Osteoporosis and Chronic Kidney Disease

By Catherine Stehman-Breen

Bone disease is heterogenous and highly prevalent among those with chronic kidney disease, stage V (CKD-V) patients. Although we know much regarding the risk factors and outcomes associated with renal osteodystrophy, less is known about osteoporosis in CKD-V. Factors that predict bone loss in the CKD-V population are similar to those in the general population and include female gender, Caucasian race, older age, chronic disease, and immobility. In addition, some studies suggest that chronic acidosis and renal osteodystrophy may also increase the risk for bone loss. Little is known about associated adverse outcomes or the impact of therapeutic interventions for osteoporosis. Although we know that the risk for hip fracture is high among CKD-V patients and that fracture is associated with an increased risk for death, the role that bone loss plays is largely unknown. Current recommendations suggest that risk-factor modification is the most appropriate course of treatment for CKD-V–associated osteoporosis.

OSTEOPOROSIS IS CHARACTERIZED by a deficiency in bone mass or volume that results in increased bone fragility. It is defined by a decrease in the volume of bone more than 2.5 SDs below the young adult mean and often is referred to as the fracture threshold. Osteopenia refers to less severe bone loss and is defined as a decrease in the volume of between 1 and 2.5 SDs below the young adult mean value and is the point at which treatment should begin.[1]

Bone loss is diagnosed by bone mineral densitometry and is assessed most commonly by dual X-ray absorptiometry. The clinical use of bone densitometry is based on data from the general population that suggest that bone mass is the most significant predictor of hip fracture and that hip fracture is associated with both increased morbidity and mortality.[2] Although vertebral fractures are associated with severe pain and result in reductions in functional capacity, hip fractures lead to the most serious adverse outcome. In the healthy population, the risk for fracture increases approximately 2.5-fold with each 1 SD decrease in bone mass.[3] Although these relationships are well established in the healthy population, caution should be taken in extrapolating data to the CKD-V population. The complex relationships between renal osteodystrophy and bone mineral density may alter the associations. In addition, extraskeletal and vascular calcification may reduce the accuracy of dual X-ray absorptiometry in determining lumbar spine bone mineral density.[4]

For both clinical and pathophysiologic reasons, osteoporosis should be distinguished from renal osteodystrophy, which is a disorder of bone remodeling and may or may not be associated with osteoporosis. Confirmation of these bone diseases is dependent on histomorphometric analysis of a bone biopsy examination. Bone mineral density does not correlate well with assessments of bone remodeling. Thus, bone mineral density determines how much mineralized bone is present and is used to diagnose osteoporosis whereas histomorphometry determines how that bone is arranged architecturally and is used to diagnose renal osteodystrophy

BONE LOSS AND FRACTURE IN CKD-V

Reductions in bone mineral density are common among CKD-V patients. We found that the prevalence of osteopenia at the femoral neck was 60% among African Americans and 86% among Caucasians. The prevalence of osteoporosis was 22% among African Americans and 59% among Caucasians.[5] Others have consistently reported bone loss among CKD-V patients at the hip.[6,7] Some studies have found increases in bone mineral density at the lumbar spine.[7] It is thought that this might be secondary to false increases resulting from extraosseous and vascular calcifications. Bone loss also appears to be accelerated among CKD-V patients.[5]

In patients with renal disease, there is a high incidence of both vertebral and hip fractures compared with the general population,[8-11] and hip fracture has been associated with an increased risk for

From the University of Washington and Veterans Affairs Puget Sound Health Care System, Seattle, WA.

Supported by a Veterans Affairs Career Development Award.

Address reprint requests to Catherine Stehman-Breen, MD, MS, VA Puget Sound Health Care System, 1660 S. Columbian Way, Mailstop 111A, Seattle, WA 98108. Email: cos@u.washington.edu

0270-9295/04/2401-0011$30.00/0

doi:10.1053/j.semnephrol.2003.08.013

Table 1. Risk Factors for Osteoporosis

Demographic	Ethnicity
	Sex
	Family history
	Age and age related
Habits	Nutrition
	Physical activity
	Medications
	Smoking
	Alcohol
Hormones	Estrogen deficiency
	Androgen deficiency
Comorbidities	Chronic disease
	Low body mass index
	Immobilization
Characteristics of bone	Density (mass)
	Size and geometry
	Microarchitecture
	Low peak bone mass
Drugs	Steriods
	Coumadin and heparin
	Antiseizure medication
Uremic-specific factors	Duration of dialysis
	Low parathyroid hormone
	Metabolic bone disease
	β2M amyloidosis
	Chronic acidosis
	Aluminum intoxication

death.[11] Overall, CKD-V patients are 4.4-fold more likely to sustain a hip fracture than those in the general population.[10] This increased risk exceeds that observed in the general population for both genders and ranges from a 99-fold higher risk among men younger than 45 years to a 1.7-fold increased risk among women older than 85 years.[10] The risk for hip fracture among transplant patients compared with dialysis patients varies with time since renal transplant. Immediately after renal transplant, dialysis is associated with a lower risk for hip fracture compared with transplant. However, with time, the relative risk among transplant patients compared with dialysis patients diminishes, becoming equivalent approximately 630 days after transplantation.[12] The reasons for this are likely complex but may be owing to the accumulated bone toxicity of uremia combined with reductions in steroid dose after transplant.

