailty contributes to greater fracture risk (*Figure 2*). Patients with chronic kidney disease may have many risk factors for osteoporosis which are not related to age such as medications (glucocorticoids), hypogonadism, hyperprolactinaemia, poor nutrition, vitamin D deficiency and inactivity (Moe et al, 2006). Hence determining whether a chronic kidney disease patient's fracture is caused by osteoporosis or another form of renal bone disease is the first step in deciding on the most appropriate treatment.

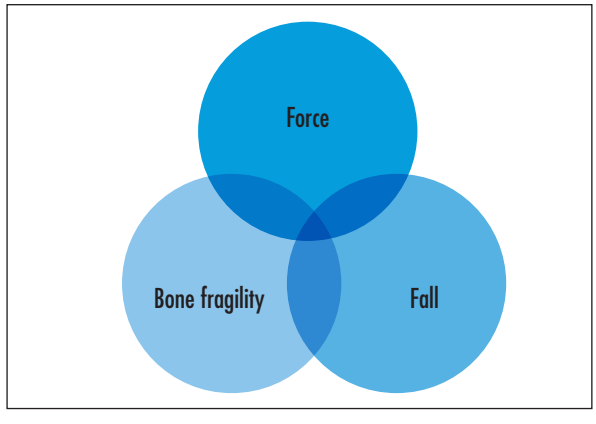
Data from a study of osteoporotic fractures which included 9704 women over 65 years of age found that fracture risk increased with worsening renal function, i.e. compared to patients with an estimated glomerular filtration rate >60 ml/min/1.73m^2 hip fracture risk increased by 1.5-fold for patients with an estimated glomerular filtration rate between 45 and 50 ml/min/1.73m^2 and doubled for women with estimated glomerular filtration rate <45 ml/min/1.73m^2 (Ensrud et al, 2007). The incidence of fractures is even higher among those with stage 5 chronic kidney disease who are on dialysis (Alem et al, 2000).

Assessment of fracture risk in chronic kidney disease

FRAX: Fracture Risk Assessment Tool

The Fracture Risk Assessment Tool (FRAX) (www.shef.ac.uk/FRAX) estimates the 10-year probability of hip fractures and major osteoporotic fractures for untreated patients using ten clinical risk factors and femoral neck bone mineral density using DEXA when available (Kanis et al, 2011). It is a validated country-specific tool for assessment of men and women over 50 years of age at risk for osteoporosis-related fracture which can help guide treatment decisions, especially in primary care. The current guidelines (Kanis et al, 2011) recommend treating

Figure 2. Association between falls and fractures.



osteoporosis patients who have FRAX 10-year risk scores of ≥3% for hip fracture or ≥20% for major osteoporotic fracture with approved osteoporosis drugs, to reduce their fracture risk but the National Osteoporosis Guideline Group (2013) gives age-adjusted advice about treatment based on FRAX scores. However, FRAX does not include any adjustment of risk with alterations in glomerular filtration rate and the value of FRAX in patients with chronic kidney disease has not been adequately studied.

Bone mineral density

Measurement of bone mineral density by DEXA is the gold standard recommended by the World Health Organization for diagnosis of osteoporosis. It is routinely used not only to diagnose osteoporosis but also to predict fracture risk in general population. However, DEXA is not sufficient to predict risk in patients with more severe chronic kidney disease because bone strength may be affected by different processes that lead to chronic kidney disease-mineral and bone disorder and not captured by two-dimensional DEXA imaging. The following suggestions are based mainly on clinical expertise and data from population studies (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009):

1. In patients with chronic kidney disease and estimated glomerular filtration rate ≥30 ml/min/1.73m^2 the World Health Organization criteria for bone mineral density (T score -2.5 standard deviation or below) or fragility fracture may be used to diagnose osteoporosis provided there are no accompanying biochemical abnormalities
2. In patients with estimated glomerular filtration rate <30 ml/min/1.73m^2 who have low bone mineral density T scores or history of fragility fractures, the diagnosis of osteoporosis can only be made by excluding other chronic kidney disease-mineral and bone disorders.

