

## Fractures in men and women with dialysis-dependent renal failure

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The number of Canadians with dialysis-dependent renal failure (DDRF) is increasing. In 1996, approximately 11,000 Canadians were being treated with hemodialysis or peritoneal dialysis and this number is projected to climb to approximately 20,000 by the year 2005.<sup>12</sup> In addition, due to medical advances, patients on dialysis are living longer. Thus, as the number of Canadians with DDRF increases, the burden of illness due to fractures will also increase. The first step in preventing fractures in this population is to identify those at greatest risk. Currently, the optimal method of evaluating fracture risk among patients with DDRF is not known.

### Epidemiology of fractures

Hip and vertebral fractures are major causes of disability and premature death. The average length of stay in an acute-care hospital after a hip fracture is 3 weeks; however, 25% of patients remain in long-term care institutions for at least 1 year following a hip fracture and up to 35% return home, but are dependent on other people or devices for mobility.<sup>1</sup> Furthermore, having a hip fracture increases a patient's chance of dying by 20%.<sup>1</sup> Fractures are also costly. In Canada, the total expenditure for fractures in 1993 was about \$1.3 billion.<sup>2</sup>

Patients with DDRF are 3 to 6 times more likely to have a hip fracture than healthy individuals.<sup>3-9</sup> A study on mortality after hip fractures in patients with DDRF reported 13 hip fractures in 12 patients over a 10-year follow-up, with 6 of the patients dying within 1 year after the fracture.<sup>10</sup> Further, the incidence of fractures increases with the number of years on dialysis; 7% of patients dialyzed for <1 year had a fracture, compared to 50% of patients who had been dialyzed for up to 9 years.<sup>11</sup>

### Dialysis-dependent bone disease

Men and women with DDRF are at risk for developing many types of bone disease that can increase fracture risk. Bone diseases that increase the risk of fracture include hyperparathyroid bone disease, osteomalacia (due to vitamin D deficiency or aluminum toxicity), and adynamic bone disease (Table 1).<sup>13</sup>

Hyperparathyroid bone disease and osteomalacia have characteristic radiologic features. The radiologic features typical of the former include: subperiosteal bone resorption, osteosclerosis typically in the axial skeleton (the so-called rugger jersey spine), and brown "tumours" or cysts, in which there is excessive osteoclastic resorption, fibrous tissue, and necrosis (osteitis fibrosa cystica). The Looser's zone is pathognomonic of osteomalacia and radiographically, it is a translucent line (unmineralized osteoid) that is perpendicular to the cortex of the bone, has a sclerotic margin, and does not extend across the entire bone shaft unless a fracture has occurred through it. There are no radiologic features typical of adynamic bone disease.



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**TABLE 1: Dialysis-dependent bone disease**

Bone disease	Histologic features	Etiology	Frequency	
			1972* n=67	1993** n=259
Adynamic	Decreased bone resorption and formation	Unknown	0	128 (49%)
Hyperparathyroid	Increased bone resorption	Hyperparathyroidism	15 (22%)	57 (22%)
Osteomalacia	Decreased mineralization	Vitamin D deficiency Aluminum toxicity	46 (69%)	56 (22%)
Mixed	Features of more than one disease		6 (9%)	18 (7%)

\* Based on a study of bone biopsy specimens from 67 patients with dialysis dependent renal failure<sup>14</sup>

\*\* Based on a study of bone biopsy specimens from 259 patients with dialysis dependent renal failure<sup>15</sup>

The types and frequency of bone disease among patients with DDRF have changed dramatically over the past 20 years (Table 1). A study published in 1974 reported the distribution of bone lesions based on bone biopsies in 67 patients receiving hemodialysis. The authors found that the most common bone lesion was osteomalacia, due to aluminum toxicity or vitamin D deficiency (46 patients; 69%), followed by hyperparathyroidism (15 patients; 22%), and then mixed bone disease (6 patients; 9%).<sup>14</sup>

Since that time, there have been major changes in the care of dialysis patients including the widespread use of calcitriol (the active form of vitamin D), and the awareness of aluminum toxicity as a serious problem in patients with renal failure. The latter finding resulted in clinicians controlling serum phosphate with calcium compounds instead of aluminum salts. These changes in clinical care have influenced the type of renal bone disease currently seen. For example, a study published in 1993 involving 259 patients with DDRF found that the most common bone lesion was adynamic bone disease (128 patients; 49%), followed by hyperparathyroid bone disease (57 patients; 22%), osteomalacia (56 patients; 22%) and mixed bone disease (18 patients; 7%).<sup>15</sup> The cause of adynamic bone disease is not known. Some researchers have hypothesized that it may be a bone response to aggressive parathyroid hormone (PTH) control, but this has not been conclusively demonstrated.

