Osteoporosis

Osteoporosis is a skeletal condition characterized by reduced bone volume, bone quality, and increased fragility, leading to an increased risk of fractures.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) Traditionally, osteoporosis has been diagnosed either by the presence of a fragility fracture or solely on bone mineral density (BMD) in the absence of a fragility fracture. Osteoporosis Canada (OC) now recognizes that although there is a strong association between BMD and the risk of fracture, there are other factors independent of BMD that influence fracture risk in patients such as age and sex. An individual's fracture risk should be categorized by determining their 10-year absolute fracture risk rather than their BMD alone. The risk assessment systems developed by either the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) or the Canadian WHO Fracture Risk Assessment Tool (FRAX) are recommended for use.\(^4\)

In Canada, one in three women and one in five men will have at least one fragility fracture attributed to osteoporosis during their lifetime.\(^2\)\(^,\)\(^5\) A fragility fracture is one that occurs as a result of minimal trauma such as a fall from standing height or less (at no greater than walking speed) or no identifiable trauma. Fractures of the skull, hands, ankles and feet are not considered fragility fractures.\(^6\)\(^,\)\(^7\)

All fragility fractures have serious consequences in terms of morbidity, often leading to increased institutionalization and health care costs.\(^3\)\(^,\)\(^5\) Mortality is significantly increased following vertebral and hip fractures, with an astounding 28% of women and 37% of men dying within one year following a hip fracture.\(^4\)\(^,\)\(^5\) While poor outcomes following osteoporotic fractures are well documented, treatment rates for osteoporosis remain low. In 2010 it was estimated that less than 20% of women and 10% of men at risk of osteoporosis were prescribed preventative medications for future fractures.\(^4\)

Chronic Kidney Disease

Chronic kidney disease (CKD) is another highly prevalent condition that can arise as a result of insult to the kidneys or as a consequence of aging.\(^8\) It is estimated that 25% of healthy individuals over 70 years old have a creatinine clearance below 25 mL/min.\(^9\) KDIGO guidelines outline five distinct stages of CKD, based on glomerular filtration rate (GFR) and defined kidney pathology, as outlined in Table 1.\(^9\)

CKD and Osteoporosis

The prevalence of CKD and osteoporosis increase with age and frequently occur as comorbid conditions.\(^10\)\(^,\)\(^11\) Fracture risk in the CKD population is estimated to be 2- to 14-fold higher than that of the general population and is also associated with a greater risk of morbidity and mortality.\(^2\)\(^,\)\(^3\)\(^,\)\(^12\)\(^,\)\(^13\) One report stated that patients with stage 3 and 4 CKD have twice the risk of fracture compared to matched controls; this is likely even higher in patients with stage 5 CKD.\(^13\) Specific to hip fractures, CKD patients have an estimated 4.4 increased risk, with approximately 2.4-fold increased mortality following hip fracture compared to patients with normal renal function.\(^9\)\(^,\)\(^14\) Fractures occur at younger ages in the presence of CKD and represent a significant source of morbidity and mortality.\(^2\)

The kidneys are responsible for many physiologic functions including regulation of fluid, electrolyte, and acid-base balance; secretion of hormones; waste excretion; regulation of blood pressure; and gluconeogenesis. In regard to bone health, the kidneys in combination with the liver, control the activation of vitamin D. This is central to regulating the homeostasis of parathyroid hormone (PTH), calcium, and phosphorous balance. These four substances are critical to the processes that maintain strong bones, and when they are altered, bone health is disrupted.\(^9\)\(^,\)\(^13\)
Bone Pathologies in CKD
Several bone pathologies can arise in patients with CKD due to disruption in mineral and hormone balance. Osteoporosis can be assumed to be the bone pathology present in CKD stages 1 and 2, when kidney dysfunction has not yet caused significant changes in mineral and hormonal balance. As CKD progresses, abnormal hormone and mineral balance becomes prominent, which can affect bone quality and density. Abnormal mineral metabolism occurs progressively throughout CKD, and tends to become evident by stage 3. Beginning in stage 3 it becomes increasingly likely that another type of bone pathology is present.