Investigations

Serum calcium and phosphate

Serum calcium can be measured as total calcium free (ionized) or corrected calcium. Calcium binds strongly to albumin and the adjusted value aims to compensate for change in serum albumin. Normal adjusted serum calcium level is between 2.1 and 2.6 mmol/litre and hypercalcaemia is >2.6 mmol/litre. In most patients with chronic kidney disease, serum calcium and phosphate levels remain normal until glomerular filtration rate declines to 25–40 ml/min/1.73m^2. Hypercalcaemia may indicate the possibility of adynamic bone disease in patients with more severe chronic kidney disease but other causes of hypercalcaemia such as hyperparathyroidism and multiple myeloma should be considered.

Serum 25-hydroxy vitamin D

Vitamin D deficiency and insufficiency is common in patients with chronic kidney disease (Gonzalez, 2004) and is associated with raised parathyroid hormone levels which may worsen manifestations of secondary hyperparathyroidism. Calcitriol (1,25 dihydroxyvitamin D) is an active metabolite of vitamin D, principally synthesized in the kidney, and circulating calcitriol levels are markedly reduced in patients with end-stage renal disease.

Serum parathyroid hormone

Elevated parathyroid hormone levels are the most sensitive marker for disordered bone and mineral metabolism in early chronic kidney disease. Parathyroid hormone levels begin to increase in early chronic kidney disease and raised levels are common in patients with estimated glomerular filtration rate <60 ml/min/1.73m^2. Parathyroid stimulation in chronic kidney disease arises from any combination of decreased calcium, increased phosphate or decreased vitamin D concentration. In early stages, there is increased synthesis of parathyroid hormone (reversible by correction of hyperphosphataemia and vitamin D deficiency). In later stages, there is increased cell proliferation leading to hyperplasia – a largely irreversible process which may require parathyroidectomy. Hence early intervention is needed, aiming to achieve a target parathyroid hormone, calcium and phosphate concentration.

Biochemical markers of bone turnover

The traditional markers of bone turnover, such as serum C telopeptide for bone resorption and serum propeptide type 1 collagen for bone formation, are both cleared by the kidney. They can be measured in clinical practice to give guidance as to the presence of adynamic bone disease but advice should be sought from the local laboratory and/or metabolic bone disease specialist as to their appropriate use. There are no data on these relationships in stages 4 and 5 chronic kidney disease (Bauer et al, 2012).

Bone-specific alkaline phosphatase

Bone-specific alkaline phosphatase is a glycoprotein found on the surface of osteoblasts. It represents biosynthetic activity of these bone-forming cells, hence is a sensitive indicator of bone metabolism. It is not cleared by the kidney and serum concentration is not affected by renal dysfunction. Bone-specific alkaline phosphatase concentration is high in Paget's disease, and osteomalacia and antiresorptive therapies lower bone-specific alkaline phosphatase levels. When estimated glomerular filtration rate is <30 ml/min/1.73m^2 the Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009) suggests measuring parathyroid hormone and bone-specific alkaline phosphatase, as a positive predictive value of parathyroid hormone with bone-specific alkaline phosphatase is 96.8% for high turnover bone disease and 80% for low turnover bone disease. This test is only available in selected laboratories in the UK. It should not be routinely used to screen for osteoporosis.

Renal ultrasound

This gives information on renal size and echogenicity, and allows detection of hydronephrosis.

Quantitative computed tomography

This measures three-dimensional volume in contrast to two-dimensional measurement by DEXA scan. It can measure cortical and trabecular bone geometry at the femur, spine and radius as trabecular bone density decreases more in women than men with increasing age. Quantitative computed tomography can measure early increases in vertebral trabecular bone density after parathyroid hormone treatment (Gasser, 1995). Both cortical and trabecular volumetric bone mineral density impairment in predialysis patients and selective cortical volumetric bone mineral density impairment in patients with end-stage renal disease have been noted (Russo et al, 1998).

High resolution magnetic resonance imaging

Magnetic resonance imaging is a non-ionizing imaging technique providing three-dimensional representation of cortical and trabecular bone microarchitecture at peripheral sites (radius, tibia, calcaneus).