It is important to remember when assessing patients with DDRF that, in addition to bone disease, these patients have many other reasons for increased fracture risk. These include poor nutrition, inactivity, and an increased risk of falling due to myopathy and peripheral neuropathy.<sup>16</sup> The relative importance of each of these factors on fracture risk is not known. Table 2 lists the common causes of increased fracture risk in patients with DDRF.

### How can we identify men and women with DDRF who are at risk for fracture?

Among healthy men and women, there are several methods to identify those at high risk for fractures. These methods include:

- bone mineral density (BMD) testing
- calcaneal ultrasound measurements
- measurements of biochemical markers of bone turnover
- evaluation of previous spine fractures
- clinical risk-factor assessment.

In men and women with DDRF, there are few studies reporting an association between these methods and subsequent fractures; as a result, the best way to identify high-fracture risk in men and women with DDRF is not known.

#### Bone mineral density testing

Several studies have demonstrated a high prevalence of osteopenia and osteoporosis by BMD testing among men and women receiving hemodialysis. However, the relationship between fractures and BMD among patients with DDRF is less clear. Five cross-sectional studies have evaluated the relationship between fractures and BMD in men and women with DDRF.<sup>4,17-19,20</sup> The number of subjects studied ranged from 67 to 187 and, in all but 1 study (which included men and women aged  $\geq 55$ ),<sup>20</sup> the age-range was broad, including patients from 18 to 87-years-old. Men and women were included in about equal numbers in all but the largest study, which was limited to men.<sup>4</sup> Four of the studies found a modest association between low BMD and fractures, and 2 of these studies reported a limited ability to predict fractures using BMD values.<sup>17,18</sup> In contrast, the other study<sup>20</sup> did not demonstrate an association between low BMD and fractures, nor an ability to predict fractures using BMD values.

**TABLE 2: Common reasons for an increased prevalence of fractures among DDRF patients**

**Osteoporosis** (decreased bone quantity) due to:

- poor nutrition
- decreased physical activity
- hypogonadism
- use of glucocorticoids, heparin
- underlying disease that precipitated renal failure

**Metabolic bone disease** (altered bone quality) due to:

- osteomalacia: vitamin D deficiency, aluminum toxicity
- hyperparathyroidism
- adynamic bone disease

**Increased risk for falling** due to:

- myopathy, peripheral neuropathy

There are several possible explanations for the discrepancy in these findings:

- First, in the study that failed to demonstrate an association between BMD and fractures, the subjects had been on dialysis for a relatively short time – an average of about 3 years<sup>20</sup> – compared with about 7 years in previous studies. It is possible that the association between BMD and fractures is only observed among patients receiving dialysis for more than 3 years.

- Second, most patients had renal failure from diabetes, whereas glomerulonephritis was the predominant cause in prior studies. Patients with glomerulonephritis differ from patients with diabetes in many ways, including the fact that they are more likely to have received steroids for treatment of their kidney disease. Accordingly, steroid use may account for the association between fracture and dialysis observed in prior studies. Of note, no prior study reported on or adjusted for steroid use.

- Third, the study that failed to demonstrate an association between BMD and fractures was the only study done in North America. While the authors did not find an association between smoking, exercise, or calcium intake, and fracture, there may be other immeasurable lifestyle factors influencing both BMD and fracture risk that are different in Canada.