In 2009, KDIGO coined the term “chronic kidney disease mineral and bone disorder” (CKD-MBD) to encompass the systemic nature of mineral abnormalities and bone disease that occur with worsening renal function. The term renal osteodystrophy has been used by KDIGO longer than CKD-MBD and describes abnormalities in bone turnover, mineralization, and volume, which constitutes a more complex disease process compared to osteoporosis (Table 2). Osteoporosis, CKD-MBD, and renal osteodystrophy can co-exist. Low BMD is not specific to osteoporosis and should not be used alone for diagnosis of osteoporosis in the presence of late stage CKD. A patient with low BMD and stage 3-5 CKD should be classified as “CKD-MBD with low BMD” until further investigation can confirm a specific bone pathology.

In stage 3 CKD, if a patient has normal PTH, calcium, phosphate, and vitamin D, osteoporosis can be assumed. If lab values are abnormal, CKD-MBD and renal osteodystrophy must be explored. In stages 4 and 5 CKD, osteoporosis can only be diagnosed if other pathologies are excluded and distinguishing between these pathologies is challenging. Biochemical markers may be used to provide an indication of bone pathology (Table 3). Prior to initiating treatment in later stage CKD, it is important to rule out hyperparathyroidism and osteomalacia by obtaining a 25-hydroxyvitamin D level and a serum PTH level. Once these conditions are ruled out, osteoporosis can be considered a diagnosis of exclusion in patients with stage 1-4 CKD.

The gold standard for diagnosis in later stages, as recommended by KDIGO, is a bone biopsy. Biopsy provides details on bone turnover and mineralization, which serves as an accurate tool for determining specific pathology. This is a very invasive procedure and skill is required in interpreting results. In Nova Scotia, biopsy can be performed but samples must be sent to Montreal for histomorphometry to be interpreted. Bone biopsy should be attained for patients with stage 5 CKD prior to initiating treatment (low prevalence of adynamic bone disease before stage 5) and for patients with stage 4 who have abnormal laboratory values such as low to normal PTH or unexplained hypercalcemia.

When considering treatment, it is necessary to differentiate osteoporosis from renal osteodystrophy (e.g. osteitis fibrosa, osteomalacia, adynamic bone disease). As shown in Table 3, specific types of renal osteodystrophy can be either high or low turnover diseases. Treatment of renal osteodystrophy is aimed at correcting underlying mineral and hormonal abnormalities, usually focusing on phosphate binders and vitamin D analogs. In low turnover bone disease, antiresorptive medications which inhibit osteoclasts and osteoblasts can worsen the condition.

Table 2. Classifications of Bone Related Disorders

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Diagnosis of low bone strength, based on existing fragility fracture and/or the presence of risk factors for fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-MBD</td>
<td>A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:</td>
</tr>
<tr>
<td></td>
<td>- Abnormalities of calcium, phosphorous, PTH, or vitamin D metabolism</td>
</tr>
<tr>
<td></td>
<td>- Abnormalities in bone turnover, mineralization, volume, or strength</td>
</tr>
<tr>
<td></td>
<td>- Vascular or other soft-tissue calcification</td>
</tr>
<tr>
<td>Renal Osteodystrophy</td>
<td>Includes renal osteodystrophy</td>
</tr>
<tr>
<td></td>
<td>An alteration of bone morphology in patients with CKD</td>
</tr>
<tr>
<td></td>
<td>One measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry on bone biopsy</td>
</tr>
<tr>
<td></td>
<td>Includes:</td>
</tr>
<tr>
<td></td>
<td>- Hyperparathyroid bone disease, osteitis fibrosa</td>
</tr>
<tr>
<td></td>
<td>- Mixed osteodystrophy</td>
</tr>
<tr>
<td></td>
<td>- Osteomalacia</td>
</tr>
<tr>
<td></td>
<td>- Aluminum bone disease</td>
</tr>
<tr>
<td></td>
<td>- Adynamic bone disease</td>
</tr>
</tbody>
</table>