High resolution peripheral quantitative computed tomography

This new technique provides three-dimensional representation of trabecular and cortical microarchitecture of the distal radius and tibia. Compared to magnetic resonance imaging, high resolution peripheral quantitative computed tomography allows direct visualization of bone and faster acquisition (3-minute measurement time) with a smaller dose of radiation (Boutroy et al, 2005). Haemodialysis patients had greater cortical and trabecular bone impairment than chronic kidney disease patients, who had greater impairment than controls (Boutroy et al, 2005). Quantitative computed tomography, magnetic resonance imaging and high resolution peripheral quantitative computed tomography are research tools.

Bone biopsy

The only reliable method for distinguishing patients with high turnover from those with low turnover bone disease is bone histomorphometric study, but this invasive test is used mainly for clinical research. Iliac crest bone biopsy may be used in specific situations (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). A review of bone biopsy studies between 1983 and 2006 showed that 84% of chronic kidney disease patients (estimated glomerular filtration rate <60 ml/min/1.73m^2) had histological evidence of bone disease (32% osteitis fibrosa, 20% mixed bone disease, 8% osteomalacia, 6% mild disease, 18% adynamic bone disease)(Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009) but only 2% of haemodialysis patients have normal histomorphometric analysis on bone biopsy.

Management

Lifestyle measures

All patients at high risk of fractures should be advised about lifestyle measures such as regular exercise, avoiding excessive smoking or alcohol, and falls prevention (Jarvinen et al, 2008). Patients with severe chronic kidney disease, especially stage 4 and 5, have sarcopenia and associated low muscle mass, and have a high frequency of falling, hence improving muscle tone, strength and balance are important in fracture risk reduction in patients with chronic kidney disease. Sufficient protein intake is necessary to avoid protein-energy wasting.

Phosphate

Dietary phosphate restriction to 800–1000 mg/day may be initiated in patients with chronic kidney disease when parathyroid hormone levels are elevated (glomerular filtration rate <60 ml/min/1.73 m^2, stage 3) or with elevated blood levels of serum phosphate (stages 4 and 5)(Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). Serum phosphate levels should be maintained between 2.7 and 4.6 mg/dl. There is conflicting evidence about the use of calcium and non-calcium-based phosphate binders. Except in special circumstances (hypercalcaemia, severe peripheral vascular disease), evidence does not favour non-calcium-based binders (sevelamer-HCI and lanthanum carbonate) as first-line treatment of hyperphosphataemia in chronic kidney disease because of their high cost. The main limitation of calcium-based phosphate binders is the risk of progression of vascular calcification. Aluminium-based binders should be avoided. Owing to their complexity this treatment should be initiated and supervised by nephrologists.

Calcium and vitamin D

Optimal diet for fracture prevention should include adequate intake of calories, calcium and vitamin D. Meta-analysis of randomized trials in osteoporosis shows that combined calcium and vitamin D supplementation modestly reduces the risk of hip and other non-vertebral fractures while vitamin D alone is ineffective (Boonen et al, 2007).

Low vitamin D levels should be treated to help suppress high parathyroid hormone levels. Vitamin D supplementation minimum of 400–800 IU/day to achieve a serum 25-hydroxy vitamin D concentration >25–30 ng/ml is advised and higher doses may be necessary to bring vitamin D up to the correct level (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). Calcitriol improves bone health as assessed by DEXA scan and serum biomarkers and can reduce mortality irrespective of parathyroid hormone levels (Teng, 2005). Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009) guidelines recommend prescribing calcitriol for patients with chronic kidney disease stage 3 and 4 if plasma parathyroid hormone level is high and serum 25-hydroxy vitamin D level is >30 ng/ml with monitoring of plasma calcium, phosphate and parathyroid hormone levels.

Patients with estimated glomerular filtration rate >30 ml/min/1.73m^2 with no biochemical evidence of

chronic kidney disease-mineral and bone disorder can have similar calcium intakes as patients without chronic kidney disease to a total of 1200–1500 mg/day. However, the effects of calcium and vitamin D supplementation on fracture risk in patients with chronic kidney disease and estimated glomerular filtration rate <30 ml/min/1.73m^2 have not been adequately studied. In patients with estimated glomerular filtration rate <30 ml/min/1.73m^2 there are potential benefits of vitamin D repletion but excess calcium supplementation in contrast may be associated with increased arterial calcification and cardiovascular disease (West et al, 2010) and closer monitoring of serum calcium levels is recommended. In patients with end-stage renal disease, Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009) guidelines recommend keeping corrected calcium within the lower end of the normal range (2.10–2.37 mmol/litre) with further restriction in patients with diabetes because of the burden of vascular calcification and associated mortality (Kramer et al, 2005).

