Published in final edited form as:
Clin Cancer Res. 2006 October 15; 12(20 Pt 2): 6315s–6319s. doi:10.1158/1078-0432.CCR-06-0846.

Treatment-Related Osteoporosis in Men with Prostate Cancer

Matthew R. Smith
Massachusetts General Hospital, Boston, Massachusetts

Abstract

The intended therapeutic effect of gonadotropin-releasing hormone (GnRH) agonists is hypogonadism, a major cause of acquired osteoporosis in men. Consistent with this observation, GnRH agonists increase bone turnover and decrease bone mineral density, a surrogate for fracture risk. Large claims-based analyses and other retrospective studies provide compelling evidence that GnRH agonists increase risk of clinical fractures. Estrogens play a central role in homeostasis of the normal male skeleton, and estrogen deficiency rather than testosterone deficiency seems to be primarily responsible for the adverse skeletal effects of GnRH agonists. In randomized controlled trials, bisphosphonates (pamidronate and zoledronic acid) and selective estrogen receptor modulators (raloxifene and toremifene) increased bone mineral density in GnRH agonist – treated men. Two ongoing large randomized placebo-controlled studies will prospectively define fracture outcomes in men with prostate cancer and assess the efficacy of novel pharmacologic interventions (AMG162, toremifene) during GnRH agonist treatment.

Osteoporosis in Men

Osteoporosis is common in both men and women. In the United States, for example, osteoporosis is prevalent in ~2 million men and another 12 million men are at risk (1). Men experience one third of all hip fractures. Mortality after hip fracture is greater in men than in women (2).

Alcohol abuse, long-term glucocorticoid therapy, and hypogonadism account for approximately half of all cases of osteoporosis in men (3). Smoking, low dietary calcium intake, vitamin D deficiency, and sedentary lifestyle contribute to risk of osteoporosis (4).

Hormone therapy for prostate cancer is a major cause of male hypogonadism. Gonadotropin-releasing hormone (GnRH) agonists are the mainstay of treatment for metastatic prostate cancer and a routine part of management for many men with locally advanced or recurrent nonmetastatic prostate cancer (5). Approximately 650,000 men are treated with a GnRH agonist annually in the United States.

Mechanisms of Hypogonadal Bone Loss

GnRH agonists increase bone turnover in men with prostate cancer (6,7). Biochemical markers of osteoclast and osteoblast activity increase progressively after treatment with a GnRH agonist and seem to reach a plateau after ~6 months (7). In prostate cancer, GnRH agonists increase parathyroid hormone-mediated osteoclast activation (8), suggesting that

Requests for reprints: Matthew R. Smith, Massachusetts General Hospital, Cox 640,100 Blossom Street, Boston, MA 02114. Phone: 617-724-5257; Fax: 617-726-4899; smith.matthew@mgh.harvard.edu.

Presented at the First Cambridge Conference on Advances in Treating Metastatic Bone Cancer, a symposium held in Cambridge, Massachusetts, October 28-29, 2005.

Note: Conflict of interest: Dr. Smith is a consultant for Amgen, GTx, Inc., and Novartis Oncology.

changes in skeletal sensitivity to parathyroid hormone play an important role in the pathogenesis of hypogonadal bone loss.

Estrogens play an important role in skeletal homeostasis in healthy men. Osteoblasts and osteoclasts express estrogen receptors (9–11). Estrogens contribute to the regulation of both osteoclast and osteoblast activity in men (12,13). Serum estradiol levels are positively associated with spinal bone mineral density and negatively associated with vertebral fracture risk in healthy older men (14–16). Additionally, medical castration with estrogens does not decrease bone mineral density (17) or increase bone turnover (18) in men with prostate cancer.

Bone Loss during GnRH Agonist Therapy

GnRH agonists significantly decrease bone mineral density in men with prostate cancer (Table 1; refs. 6,7,19–22). Most studies have reported a 2% to 3% decrease per year in bone mineral density of the hip and spine during initial therapy. Notably, significant bone loss has been observed despite concurrent administration of supplemental calcium and vitamin D and careful exclusion of secondary causes of osteoporosis (7,22). Bone mineral density seems to decline steadily during long-term treatment (23,24).

