Osteoporosis: The connection to urologic health

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Abstract

Men with prostate cancer are often treated with androgen deprivation therapy (ADT), which is associated with reduced bone mineral density (BMD) and a higher risk for fractures. Maintenance of optimum bone health throughout the natural course of prostate cancer is an important aspect in the management of this patient population. Bone targeted therapies, such as bisphosphonates and the RANK ligand inhibitor denosumab, have been demonstrated to reduce skeletal-related events in patients with metastatic cancer, while denosumab has also been shown to reduce the risk of fracture in men undergoing ADT for prostate cancer.

Introduction

Osteoporotic fractures are common in men, particularly in men undergoing androgen deprivation therapy (ADT) for prostate cancer treatment. As outcomes for men who experience an osteoporotic fracture are poor, treatments that have been shown to improve bone mineral density (BMD) and decrease fractures in this patient population, such as a bisphosphonate (alendronate, risedronate or zoledronic acid) or denosumab, are recommended.

Osteoporosis and osteoporosis-related fractures are usually considered conditions of postmenopausal or elderly women, but nearly 30% of hip fractures occur in men.[1] Both men and women experience age-related losses in BMD, which has been linked to an increase in fractures and disability. However, the changes that occur to bone with aging are different between the sexes. Although both men and women experience declines in femoral neck BMD and cross-sectional area, women experience a loss of bone rigidity, while men seem to compensate with a small but significant increase in girth of the femoral neck.[2] As a result, men tend to present with osteoporotic fractures about 10 years later than women.[3] However, once hip fractures occur, mortality is higher among men than among women (Fig. 1).[4]

–Men and women should undergo BMD testing starting at age 65 years; certain high-risk individuals should be tested earlier.[5] A man's 10-year risk of fracture can be assessed based on clinical factors, the most important of which are the presence of a prior low-trauma or so called "fragility" fracture after age 40 and recent prolonged use of systemic glucocorticoids (Table 1).[5] Regardless of BMD, men who have had a hip fracture, vertebral fracture, more than one fragility fracture, or one fragility fracture in the presence of steroid use are considered to have a high 10-year risk of fracture. Men over 50 who have had one fragility fracture, or those with a T score of -2.5 or lower at the lumbar spine, total hip or femoral neck, are considered to have at least a moderate 10-year risk of fracture.[5]

The management of men at high risk of a fragility fracture is straightforward. Those at high risk should be offered pharmacologic therapy, which may include an antiresorptive therapy such as a bisphosphonate (e.g., alendronate, risedronate or zoledronic acid) or denosumab, or a bone-formation therapy, such as teriparatide; however, men with prostate cancer should stay away from bone formation therapy as these therapies may stimulate the growth of malignant cells in bone. For men who are at moderate risk for fracture, the decision to consider pharmacologic treatment depends on other factors. Patients who fall into this category should undergo a careful clinical evaluation to identify additional risk factors that are not considered in the risk assessment system. For example, men on ADT may be one category of patients who require pharmacologic therapy, even if they are considered to have only moderate risk of fracture. Because ADTs are associated with declines in BMD and increased risk of fractures, these men may be considered for treatment with a bone-targeted agent, such as a bisphosphonate or denosumab. In a randomized trial of 104 patients undergoing ADT in conjunction with radiation therapy for non-metastatic prostate cancer, those treated with weekly oral risedronate had significantly less bone loss, and bone turnover markers were significantly suppressed for 2 years compared with placebo controls.[6] In a large multicentre trial