Pharmacological therapy

Distinguishing renal metabolic bone abnormalities from those caused by osteoporosis and correcting any metabolic derangements is necessary to adequately treat patients at risk of fragility fractures. Treatment of osteoporosis is aimed at stabilizing or increasing bone mass and reducing the risk of fragility fractures whereas treatment of chronic kidney disease-mineral and bone disorder is aimed at normalizing parathyroid hormone–calcium–phosphate–vitamin D to maintain normal mineral metabolism and bone turnover. An approach to the pharmacological management as suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group working group (2009) is shown in *Figure 3*.

Bisphosphonates

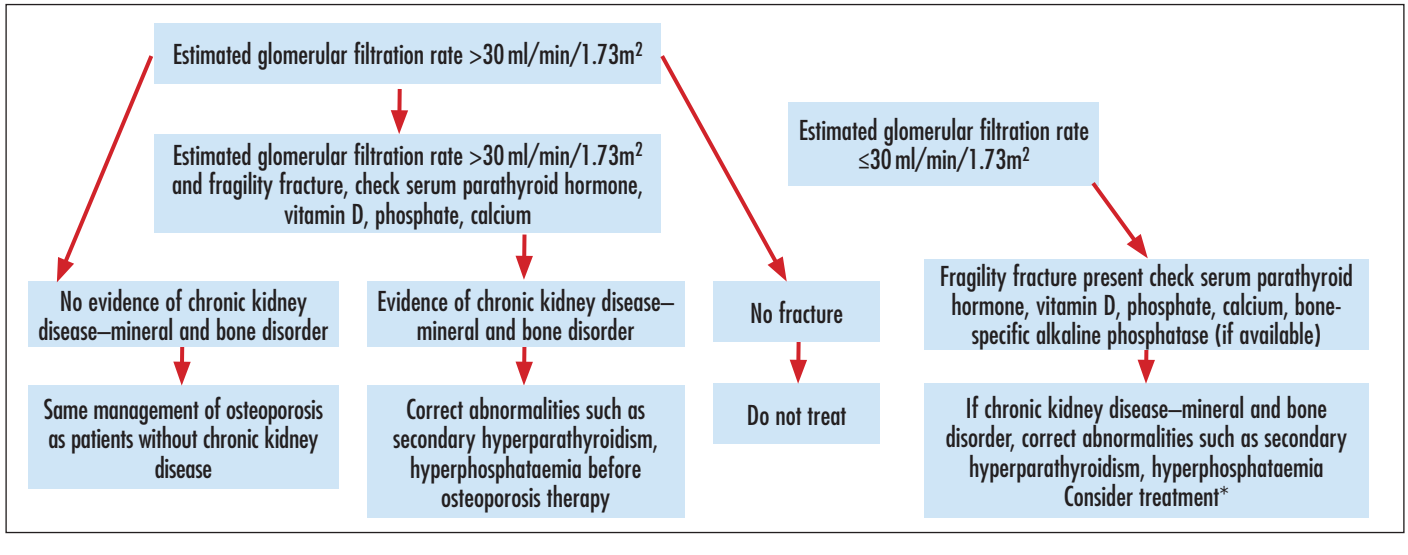
Alendronate, risedronate, ibandronate and zoledronate are established treatments for post-menopausal osteoporosis. They reduce vertebral and non-vertebral fractures and are approved for use in men and women (National Institute for Health and Clinical Excellence, 2011).

Bisphosphonates bind strongly, accumulate in bone and are gradually released into the circulation with a half life of more than 10 years. Renal impairment may lead to accumulation of administered bisphosphonates. Prolonged use of bisphosphonates can lead to adynamic bone disease which may increase the risk of atypical fractures, e.g. femoral shaft fractures, and therefore should be excluded before initiating bisphosphonates in people with chronic kidney disease or on renal dialysis.