Table 3. Overview of Specific Bone Diseases in CKD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Turnover</th>
<th>PTH</th>
<th>Bone-Specific Alkaline Phosphatase</th>
<th>Treatment</th>
<th>Prevalence Stages 3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteitis Fibrosa</td>
<td>High</td>
<td>High</td>
<td>Increased</td>
<td>Vitamin D analog, Phosphate binders</td>
<td>32%</td>
</tr>
<tr>
<td>Mixed Osteodystrophy</td>
<td>--</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>20%</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Low</td>
<td>Variable</td>
<td>Mild increase</td>
<td>Vitamin D analog, Correct acidosis</td>
<td>8%</td>
</tr>
<tr>
<td>Adynamic Bone Disease</td>
<td>Low</td>
<td>Low</td>
<td>Normal, reduced</td>
<td>Decrease or discontinue vitamin D analog, Calcium to increase PTH</td>
<td>18%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>--</td>
<td>Normal</td>
<td>Normal</td>
<td>Bisphosphonate, Denosumab, Selective Estrogen Receptor Modulators (SERM), Estrogen, Teriparatide</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Turnover is a marker of bone formation, where high turnover corresponds to more rapid bone formation. Parathyroid hormone
This is the reason bisphosphonates are contraindicated in adynamic bone disease.\(^3\)

While the literature is very clear concerning treatment of osteoporosis in the early stages of CKD, there appears to be a paucity of knowledge in terms of how to treat patients with low BMD in later CKD stages, namely 4 and 5.

**Treatment of Osteoporosis in Late Stage CKD**

The ultimate goal in the management of osteoporosis is to prevent fractures. At this time, there are no studies prospectively evaluating osteoporosis therapies and fracture outcomes in patients with stage 4 and 5 CKD. All of the following studies, unless otherwise specified, had exclusion criteria which eliminated subjects with abnormal PTH, calcium or phosphate from trials. Thus patients evaluated had significant renal impairment but did not meet criteria for CKD-BMD. The strict PTH criteria prevented patients with particularly high or low bone turnover disease from being included.

**Bisphosphonates**

Bisphosphonates are the most commonly prescribed treatment for osteoporosis. This is based on proven efficacy and cost. The oral bisphosphonates currently used in Canada are alendronate and risedronate. Zoledronic acid is the only intravenous bisphosphonate indicated in osteoporosis.

When bisphosphonates enter the body, they are either taken up into bone or excreted via renal mechanisms.\(^{17,18}\) For this reason, in addition to reports of nephrotoxicity, there is concern about using bisphosphonates in the presence of renal impairment.\(^{17,18}\) Use of alendronate and zolendronic acid is contraindicated when creatinine clearance is less than 35 mL/min and use of risedronate is contraindicated when creatinine clearance is less than 30 mL/min.\(^{2,18}\) The majority of reports of kidney injury with bisphosphonates comes from high doses used intravenously for oncology related indications.\(^8\)

The Fracture Intervention Trial (FIT) showed a reduced risk of fractures with alendronate compared to placebo.\(^{19,20}\) The study randomized women to receive alendronate 5 mg or placebo once daily for 24 months, with the dose increased to 10 mg daily thereafter for a total of 36 months of follow up.\(^{19,20}\) A post-hoc analysis of the FIT trial was performed to evaluate the efficacy of alendronate in patients with chronic kidney disease.\(^{21}\) This secondary analysis evaluated a total of 6458 women treated with alendronate and compared subjects with an eGFR less than 45 mL/min to subjects with an eGFR greater than, or equal to, 45 mL/min.\(^{21}\) The number of patients with an eGFR less than 30 mL/min was not specified which limits the clinical applicability of the analysis. Only 9.9% of total subjects had an eGFR less than 45 mL/min.\(^{21}\) At 36 months there was a trend for an increase in BMD across all sites measured (whole body, femoral neck, total hip, and lumbar spine) for subjects with a creatinine clearance less than 45 mL/min; however, significance was only achieved for total hip BMD (p=0.04).\(^{21}\) There was no difference in clinical fractures (p=0.89) between the groups or adverse events, suggesting safety in subjects with impaired renal function.\(^{21}\)