GnRH Agonists and Fracture Risk

Three large claims-based studies provide compelling evidence that GnRH agonists increase the risk of clinical fractures. In a study of medical claims from the Surveillance, Epidemiology, and End Results program and Medicare database, 19.4% of men with prostate cancer who received androgen deprivation therapy (bilateral orchiectomies or GnRH agonist) had a fracture compared with 12.6% of those not receiving androgen deprivation therapy ($P < .001$; ref. 25). Treatment duration independently predicted fracture risk. In men who received nine or more doses of a GnRH agonist, for example, the relative risk of any fracture was 1.45 [95% confidence interval (95% CI), 1.36–1.56]. Androgen deprivation therapy independently predicted fracture risk after controlling for other covariates.

In a study of medical claims data from a 5% national random sample of Medicare beneficiaries, men receiving GnRH agonist treatment for prostate cancer were more likely to develop fractures than a control group of men with prostate cancer who had not received a GnRH agonist (relative risk, 1.21; 95% CI, 1.14–1.29; $P < .001$). Rates of vertebral fractures (relative risk, 1.45; 95% CI, 1.14–1.69; $P = 0.002$) and hip-femur fractures (relative risk, 1.30; 95% CI, 1.10–1.53; $P = 0.002$) were also significantly greater in men who received a GnRH agonist. After controlling for age, race, geographic location, and comorbidity, GnRH agonist treatment independently predicted fracture risk.

Increased fracture risk was also observed in a study that used a database of medical and pharmacy claims from 16 large companies in the United States (26). Rates of any fracture were 7.91 per 100 person-years at risk for men who received a GnRH agonist compared with 6.55 per 100 person-years at risk for men who did not receive a GnRH agonist (relative risk, 1.21; 95% CI, 1.09–1.34). After controlling for other factors, GnRH agonist treatment was independently associated with fracture risk. Age and comorbidity were also independent risk factors for fractures.

Other retrospective studies have consistently reported high rates of clinical fracture in GnRH agonist–treated men with prostate cancer (27–30). Bilateral orchiectomies are also associated with increased fracture risk in men with prostate cancer (31,32).

Several factors may account for the increased rates of clinical fractures in men receiving androgen deprivation, including increased fall risk due to metastatic disease, increased fall risk due to treatment-related frailty, and decreased bone mineral density, a surrogate for fracture risk. The relative contributions of each of these factors have not been adequately characterized, but treatment-related changes in bone mineral density seem to be sufficient to explain most of the increase in fracture risk in men with prostate cancer.

Prevention and Treatment

Calcium and vitamin D

High dietary calcium intake (>2,000 mg/d) is associated with increased risk of prostate cancer (33,34). This association has been attributed to low concentrations of active 1,25-dihydroxyvitamin D due to decreased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (35). The link between dietary calcium and prostate cancer risk has led to concern about the potential effect of supplemental calcium on disease progression in men with prostate cancer. There is no evidence, however, that dietary calcium intake is causally related to prostate cancer risk or that the recommended dietary calcium intake of 1,200 to 1,500 mg/d influences prostate cancer progression. Moreover, treatment with the combination of supplemental calcium and vitamin D during GnRH agonist therapy increases serum levels of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (7).

The Food and Nutrition Board of the NIH recommends supplemental vitamin D (400 IU/d) and supplemental calcium to maintain a total dietary calcium intake between 1,200 and 1,500 mg/d (3). In older men and women, dietary supplementation with calcium and vitamin D moderately reduces bone loss in the hip and spine and decreases fracture incidence (36). Calcium and vitamin D are recommended to help prevent bone loss during GnRH agonist therapy. Consistent with recent data in postmenopausal women, however, supplemental calcium and vitamin D are not sufficient to prevent bone loss in most men receiving androgen deprivation therapy for prostate cancer.