First generation intravenous bisphosphonates in older literature were associated with acute renal failure and clinical trials of osteoporosis excluded patients based upon prespecified renal measurement cut offs. Limited evidence from retrospective analysis of the Fracture Intervention Trial (Jamal et al, 2007) and pooled data from nine risedronate studies (Miller et al, 2005) suggested that among the subset of patients with moderate renal impairment, alendronate and risedronate increased bone mineral density and prevented vertebral fractures regardless of the degree of renal impairment with no significant increase in event rate. In zoledronate trials, a small but significant number of patients who received zoledronic acid 5 mg doubled their serum creatinine concentration 9–11 days later which returned to baseline, but renal failure is a serious side effect associated with zoledronic acid so it is contraindicated in patients with creatinine clearance <35 ml/min (Miller, 2011).

There are inadequate data on the use of bisphosphonates for fracture prevention in patients with severe kidney disease associated with secondary hyperparathyroidism and

Figure 3. Approach to management of osteoporosis suggested by Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). *If bone-specific alkaline phosphatase high and intact serum parathyroid hormone >350 pg/ml adynamic bone disease is unlikely and antiresorptive treatment could be considered.



end-stage renal failure (chronic kidney disease stage 4 and 5), so bisphosphonates are not recommended for those with estimated glomerular filtration rate below 30 ml/min/1.73m^2 (for alendronate, risedronate or ibandronate) to 35 ml/min/1.73m^2 (for zoledronic acid) (Miller, 2011). For patients with chronic kidney disease stage 4 and 5, bisphosphonates should only be considered by specialists in metabolic bone disease after excluding adynamic bone disease and carefully considering risks/benefits. *Table 2* shows some important characteristics of bisphosphonates to consider when using with patients who have renal disease.

The serum creatinine level should be checked before every infusion of bisphosphonate and the patient should be well hydrated.

Denosumab

This is a fully human monoclonal antibody which, unlike bisphosphonates, is not cleared by the kidney. The FREEDOM trial used an estimated glomerular filtration rate cut off of <30 ml/min/1.73m^2 for exclusion. Given subcutaneously twice yearly for 36 months, denosumab showed significant reduction in vertebral and non-vertebral fractures in postmenopausal women. Post-hoc analysis stratified by level of kidney function in patients with estimated glomerular filtration rate >15 ml/min/1.73m^2 and estimated glomerular filtration rate >30 ml/min/1.73m^2 showed evidence of effectiveness (improved bone mineral density) and no increase in adverse events (Jamal et al, 2011). Patients with chronic kidney disease and creatinine clearance <30 ml/min are at higher risk of hypocalcaemia following denosumab injection, and serum calcium and vitamin D levels should be checked before and after injection. In the UK, it is approved for treatment of osteoporosis in postmenopausal women at high risk of fractures when bisphosphonates have failed or are not tolerated.

Teriparatide

This is recombinant 1-34 parathyroid hormone, which has anabolic properties for bone. Given 20 μg subcutaneously daily for 18–24 months it reduces vertebral and non-vertebral fractures in postmenopausal women. In post-hoc analysis of the Fracture Prevention trial, teriparatide had efficacy (improved bone mineral density) and safety in patients with estimated glomerular filtration rate as low as 30 ml/min/1.73m^2 (Miller et al, 2007). However, the sample size was small and patients with elevated serum parathyroid hormone levels were excluded. It is expensive and its use is restricted in the UK to those with the most severe osteoporosis under specialist care (National Institute for Health and Clinical Excellence, 2011).

Raloxifene

Raloxifene is a less potent osteoporosis drug than bisphosphonates which reduces vertebral fractures but does not prevent fractures at other sites and is used less frequently. It protects against breast cancer but has a three-fold increased risk of venous thromboembolism. Compared with placebo raloxifene improved bone mineral density and reduced vertebral fractures irrespective of kidney function, although very few patients had estimated glomerular filtration rate <30 ml/min/1.73m^2 (Ishani et al, 2008). It should be used with caution in patients with moderate to severe renal impairment as safety and efficacy has not been established in this group. It is only licensed for use in women.