### **Calcaneal ultrasound**

Calcaneal ultrasound is another test that may be used to evaluate fracture risk. Calcaneal ultrasound reflects not only BMD, but also bone elasticity and microarchitecture.<sup>21-24</sup> In healthy postmenopausal women, calcaneal ultrasound measurements are strongly associated with fracture risk<sup>24-26</sup> and, it has been hypothesized that in

patients with DDRF, calcaneal ultrasound measurements are more strongly correlated with fracture than BMD measurements, due to underlying metabolic bone disease. Only 1 study has examined the relationship between calcaneal ultrasound measurements and fractures in patients with DDRF. This study failed to show an association between ultrasound measures and fractures.<sup>20</sup>

### **Biochemical markers of bone turnover**

Serum parathyroid hormone and other biochemical markers (eg, bone specific alkaline phosphatase, osteocalcin) have been shown in many cross-sectional studies to be correlated with bone turnover (eg, high levels of serum PTH are correlated with increased bone turnover on bone biopsy). However, no one has examined the relationship between these tests and the occurrence of subsequent fractures.<sup>27</sup>

### **Previous fractures**

There are no published studies on the relationship between the presence of spinal fractures on X-ray and subsequent spine and nonspine fractures among men and women with DDRF. Among postmenopausal women, we know that the presence of 1 spine fracture increases the risk of having a second spine fracture by 4-fold and the risk of having a nonspine fracture, such as a hip fracture, increases by 1.5 to 2-fold, independent of BMD.<sup>28</sup>