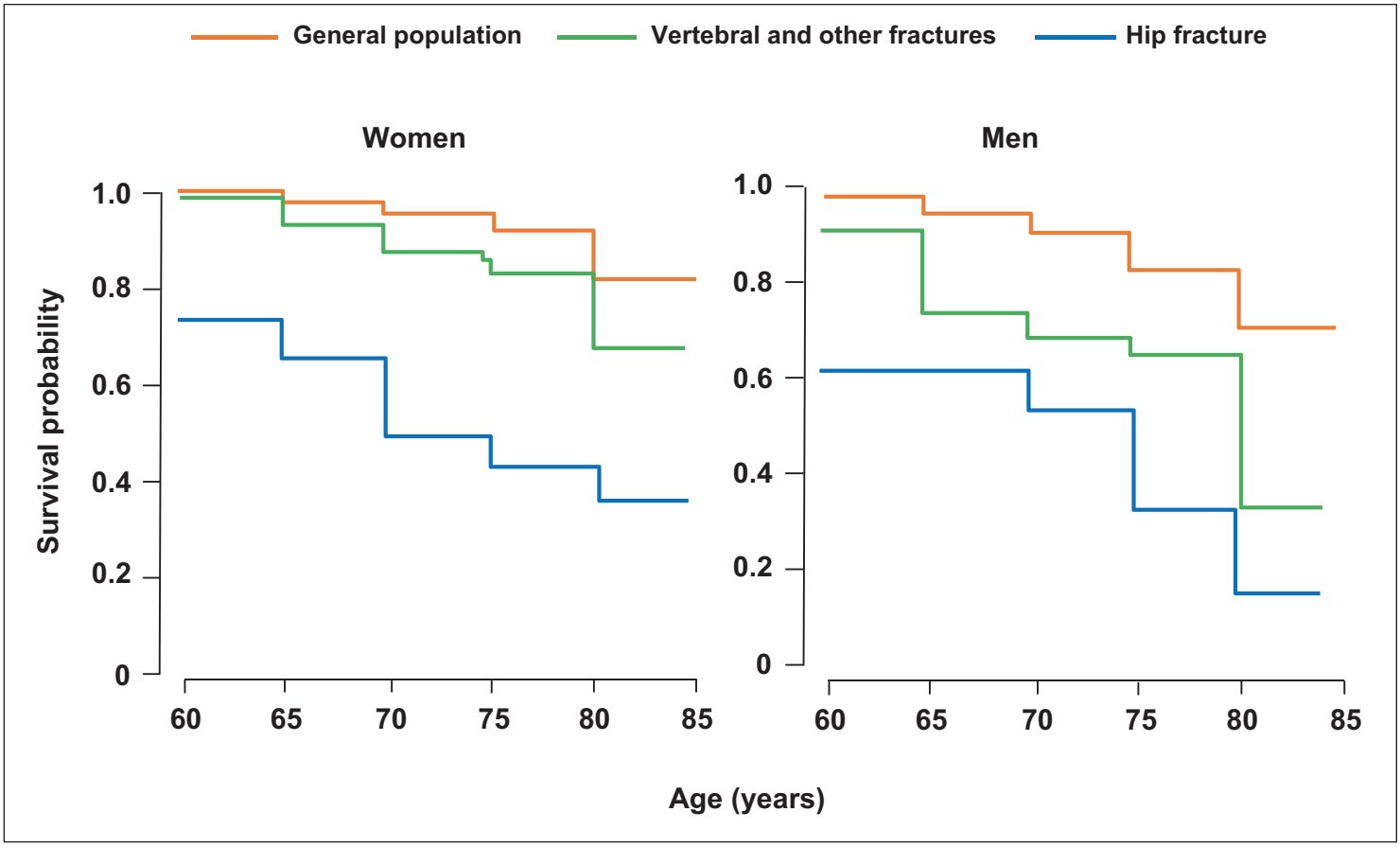

Fig. 1. Mortality following fracture in men and women.[4] Reprinted from Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: An observational study. *Lancet* 1999;353:878-82. Copyright ©1999 with permission from Elsevier.

of 1468 men with non-metastatic prostate cancer undergoing ADT, twice yearly treatment with the RANK ligand inhibitor denosumab was associated with increased BMD at all sites, as well as fewer new vertebral fractures after 2 years of treatment (Fig. 2).[7]