A randomized controlled trial by Wemore et al evaluated the use of alendronate versus placebo in 31 hemodialysis patients. The trial duration was six weeks of therapy with six months follow up. The dose of alendronate was reduced from the standard dose of 70 mg weekly to 40 mg weekly because of potential pharmacokinetic changes. BMD at all measured sites (Ward’s triangle, femoral neck, total hip, and lumbar spine) did not change from baseline to six months post-treatment in the group that received alendronate. The short trial duration prevents interpretation of the outcome.\(^{22}\)

Miller et al used a pooled analysis of nine phase III trials to evaluate the impact of reduced renal function on the efficacy and safety of risedronate 5mg daily for up to three years. Of the 9883 subjects, 572 had a baseline creatinine clearance less than 30 mL/min and were treated for an average of 22 months. BMD increased significantly in the risedronate group versus the control group at the lumbar spine (p<0.001) and trochanter (p<0.001), but not the femoral neck. Significantly less subjects treated with risedronate had vertebral fractures (p=0.021). There were no significant differences between treatment and placebo groups in adverse events, change in serum creatinine, or change in metabolic parameters.\(^{23,24}\)

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly – Pivotal Fracture Trial (HORIZON-PFT) was a large phase III trial that demonstrated efficacy of zoledronic acid in preventing osteoporotic fractures. This trial had more rigorous screening in terms of renal function and patients were excluded if creatinine clearance was less than 30 mL/min. This eliminates the ability of post-hoc analyses in patients with late stage CKD.\(^{24}\)

In summary, post hoc analyses have demonstrated improvement in BMD in patients with creatinine clearance ranging from less than 45 mL/min for alendronate and less than 30 mL/min for risedronate. Similar data is currently lacking for zoledronic acid. There is no data for patients with a creatinine clearance less than 15 mL/min.

**Denosumab**

Denosumab is an antiresorptive agent indicated for osteoporosis in Canada. It is a human monoclonal antibody that inhibits osteoclast activity by binding to the receptor activator of nuclear factor-xB ligand (RANKL).\(^{25}\) Unlike bisphosphonates, denosumab is not eliminated by the kidneys.\(^{11,25,26,27}\) There is no dose reduction necessary in patients with impaired renal function.\(^{28}\)

Hypocalcemia is a well-documented, and sometimes serious, adverse effect of denosumab that occurs more frequently in the presence of abnormal renal function.\(^{11,25,26,27}\) When calcium supplements are used properly with denosumab, the incidence can be reduced.\(^{25}\)