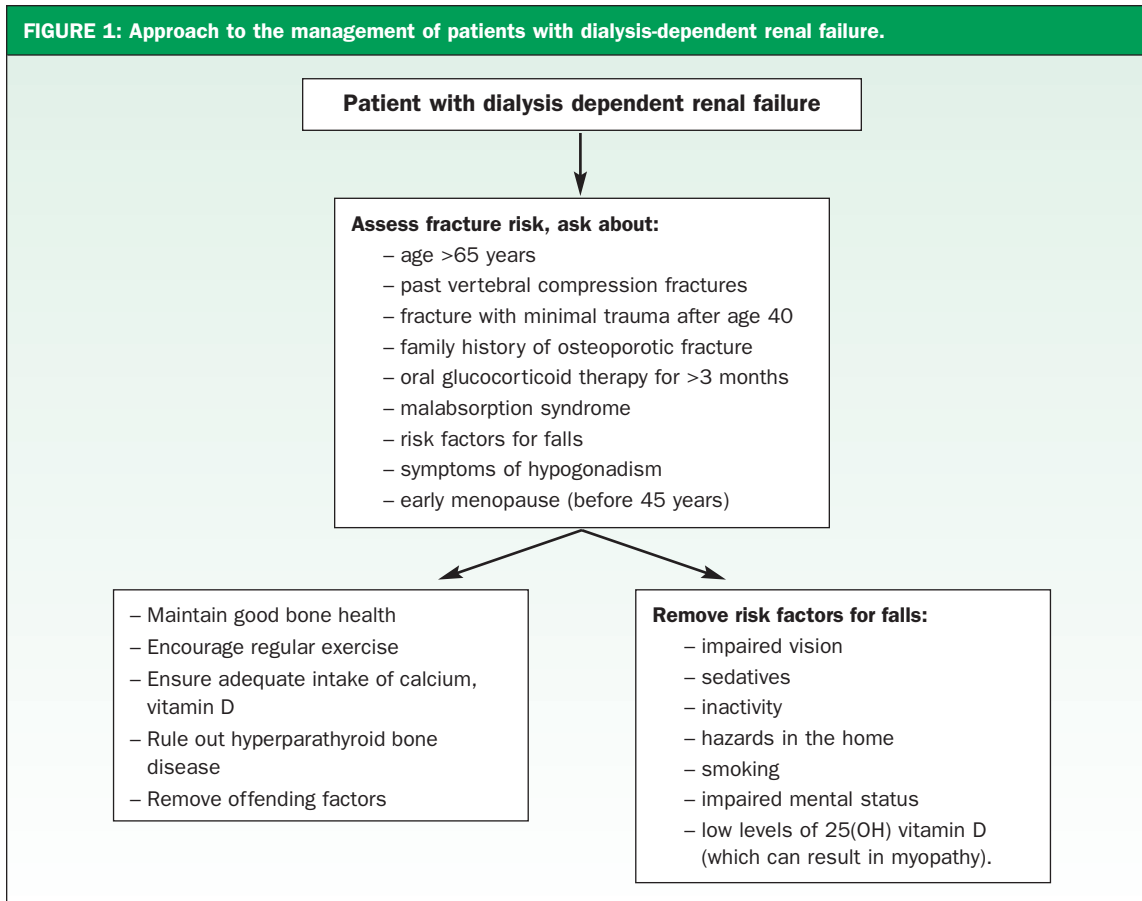
### **Clinical risk factors**

The presence of clinical risk factors, known to be associated with increased fracture risk in otherwise healthy men and women, have not been evaluated in prospective studies to see if they are associated with an increased risk for fracture in patients with DDRF. It seems reasonable, however, to assume that the risk factors for fractures in healthy men and women would also increase the risk of fracture in patients with DDRF.

### **Assessing fracture risk – a pragmatic approach**

Given the paucity of data about factors that are associated with increased fracture risk among men and women with DDRF, the following approach is suggested. Given the high prevalence of fractures in these patients, assume that everyone is at high risk. Inquire specifically about factors that are known to increase the risk of fracture among healthy men and women. These include: age > 65 years, past vertebral compression fractures, fracture with minimal trauma after age 40, family history of osteoporotic fracture, oral glucocorticoid therapy for > 3 months, malabsorption syndrome, propensity to fall, hypogonadism, and in women, early

**FIGURE 1: Approach to the management of patients with dialysis-dependent renal failure.**



menopause (before 45 years).<sup>29</sup> If there are suspicions of a vertebral fracture, confirm by radiograph. Use BMD testing cautiously and consider that a “normal BMD test” does not necessarily mean that the patient is not at an increased risk for fracture.

### **Treatment for bone disease in dialysis-dependent renal failure**

No studies have examined the effects of treatment on bone disease in patients with dialysis-dependent renal failure. As such, the recommendations in Figure 1 are based on clinical experience.

#### **General recommendations for treatment**

All patients with DDRF should be encouraged to participate in regular weight-bearing exercise (eg, walking for 20 minutes, 2 to 3 times a week). If this is not possible, nonweight-bearing exercise should be encouraged to increase muscle strength and improve coordination (eg, riding a stationary bike during dialysis, swimming). Ensure patients have an adequate intake of calcium and vitamin D. Consider checking serum 25(OH) D levels and adjust the vitamin D supplement based on these levels. The aim should be for a

25-hydroxyvitamin D level of at least 50 nmol/L. As well, evaluate, and if present, treat patients for hyperparathyroid bone disease. An elevated serum calcium with an elevated alkaline phosphatase and a serum PTH level 3 times higher than the upper limit of normal is characteristic of hyperparathyroid bone disease. Finally, one should remove offending factors (encourage patients to stop smoking, reduce caffeine intake to at most 4 cups of coffee a day).

#### **Remove risk factors for falls**

Falls are a significant cause of hip fracture. More than 90% of hip fractures occur after a fall. About 30% of people > 65 years and 45% > 80 years fall each year; 5% to 10% of these falls result in fractures.<sup>28</sup> Patients with DDRF have a particularly increased risk of falling and it is important to evaluate these patients for the presence of modifiable risk factors. These include impaired vision, use of sedatives, physical inactivity, hazards in the home that increase the risk of falling (eg, scatter rugs, slippery surfaces, poor lighting), smoking, impaired mental status (depression), and low levels of 25(OH) vitamin D (which can result in myopathy).

## Pharmacologic treatment

Drug treatment for patients with DDRF is problematic. The antiresorptive agents currently available for the prevention and treatment of osteoporosis have not been studied in patients with DDRF. Further, the bisphosphonates are excreted via the kidney and the pharmacokinetics of these agents in patients with renal failure are unknown. As such, it is not clear when patients should be given a dose of bisphosphonate or how frequently they should be taking it. A further difficulty in prescribing drugs for patients with DDRF is that, as noted earlier, the most common bone disease is adynamic bone disease. This disease is characterized by decreases in bone resorption and in bone formation, implying that treatment with antiresorptive agents may not be effective. However, some patients still require drug therapy (eg, patients who have fractures despite elimination of clinical risk factors). One option for these patients is salmon calcitonin. In the near future, parathyroid hormone will be available and may be particularly useful in patients with DDRF because its primary mechanism of action is to increase bone formation.