In addition to pharmacotherapy, men undergoing ADT for prostate cancer should be counselled to ensure adequate calcium and vitamin D supplementation. The recommended calcium intake from diet and supplements combined is 1000 mg to 1200 mg/day.[8] However, levels higher than this are not recommended due to concerns with serious adverse effects associated with high-dose calcium supplementation.[9-11] Recommended vitamin D intake for men with prostate cancer undergoing ADT is 800 IU daily, but some men may need up to 2000 IU.[5,8]

For individuals with a low risk of fracture, lifestyle measures, such as exercise, prevention of falls, optimization of calcium and vitamin D intake, and smoking cessation are usually sufficient.[5]

Conclusion

Osteoporotic fractures are common in men, particularly those undergoing ADT for prostate cancer treatment. As outcomes for men who experience an osteoporotic fracture are poor, treatments that have been shown to improve BMD and/or decrease fractures in this patient population, such as a bisphosphonate (alendronate, risedronate or zoledronic acid) or denosumab are recommended for those at moderate to high risk of fracture.

Competing interests: Dr. Cheung declares no competing financial or personal interests.

References

1. Cooper C, Campion G, Melton LJ 3d. Hip fractures in the elderly: A worldwide projection. *Osteoporos Int* 1992;2:285-9. http://dx.doi.org/10.1007/BF01623184
2. Beck TJ, Ruff CB, Scott WW Jr, et al. Sex differences in geometry of the femoral neck with aging: A structural analysis of bone mineral data. *Calcif Tissue Int* 1992;50:24-9. http://dx.doi.org/10.1007/BF00297293
3. Cooper C, Melton LJ 3d. Epidemiology of osteoporosis. *Trends Endocrinol Metab* 1992;3:224-9. http://dx.doi.org/10.1016/1043-2760(92)90032-V
4. Center JR, Nguyen TV, Schneider D, et al. Mortality after all major types of osteoporotic fracture in men and women: An observational study. *Lancet* 1999;353:878-82. http://dx.doi.org/10.1016/S0140-6736(98)09075-8
5. Papaioannou A, Morin S, Cheung AM, et al; Scientific Advisory Council of Osteoporosis Canada. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010;182:1864-73. http://dx.doi.org/10.1503/cmaj.100771
6. Choo R, Lukka H, Cheung P, et al. Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy. I*nt J Radiat Oncol Biol Phys* 2013;85:1239-45. http://dx.doi.org/10.1016/j.ijrobp.2012.11.007

Table 1. Indications for bone mineral density testing[5]

Older adults (age ≥50 years)	Younger adults (age <50 years)
• Age ≥65 years (both women and men) • Clinical risk factors for fracture (menopausal women, men age 50–64 years) - Fragility fracture after age 40 years - Prolonged use of glucocorticoids* - Use of other high-risk medications† - Parental hip fracture - Vertebral fracture or osteopenia identified on radiography - Current smoking - High alcohol intake - Low body weight (<60 kg) or major weight loss (>10% of body weight at age 25 years) - Rheumatoid arthritis - Other disorders strongly associated with osteoporosis	• Fragility fracture • Prolonged use of glucocorticoids* • Use of other high-risk medications† • Hypogonadism or premature menopause (age <45 years) • Malabsorption syndrome • Primary hyperparathyroidism • Other disorders strongly associated with rapid bone loss and/or fracture

*At least 3 months' cumulative therapy in the previous year at a prednisone-equivalent dose ≥7.5 mg daily; †For example: aromatase inhibitors or androgen deprivation therapy. Reprinted with permission from Papaioannou A, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010;182:1864-73.©2010 Canadian Medical Association or its licensors.

7. Smith MR, Egerdie B, Hernández Toriz N, et al; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361:745-55. http://dx.doi.org/10.1056/NEJMoa0809003
8. BC Cancer Agency. Guidelines for the Prevention of Osteoporosis for Men with Prostate Cancer on Hormone Therapy. 2013. http://www.bccancer.bc.ca/NR/rdonlyres/CF15D0CB-3402-46DF-9DE4-A59A8B1D8904/70080/ProstateOsteoporosisGuide_REVISED_2012withSwoosh.pdf. Accessed July 18, 2014.
9. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008;336:262-6. http://dx.doi.org/10.1136/bmj.39440.525752.BE
10. Bolland MJ, Grey AB, Gamble GD, et al. Effect of osteoporosis treatment on mortality: A meta-analysis. *J Clin Endocrinol Metab* 2010;95:1174-81. http://dx.doi.org/10.1210/jc.2009-0852
11. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. *Osteoporos Int* 2008;19:1119-23. http://dx.doi.org/10.1007/s00198-008-0563-9