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial randomized women aged 60 to 90 to receive either denosumab 60 mg or placebo subcutaneously every six months for a total of 36 months and showed a reduction in vertebral, nonvertebral, and hip fractures in the denosumab group.\(^{29}\) A post-hoc analysis by Jamal et al of the FREEDOM trial aimed to determine the safety and efficacy of denosumab in patients with CKD.\(^{11}\) Of 7808 patients randomized, only 73 subjects had stage 4 CKD as determined by Cockcroft-Gault estimated GFR and no subjects had stage 5 CKD.\(^{11}\) Vertebral and nonvertebral fracture reduction with denosumab did not reach statistical significance compared with placebo in subjects with stage 4 CKD, likely due to the small group size.\(^{11}\) There was no significant difference in change in serum creatinine from baseline after 36 months in patients with stage 4 CKD compared to placebo. No differences in adverse effects by stage of CKD were identified. The safety of denosumab in patients with renal dysfunction is promising based on the results of this analysis. A longer trial prospectively evaluating both efficacy and safety in this patient population is required.
A 16-week open-label study by Block et al evaluated the effects of a single dose of denosumab 60 mg subcutaneously in men and women with varying degrees of renal impairment, including those with eGFR less than 30 mL/min (n=9) and dialysis patients (n=8). There were no differences in pharmacokinetic parameters between groups which is consistent with the lack of kidney involvement in denosumab elimination. The only group that did not develop hypocalcemia was the group with normal renal function. Limitations of this study were its short duration and lack of evaluation of fracture incidence. Initially, the study did not evaluate PTH status, which can be indicative of a mineral bone disorder. Patients with low PTH at baseline had more serious hypocalcemia, including two patients who required hospitalization. Hypocalcemia was avoided when the study protocol was modified to include an assessment of PTH status and calcium supplementation. This study highlights the importance of assessing baseline hormones and minerals prior to initiation of therapy.25

A small open label study by Chen et al investigated the use of denosumab in 12 dialysis patients with secondary hyperparathyroidism and low bone mass. After 24 weeks, BMD was increased at the femoral neck and lumbar spine in patients receiving a single dose of denosumab 60 mg subcutaneously. In the first one to two weeks, four patients experienced significant hypocalcemia which was managed by adjusting calcium intake, dialysate calcium levels and administering high dose calcitriol. At baseline all patients had high levels of PTH, calcium x phosphate (Ca x P) product and alkaline phosphatase suggesting severe hyperparathyroidism and high turnover bone disease. Upon study completion, there were large reductions in PTH (1702.1+/−181.9 to 518.8+/−126.8 pg/mL), alkaline phosphatase and serum phosphorus levels as well as Ca x P product. Despite the trial’s small size and open label design, denosumab demonstrated value in terms of increasing bone mass and correcting metabolic abnormalities in dialysis patients. An adequately sized randomized trial is required to confirm the efficacy and safety of denosumab in this patient population.26

**Raloxifene**

Raloxifene is a selective estrogen receptor modulator that is an option for the prevention of vertebral fractures in postmenopausal women. Raloxifene exerts estrogenic effects at receptors in the bone and cardiovascular system and antiestrogenic effects in the breast and endometrial tissue.30

Tanaka et al conducted a small trial (n=27) in Japanese women aged 50-70 years on hemodialysis treated with raloxifene 60 mg daily for 12 months and compared them to age-matched controls. There was a statistically significant increase in the lumbar spine BMD in patients treated with raloxifene compared to controls (p<0.0001); however, the effect was not observed at the radius. There was no discussion of adverse events, which could be important for a drug that possesses hormonal activity.31

Another trial in dialysis patients (n=47) by Eriguchi et al showed a non-significant benefit in radial BMD in postmenopausal women on hemodialysis treated with raloxifene 60 mg three times weekly for one year compared to a group that received no treatment.41

When considering a hormonal option for bone health, it is very important to consider both the risks and benefits of therapy for individual patients. At this time, the data supporting the efficacy of raloxifene in dialysis patients is weak. Therapy should be reserved for patients with additional indications.

**Teriparatide**

Teriparatide is currently the only anabolic product marketed for osteoporosis in Canada. Teriparatide works to increase osteoblast activity by mimicking the actions of endogenous parathyroid hormone, including increasing gastrointestinal absorption and kidney reabsorption of calcium.32 As stated previously, antiresorptive agents decrease bone resorption by inhibiting osteoclast function and as a result, these agents can have negative impacts on low turnover pathologies such as adynamic bone disease. It would seem reasonable that agents that increase osteoblast activity might benefit these types of bone disease. However, there has been little research in this area.