Calcitonin

This inhibits renal phosphorus and increases renal calcium absorption, helping to decrease serum parathyroid hormone levels. It improves bone mineral density, has an analgesic action on bone pains and reduces the risk of vertebral fracture. It can be given regardless of chronic kidney disease. However, it has less robust efficacy data on vertebral fracture risk than other agents and did not show risk reduction for non-vertebral fractures, hence it has limited clinical use. Moreover in long-term clinical trials the risk of developing cancer was 0.7–2.4% higher in patients receiving calcitonin than placebo, especially in trials with intranasal calcitonin. The European Medicine Agency recommended that calcitonin should be used only for short term and with the minimal effective dose.

Table 2. Product characteristics of bisphosphonates

Alendronate (Fosamax)	No dose adjustment necessary for patients with glomerular filtration rate >35 ml/min/1.73m^2
Disodium etidronate (Didronel PMO)	Contraindicated in patients with severe renal impairment. Owing to lack of clinical experience treatment of patients with impaired renal function should be undertaken with caution, monitor serum and urine calcium regularly
Risedronate (Actonel)	No dosage adjustment needed for mild to moderate renal impairment. Contraindicated in patients with severe renal impairment creatinine clearance <30 ml/min
Ibandronate (Bonviva)	No doasage adjustment needed for mild or moderate renal impairment where creatinine clearance >30 ml/min. Not recommended if creatinine clearance<30 ml/min
Zolendronic acid (Aclasta)	Contraindicated in patients with creatinine clearance <35 ml/min

Conclusions

There is increasing incidence of both osteoporosis and chronic kidney disease with increasing age. Chronic kidney disease is associated with metabolic abnormalities of calcium, phosphate, parathyroid hormone and vitamin D, and with differences in mineralization, bone turnover, strength, and vascular and soft tissue calcification. Pharmacological management of osteoporosis in patients with stages 1–3 chronic kidney disease does not differ from that of postmenopausal women with normal glomerular filtration rate because clinical trials for osteoporosis treatments randomized patients down to glomerular filtration rate of 30 ml/min/1.73m^2. However, in more severe chronic kidney disease, management options tend to be based on opinion rather than clinical trial data. There is limited evidence of efficacy and safety of bisphosphonates in

patients with chronic kidney disease and estimated glomerular filtration rate <30 ml/min/1.73m^2. In patients with glomerular filtration rate below 30 ml/min/1.73m^2, identification and management of associated metabolic abnormalities is essential. Patients with adynamic bone disease should never be treated with drugs such as bisphosphonates which reduce bone turnover. Bone-specific alkaline phosphatase testing may be useful if available in certain situations. Considering the heterogeneity of bone disease in the chronic kidney disease population more studies using bone biopsies are needed in the future, focussing on developing therapies which have the potential to increase bone formation and reduce fracture risk. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Osteoporosis and chronic kidney disease are both common in old age, often coexisting together, and both are associated with increased fracture risk.
- Chronic kidney disease is associated with a range of different metabolic bone diseases.
- A fracture in a patient with chronic kidney disease may indicate osteoporosis, another bone disorder or just an age-related decrease in glomerular filtration rate.
- In patients with early chronic kidney disease (stage 1–3) fractures are more likely to be the result of osteoporosis than a specific form of chronic kidney disease-mineral bone disorder.
- Measurement of bone mineral density by DEXA (dual energy X-ray absorptiometry) is of limited benefit in predicting fracture risk in patients with severe stage 4–5 chronic kidney disease but has good value in stage 1–3 chronic kidney disease.
- Several pharmacological agents are approved for the management of osteoporosis in patients with chronic kidney disease stage 1–3 but there is a lack of clinical trial data in patients with severe chronic kidney disease.
- Bisphosphonates have limited efficacy and safety data in patients with severe chronic kidney disease if creatinine clearance <30 ml/min, but are contraindicated in adynamic bone disease.
- Denosumab is effective and safe in patients with glomerular filtration rate up to 15 ml/min/1.73m^2 but serum calcium and vitamin D levels need to be monitored.