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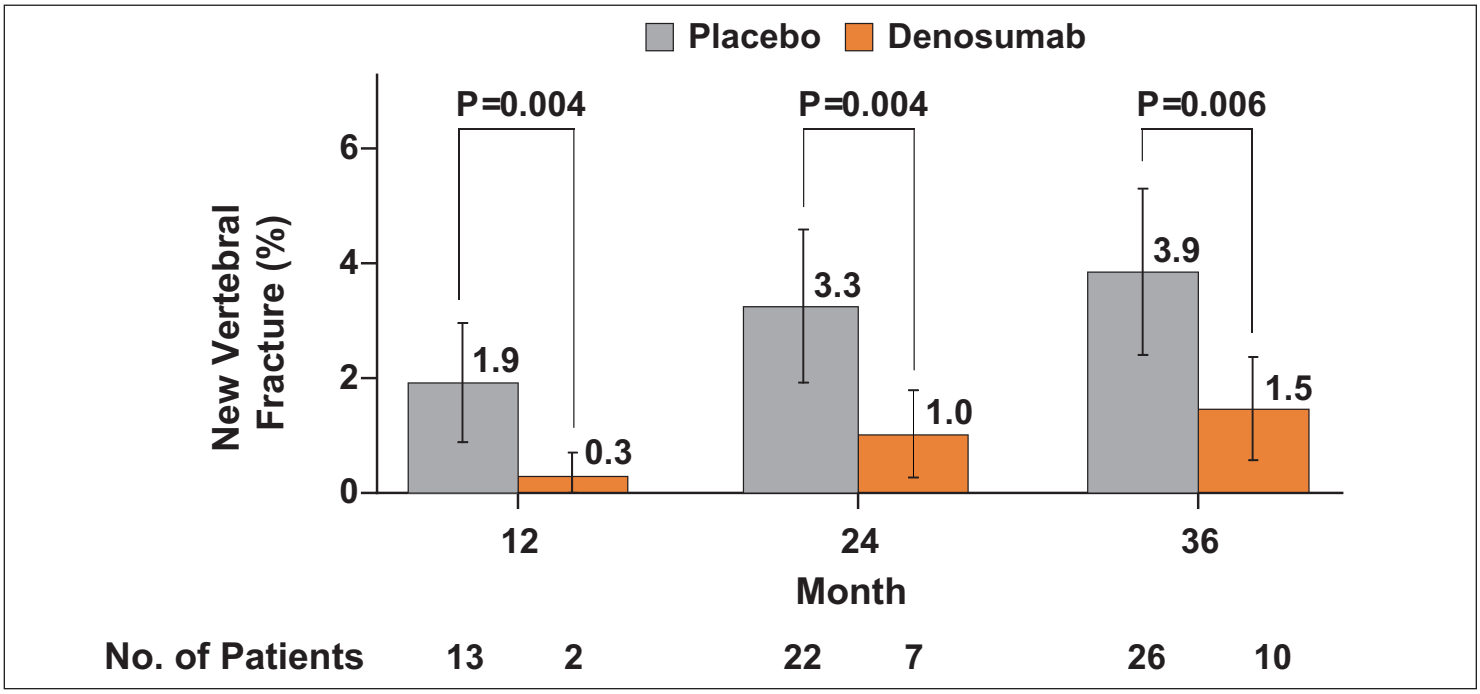

Fig. 2. Cumulative incidence of new vertebral fractures in a double-blind, multicentre study comparing denosumab with placebo in men undergoing ADT for prostate cancer.[7] From Smith MR, Egerdie B, Hernández Toriz N, et al; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361:745-55. Copyright ©2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.