Cejka et al studied the use of teriparatide 20 mcg injected subcutaneously daily in seven hemodialysis patients with adynamic bone disease in an open label trial. After six months of treatment, there was a statistically significant increase in BMD at the lumbar spine from baseline, however the increase in the femoral neck did not reach statistical significance. There were no significant changes in laboratory parameters from baseline. Limitations include small number of patients, uncontrolled nature of the study, and lack of clinical outcomes.33

Teriparatide may be useful in adynamic bone disease; however, a properly powered RCT is necessary to demonstrate efficacy and safety.34

**Conclusion**

In stages 1 and 2 CKD, patients with bone disease should be treated the same as patients with normal renal function. Patients with stage 3 CKD are generally also treated in the same way as patients with normal renal function, after evaluating calcium, parathyroid, and vitamin D status. Treatment of bone disease in stages 4 and 5 CKD is a challenge. Proper diagnosis is imperative since patients may have renal osteodystrophy, CKD-MBD, or adynamic bone disease. Distinguishing and diagnosing specific pathologies is a major challenge although vitamin D, calcium, bone-specific alkaline phosphatase or alkaline phosphatase, and PTH can be used to help predict the type of renal osteodystrophy. When diagnosis is uncertain, bone biopsy is recommended and unfortunately, this test remains largely unavailable in Nova Scotia and many other centers worldwide. Current research is attempting to identify practical, less invasive methods to differentiate between the types of bone pathologies.2

The development of a validated fracture risk assessment tool as well as reliable methods to establish bone pathologies in this patient population would positively impact the way patients are treated and clinical outcomes. Currently, the literature lacks high-quality evidence to guide clinicians in treating stage 3-5 CKD. There is evidence to suggest that oral bisphosphonates, alendronate and risedronate, safely maintain BMD in late stage CKD when other conditions are ruled out and osteoporosis is diagnosed.1,12,33 Bisphosphonates are contraindicated in adynamic bone disease. Current practice often includes a 50% dose reduction in these agents, based on pharmacokinetic properties. Zoledronic acid, an IV bisphosphonate, lacks evidence to demonstrate efficacy and safety and use should be avoided until data is available. Denosumab has been safely used in small trials with positive effects on BMD. It requires proper supplementation with calcium and calcitriol to prevent serious hypocalcemia. Raloxifene currently lacks sufficient data on efficacy and safety.

Unlike the other agents discussed, teriparatide is not an antiresorptive medication. This quality makes teriparatide a potentially valuable option for treating patients with adynamic
bone disease; future studies are required to confirm its efficacy and safety in this condition. The evidence supporting the optimal treatment of other types of renal osteodystrophy such as CKD-MBD or conditions such as adynamic bone is even less well described.

At this time, therapy must be individualized. Limited clinical data can be used to guide therapy. Drug cost may also play a role and is summarized in Table 4.

### Table 4: Approximate Annual Cost of Osteoporosis Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronate</strong></td>
<td>10 mg po daily</td>
<td>$180</td>
</tr>
<tr>
<td></td>
<td>70 mg po weekly</td>
<td>$130</td>
</tr>
<tr>
<td><strong>Risedronate</strong></td>
<td>5 mg po daily</td>
<td>$560</td>
</tr>
<tr>
<td></td>
<td>35 mg po weekly</td>
<td>$130</td>
</tr>
<tr>
<td><strong>Zoledronic Acid</strong></td>
<td>5 mg IV yearly</td>
<td>$340</td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td>60 mg subcut every 6 months</td>
<td>$790 (brand only)</td>
</tr>
<tr>
<td><strong>Raloxifene</strong></td>
<td>60 mg po daily</td>
<td>$170</td>
</tr>
<tr>
<td><strong>Teriparadine</strong></td>
<td>20 mcg subcut daily</td>
<td>$13 200 (brand only)**</td>
</tr>
</tbody>
</table>

*McKesson wholesale generic cost unless specified, 2016*  
**Lilly, personal communication, 2016**

### References


At the time of writing, Amanda Daniels was a Pharmacy Resident at Nova Scotia Health Authority (Central Zone)