Bisphosphonates

Intermittent administration of either i.v. pamidronate or zoledronic acid prevents treatment-related bone loss in men with prostate cancer (refs. [7],22,37;Table 2). We evaluated the efficacy of pamidronate during androgen deprivation therapy for nonmetastatic prostate cancer (7). Forty-seven men with prostate cancer were randomly assigned to receive leuprolide alone or leuprolide and pamidronate (Aredia, Novartis Oncology; 60 mg i.v. every 12 weeks). All subjects were treated with supplemental calcium and vitamin D. Study participants had locally advanced, lymph node–positive, or recurrent prostate cancer and no bone metastases by bone scan. The primary outcome measure was the percentage change in bone mineral density of the lumbar spine after 1 year. Mean changes in bone mineral density at 1 year differed significantly between groups in posterior-anterior lumbar spine ($P < .001$), trochanter ($P = 0.003$), and total hip ($P = 0.005$). In men treated with leuprolide alone, mean bone mineral density decreased by 3.3% in posterior-anterior lumbar spine and 1.8% in total hip ($P < 0.001$ for each comparison with baseline). In contrast, mean bone mineral density did not change significantly at any skeletal site in men treated with both leuprolide and pamidronate.

In another prospective study, 21 men with prostate cancer and bone metastases were randomly assigned to treatment with pamidronate (90 mg) or placebo at study entry (37). Subjects were crossed over to the other treatment at 6 months. The study included only men who had received androgen deprivation therapy for at least 6 months before study entry. Primary study end points were bone mineral density by dual energy X-ray absorptiometry and quantitative computed tomography. Subject data for the two placebo treatment periods

(first 6 months and the 6 months after crossover) were pooled and compared with the pooled data for subjects during the pamidronate treatment periods. Among 18 evaluable men, pamidronate significantly increased bone mineral density of the hip and spine.

A third study evaluated the efficacy of zoledronic acid. In a multicenter prospective study, 106 men with locally advanced or recurrent prostate cancer and no bone metastases were randomly assigned to receive androgen deprivation therapy plus zoledronic acid (Zometa; Novartis Oncology; 4 mg i.v. every 12 weeks) or androgen deprivation therapy plus placebo (22). Men with other conditions associated with osteoporosis were excluded. Bone mineral densities of posterior-anterior lumbar spine and proximal femur were measured by dual energy X-ray absorptiometry. Changes in bone mineral density differed significantly between the groups at all skeletal sites. In men receiving zoledronic acid, mean bone mineral density increased from baseline by 5.3% in the lumbar spine and 1.1% in the total hip. In the placebo group, mean bone mineral density decreased by 2.0% in the lumbar spine and 2.8% in the total hip. These results indicate that zoledronic acid (4 mg i.v. every 3 months) not only prevents bone loss but also increases bone mineral density during androgen deprivation therapy for prostate cancer.

Receptor activator of nuclear factor κB ligand inhibition

The receptor activator of nuclear factor κB (RANK) signaling pathway regulates the activation, differentiation, proliferation, and apoptosis of osteoclasts (38). The pathway consists of RANK ligand, its receptor RANK, and its decoy receptor osteoprotegerin. RANK ligand binds and activates RANK, a transmembrane receptor expressed on hematopoietic stem cells, monocytes, and osteoclasts. RANK expression on stem cells is required for osteoclast differentiation and activation. Hormones and other factors that stimulate bone resorption induce the expression of RANK ligand by bone stromal cells and osteoblasts.

AMG162 is a human monoclonal antibody that binds and neutralizes human RANK ligand. In postmenopausal women, a single administration of AMG162 resulted in marked (>80%) and sustained (6 month) suppression of osteoclast activity (39). AMG162 is under development for the treatment and prevention of postmenopausal osteoporosis, treatment-related osteoporosis in men with prostate cancer and in women with breast cancer, and bone metastases. In an ongoing phase 3 study, termed Hormone Ablation Bone Loss Trial in Prostate Cancer, ~1,400 men receiving a GnRH agonist for prostate cancer were randomly assigned to either AMG162 s.c. every 6 months or placebo (Table 3). Study outcomes include incident vertebral body fractures and bone mineral density.

Estrogens

In contrast to bilateral orchiectomies or treatment with a GnRH agonist, medical castration with estrogens is not associated with treatment-related osteoporosis. In a small nonrandomized study of men with prostate cancer, for example, changes in bone mineral density were compared between men who underwent castration by either bilateral orchiectomies or treatment with estrogen (17). Hip bone mineral density decreased by 10% after 1 year in men who underwent bilateral orchiectomies compared with only 1% in men treated with estrogen.