## Conclusion

Fractures among men and women with dialysis-dependent bone disease are common and they increase with increasing time on dialysis. The causes of fractures are complex and multifactorial. Typically, these patients will have underlying metabolic bone disease, as well as osteoporosis and an increased propensity to fall. Currently, no tests can definitively identify patients with renal failure who are at increased risk for fracture, although the presence of clinical risk factors is likely associated with an increased risk for fracture. All patients on dialysis should be given general advice about maintaining bone health and should be assessed for the propensity to fall. There are no data on pharmacologic treatments in these patients and as such, these agents should be used cautiously, if at all.

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## Abstracts of Interest

### Strategies to minimize bone disease in renal failure.

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The skeletal disorders associated with renal insufficiency result from alterations in calcium, phosphorus, and vitamin D metabolism. Each requires intervention to prevent and control the problem. Hyperparathyroidism and its treatment can also result in extraskeletal complications. To prevent the development of parathyroid hyperplasia and the skeletal complications of chronic kidney disease, it is desirable to initiate interventions early in the course of kidney disease; however, many patients present with established hyperparathyroidism and additional strategies are necessary to suppress hyperparathyroidism. Mainstays of this approach are the control of phosphorus and the use of vitamin D analogs. Phosphorus control requires the use of phosphate binders, preferably non-calcium-containing binders, to prevent intestinal phosphorus absorption. Vitamin D analogs are used to suppress hyperparathyroidism and have the potential to have lesser toxicity than calcitriol. Paricalcitol is the most widely used vitamin D analog in this country and it effectively suppresses hyperparathyroidism with only minimal effects on calcium and phosphorus. A substantial body of data in experimental animals supports the use of paricalcitol as a preferential therapeutic agent. Recently, an additional vitamin D sterol, doxercalciferol, has been introduced, which is metabolized to 1,25-dihydroxyvitamin D(2). Although initially thought to have lesser toxicity than its vitamin D(3) counterpart, recent studies have not provided support for a major difference in this regard. Doxercalciferol is also effective in lowering parathyroid hormone (PTH), though hypercalcemia in hyperphosphatemic episodes occurred relatively frequently during the clinical studies. As these therapeutic strategies are undertaken, it is important not to oversuppress PTH and decrease bone turnover to abnormally low levels because of the risk for adynamic renal bone disease. It is possible that when bone turnover is abnormally low, the extraskeletal deposition of calcium in blood vessels and other tissues is enhanced. Accordingly, constant monitoring is required during treatment, with emphasis on minimizing the calcium load, and, if monitored correctly, a satisfactory control of hyperparathyroidism may be achieved with the agents currently available.

*Am J Kidney Dis* 2001;38(6):1430-6.

### Bone density and heel ultrasound testing do not identify patients with dialysis-dependent renal failure who have had fractures.

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Patients with dialysis-dependent renal failure are at increased risk for low-trauma fractures. However, the optimal means of identifying patients at high risk for fracture is not known. We assessed the association between fracture history and two tests of bone mineral

density (dual x-ray absorptiometry [DEXA] and calcaneal ultrasound) among patients with hemodialysis-dependent renal failure. We evaluated 71 men and 33 women aged 55 years or older who had been receiving hemodialysis for at least 1 year. All patients underwent spinal radiography, DEXA of the hip and lumbar spine, and calcaneal ultrasonography. We assessed risk factors for low-trauma fractures by questionnaire and medical chart review. Of patients, 52% had a fracture on spinal radiographs or a history of a low-trauma fracture, 69% had osteopenia by DEXA, and 26% had a low heel ultrasound measurement. Neither DEXA nor calcaneal ultrasound was associated with fracture history, however. Our findings indicate that fractures among patients with dialysis-dependent renal failure are common. Tests of bone strength do not adequately identify patients with a history of fractures. Prospective studies to determine the optimal method of identifying patients with dialysis-dependent renal failure at high risk for fracture are needed. Copyright 2002 by the National Kidney Foundation, Inc.

*Am J Kidney Dis* 2002;39(4):843-9.

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This publication is made possible by an educational grant from

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