RISK FACTORS FOR BONE LOSS AND FRACTURE IN CKD-V

Studies have shown a variety of risk factors for bone loss among CKD-V patients (Table 1). These factors can be divided into those that are known to be risk factors in the general population but are more common among CKD-V patients and those that are specific to uremia or its treatment. Factors that are more common among CKD-5 patients include low body mass index, peripheral vascular disease, and chronic illness. Low body mass index has been associated with lower bone mineral density in the general population, probably by independently influencing the characteristics of bone by increasing the mass of adipose tissue available for estrogen production or by increasing the padding at the hips to reduce the forces on bone during a fall.[13] Peripheral vascular disease has been associated with bone loss in the general population.[14] Peripheral vascular disease affects bone remodeling by reducing blood flow to the extremities, but may also be a marker for health, duration of smoking, and functional status or immobility, all of which result in loss of bone, a risk factor for fracture. In addition, subjects with peripheral vascular disease also may be more likely to fall because of amputations or peripheral neuropathy. Chronic illness and disability have been associated with an increased risk for hip fracture in both the general population and among CKD-V patients.[15-18] Current cigarette smoking results in bone loss in the healthy population and is an important risk factor for hip fracture in CKD-V patients.[19-21] Bone loss is thought to be the result of weight loss, adversely affecting general health and exercise, and altering sex hormone metabolism.[22] Factors specific to CKD-V therapy also may contribute to altered bone loss and include longer time on dialysis, metabolic bone disease, β2 microglobulin–related amyloidosis, aluminum intoxication, hypogonadism, avascular necrosis, and chronic acidosis.[6,10]

The factors that place CKD-V patients at increased risk for fracture are many and probably lead to both loss and altered architecture, resulting in increased bone fragility and increased risk for fracture. The excess risk for fracture among CKD-V patients may be in part owing to a greater burden of factors that are known to cause bone loss and altered bone architecture in the general population, such as immobility, ethnicity, abnormalities in vitamin D metabolism, protein wasting, low body mass, and diabetes.[15,21,23-27] Low bone mass is prevalent among CKD-V patients and osteopenia has been associated with an increased risk for vertebral fracture among CKD-V patients.[8] The

association of bone mineral density with hip fracture is not known. Among CKD-V patients, each decade of life is associated with a 40% increased risk for hip fracture. The relative risk for hip fracture among women and African Americans is 2.26 and 0.58, respectively. Each unit increase in body mass index is associated with a 0.89-fold lower risk for hip fracture whereas the presence of peripheral vascular disease places CKD-V patients at 1.94-fold greater risk. Other factors that increase the risk for hip fracture may be uremia specific. Coco and Rush[11] showed that low parathyroid hormone levels are associated with an increased risk for hip fracture. Other dialysis-specific factors that may contribute to hip fracture include longer time on dialysis, β2 microglobulin–related amyloidosis, aluminum intoxication, hypogonadism, avascular necrosis, and chronic acidosis.[6,10,28]

TREATMENT

In the general population, calcium, vitamin D, estrogen, selective estrogen receptor modulators, calcitonin, and bisphosphonates all have been shown to be effective treatments for osteoporosis.[29] Few similar studies have been performed in CKD-V patients. A nonrandomized study assessing the role of estrogen replacement in CKD-V patients found significant improvement in bone mineral density after 12 months of treatment compared with no treatment using dual X-ray absorptiometry assessed at the lumbar spine.[30] Bone mineral density increased in the treatment group and decreased in the control group, suggesting a possible role in hypogonadal women with CKD-V. However, the impact of estrogen replacement among CKD-V patients on other outcomes including cardiovascular events is unknown.

A recent study assessed the impact of raloxifene, a selective estrogen receptor modulator, on bone metabolism in postmenopausal women on chronic hemodialysis.[31] In this placebo-controlled study, 50 postmenopausal women with severe osteopenia or osteoporosis were randomized to receive raloxifene or placebo. After 1 year of treatment, lumbar spine bone mineral density improved, although femoral neck bone mineral density did not change. More data are needed to better understand the impact of treatment options in this complex group of patients.

Although bisphosphonates have been suggested as a potential intervention for the treatment of osteoporosis in CKD-V, caution should be used in the initiation of treatment.[32] In CKD-V patients with high turnover bone disease, there may be osteoclast activation and vitamin D deficiency. In low turnover renal osteodystrophy, there may be a lack of cellular activity. Although there are no studies examining this, treatment with osteoclast inhibitors such as bisphosphonates and calcitonin potentially could cause worsening of low turnover while causing improvement of high turnover disease. For these reasons, current recommendations for osteoporosis management in patients with CKD-V include calcium and vitamin D supplementation, smoking cessation, and increased physical activity.[33]

SUMMARY

Bone loss and hip fracture are common among patients with CKD-V. Although some risk factors have been identified, there are no therapies that have been shown to effectively improve bone mineral density or reduce the risk for hip fracture. Studies are necessary to identify interventions and determine the impact on the incidence of hip fracture.