Estrogen replacement therapy may prevent osteoporosis in GnRH agonist–treated men, although information about the efficacy and safety of estrogens in castrated men with prostate cancer is limited. In a randomized controlled trial of 25 castrated men with nonmetastatic prostate cancer, estradiol (1 mg/d) significantly decreased biochemical

markers of osteoclast activity after 9 weeks (40). A small cross-sectional study reached similar conclusions (18).

To date, no controlled trial has assessed the effects of medical castration with estrogen on bone mineral density or fracture risk in men with prostate cancer. Similarly, no controlled trials have assessed estrogen replacement therapy on clinical outcomes in castrated men with prostate cancer.

Selective estrogen receptor modulators

Raloxifene is a selective estrogen receptor modulator approved to prevent and treat osteoporosis in women. Raloxifene mimics the beneficial effects of estrogens in bone without stimulatory effects in most other tissues (41). Raloxifene prevents early postmenopausal bone loss in women and reduces the rate of vertebral fractures in women with postmenopausal osteoporosis (42,43). In a 12-month open-label study, men with nonmetastatic prostate cancer (n = 48) who were receiving a GnRH agonist were assigned randomly to raloxifene (60 mg/d) or no raloxifene. Bone mineral density of the posteroanterior lumbar spine and proximal femur was measured by dual energy X-ray absorptiometry. Raloxifene significantly increased bone mineral density of the hip and tended to increase bone mineral density of the spine. Raloxifene also decreased biochemical markers of bone turnover, suggesting that raloxifene increases bone mineral density by similar mechanism(s) in postmenopausal women and hypogonadal men.

Toremifene is a selective estrogen receptor modulator approved for the treatment of advanced breast cancer. Toremifene is also being developed for treatment of osteoporosis and other complications associated with hormone therapy for prostate cancer. In a 6-month placebo-controlled study, 46 men with prostate cancer who were receiving a GnRH agonist were assigned randomly to either toremifene or placebo (44). Toremifene (60 mg/d) significantly increased bone mineral density and reduced hot flashes. In an ongoing phase 3 study, >1,200 men who are receiving a GnRH agonist for prostate cancer have been randomly assigned to either toremifene or placebo (Table 3). Study outcomes include fractures, bone mineral density, and hot flashes.

Antiandrogen monotherapy

Bicalutamide is a peripherally selective, nonsteroidal antiandrogen that competitively inhibits the action of androgens by binding to androgen receptors in the target tissue. Bicalutamide (50 mg/d by mouth) is indicated for use in combination with a GnRH agonist to treat metastatic prostate cancer. Monotherapy with bicalutamide at higher doses (150 mg/d by mouth) has been evaluated as adjuvant therapy for early-stage prostate cancer and as alternative to medical or surgical castration in men with nonmetastatic prostate cancer. Bicalutamide, 150 mg monotherapy, is approved to treat locally advanced nonmetastatic prostate cancer in more than 50 countries but not in the United States. *Bicalutamide does not have an established role in early-stage disease.*

Bicalutamide monotherapy increases serum concentrations of estradiol (45). Consistent with the important role of estrogen in male skeletal homeostasis, bicalutamide mono-therapy has beneficial effects on bone. In two prospective randomized controlled trials of men with nonmetastatic prostate cancer, bicalutamide monotherapy significantly decreased markers of bone turnover and increased bone mineral density compared with treatment with a GnRH agonist (46,47).

Conclusions

GnRH agonists increase bone turnover, decrease bone mineral density, and increase fracture risk in men with prostate cancer. Estrogens play a central role in homeostasis of the normal male skeleton, and estrogen deficiency rather than testosterone deficiency seems to be primarily responsible for the adverse skeletal effects of GnRH agonists. In small randomized controlled trials, bisphosphonates (pamidronate and zoledronic acid) and selective estrogen receptor modulators (raloxifene and toremifene) increased bone mineral density in GnRH agonist–treated men. At present, no consensus guidelines exist for the diagnosis, prevention, and treatment of osteoporosis in men with prostate cancer. In recent reviews, most authors recommend screening for osteoporosis with dual energy X-ray absorptiometry scans, weight-bearing exercise, supplemental calcium and vitamin D, and selective treatment with bisphosphonates for men at the greatest risk of fracture (48,49). At least two large randomized placebo-controlled fracture studies in GnRH agonist–treated men are ongoing. These studies prospectively define fracture outcomes in men with prostate cancer and assess the efficacy of novel pharmacologic interventions (AMG162, toremifene) in this setting.