REFERENCES

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of the World Health Organization Study Group. Geneva, World Health Organization, 1994

2. Levis S, Altman R: Bone densitometry. Clinical considerations. Arthritis Rheum 41:577-587, 1998

3. Cummings S, Black D, Nevitt M, et al: Bone density at various sites for prediction of hip fractures. Lancet 341:72-75, 1993

4. Johnson D, McIntyre H, Brown A, et al: The role of DEXA bone densitometry in evaluating renal osteodystrophy in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 16:34-40, 1996

5. Stehman-Breen C, Sherrard D, Walker A, et al: Racial differences in bone mineral density and bone loss among end-stage renal disease patients. Am J Kidney Dis 33:941-946, 1999

6. Stein M, Packham D, Ebeling P, et al: Prevalence and risk factors for osteopenia in dialysis patients. Am J Kidney Dis 28:515-522, 1996

7. Gabay C, Ruedin P, Slosman D, et al: Bone mineral density in patients with end-stage renal failure. Am J Nephrol 13:115-123, 1993

8. Atsumi K, Kushida K, Yamazaki K, et al: Risk factors for vertebral fractures in renal osteodystrophy. Am J Kidney Dis 33:287-293, 1999

9. Chaisson R, Fuchs E, Stanton D, et al: Racial heterogeneity of HIV antigenemia in people with HIV infection. AIDS 5:177-180, 1991

10. Alem A, Sherrard DJ, Gillen DL, et al: Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int 58:369-369, 2000

11. Coco M, Rush H: Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis 36:1115-1121, 2000

12. Ball AM, Gillen DL, Sherrard D, et al: Risk of hip fracture among dialysis and renal transplant recipients. JAMA 288:3014-3018, 2002

13. Cummings S, Kelsey J, Nevitt M, et al: Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 7:178-208, 1985

14. Vogt M, Cauley J, Kuller L, et al: Bone mineral density and blood flow to the lower extremities: The study of osteoporotic fractures. J Bone Miner Res 12:283-289, 1997

15. Mussolino M, Looker A, Madans J, et al: Risk factors for hip fracture in white men: The NHANES I Epidemiologic Follow-up Study. J Bone Miner Res 13:918-924, 1998

16. Gregg E, Cauley J, Seeley D, et al: for the Osteoporotic Fractures Research Group: Physical activity and osteoporotic fracture risk in older women. Ann Intern Med 129:81-88, 1998

17. Wickham C, Walsh K, Cooper C, et al: Dietary calcium, physical activity, and risk of hip fracture: A prospective study. Br Med J 299:889-892, 1989

18. Nevitt M, Cummings S, Kidd S, et al: Risk factors for recurrent non-syncopal falls: A prospective study. JAMA 261: 2663-2668, 1989

19. Melhaus H, Michaelsson K, Holmberg L, et al: Smoking, anitoxidant vitamins, and the risk of hip fracture. J Bone Miner Res 14:129-135, 1999

20. Cornuz J, Feskanich D, Willett W, et al: Smoking, smoking cessation, and risk of hip fracture in women. Am J Med 106:311-314, 1999

21. Cummings S, Nevitt M, Browner W, et al: Risk factors for hip fracture in white women: Study of osteoporotic fractures research group. N Engl J Med 332:767-773, 1995

22. Daniel M, Martin A, Faiman C: Sex hormones and adipose tissue distribution in premenopausal cigarette smokers. Int J Obes 16:245-254, 1994

23. De Laet C, Van Hout B, Burger H, et al: Hip fracture prediction in elderly men and women: Validation in the Rotterdam study. J Bone Miner Res 13:1587-1593, 1998

24. Grady D, Rubin S, Petitti D, et al: Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 117:1016-1037, 1992

25. Orwoll E: Androgens as anabolic agents for bone. Trends Endocrinol Metab 7:77-84, 1996

26. Bonjour J, Schurch M, Chevalley T: Protein intake, IGF-1 and osteoporosis. Osteoporos Int 7:S36-S42, 1997

27. LeBoff M, Kohlmeier L, Hurwitz S, et al: Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA 281:1505-1511, 1999

28. Stehman-Breen C, Sherrard D, Alem A, et al: Risk factors for hip fracture among patients with end-stage renal disease. Kidney Int 58:2200-2205, 2000

29. Hauselmann H, Rizzoli R: A comprehensive review of treatments for postmenopausal osteoporosis. Osteoporos Int 14:2-12, 2003

30. Matuszkiewicz-Rowinska J, Skorzewska K, Radowicki S, et al: The benefits of hormone replacement therapy in premenopausal women with oestrogen deficiency on haemodialysis. Nephrol Dial Transplant 14:1238-1243, 1999

31. Hernandez E, Valera R, Alonzo E, et al: Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. Kidney Int 63:2269-2274, 2003

32. Rossini M, Gatti D, Isaia G, et al: Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. J Bone Miner Res 16:113-119, 2001

33. Lindberg J: Osteoporosis in end-stage renal disease. Semin Nephrol 19:115-122, 1999