Open Discussion

Dr. Bruland: One aspect in these men with androgen deprivation is obviously the direct endocrine effect on the skeleton. Furthermore, many of our patients have cognitive dysfunction and are in a state of low physical activity. Do you think physical exercise can do some good?

Dr. Smith: Absolutely. These are older men, and fracture risk is one issue they face while receiving hormone therapy. Changes in bone mineral density are sufficient to explain the increase in fracture risk, but there are certainly other issues, including muscle loss. I recommend diet and exercise to all of my patients whether or not they are receiving hormone therapy.

Dr. Pearse: What is the anticipated rate of bone metastases? How many patients are you going to have to look at before you know whether administration of a bisphosphonate will have an impact?

Dr. Smith: Nearly all of the 30,000 to 40,000 men per year who die in the United States have bone metastases. Many men with fatal prostate cancer develop metastases early. A lot of the patients receiving long-term treatment, even when hormone therapy fails, were previously thought to be at extraordinarily high risk of developing bone metastases. We now have other ways to identify a higher risk.

Dr. Coleman: I was amazed when I saw in the *New England Journal of Medicine* that the risk of fracture at 10 years is 50%. Do you think there is any reason now not to give some kind of bone protection?

Dr. Smith: Fracture-free survival was about 50%. About 20% of men receiving hormone therapy had any at 3 years compared with 12% for men not receiving hormone therapy. However, it is high and that becomes one of the challenges. In breast cancer and prostate cancer, we have fairly convincing data that we increase fracture risk with our treatments. Then the question becomes, “Do we know enough to intervene in all or most patients or do we need to do fracture prevention studies?”

Dr. Suva: Wouldn’t a certain proportion of men already be eligible for bisphosphonate therapy independent of their prostate cancer?

Dr. Smith: That's how I treat a lot of the patients on trials, but those who aren't on trials I manage in the same way. If they are going to receive long-term treatment to salvage therapy, we perform a baseline dual energy X-ray absorptiometry scan. If they have osteoporosis they get treated, and if they don't I typically give them calcium and multivitamins.

Dr. Weilbaecher: Are there data that raloxifene kills cancer?

Dr. Smith: In prostate cancer there are no good human data, but there are some preclinical data that would suggest that may be the case. We've studied a number of approaches and it turns out estrogen works in androgen-independent prostate cancer, at least with prostate-specific antigen responses.

References

1. Foundation NO. Osteoporosis in men. 2005. Available at: http://www.nof.org
2. Seeman E. The structural basis of bone fragility in men. Bone 1999;25:143–7. [PubMed: 10423041]
3. Bilezikian JP. Osteoporosis in men. J Clin Endocrinol Metab 1999;84:3431–4. [PubMed: 10522975]
4. Orwoll ES. Osteoporosis in men. Endocrinol Metab Clin North Am 1998;27:349–67. [PubMed: 9669142]
5. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005;294:238–44. [PubMed: 16014598]
6. Maillefert JF, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol 1999;161:1219–22. [PubMed: 10081873]
7. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss in men receiving gonadotropin releasing hormone agonist therapy for prostate cancer. N Engl J Med 2001;345:948–55. [PubMed: 11575286]
8. Leder BZ, Smith MR, Fallon MA, Lee ML, Finkelstein JS. Effects of gonadal steroid suppression on skeletal sensitivity to parathyroid hormone in men. J Clin Endocrinol Metab 2001;86:511–6. [PubMed: 11158001]
9. Need AG, Horowitz M, Stiliano A, Scopacasa F, Morris HA, Chatterton BE. Vitamin D receptor genotypes are related to bone size and bone density in men. Eur J Clin Invest 1996;26:793–6. [PubMed: 8889442]
10. Eriksen EF, Colvard DS, Berg NJ, et al. Evidence of estrogen receptors in normal human osteoblast-like cells. Science 1988;241:84–6. [PubMed: 3388021]
11. Oursler MJ, Pederson L, Fitzpatrick L, Riggs BL, Spelsberg T. Human giant cell tumors of the bone (osteoclastomas) are estrogen target cells. Proc Natl Acad Sci U S A 1994;91:5227–31. [PubMed: 8202473]
12. Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest 2000;106:1553–60. [PubMed: 11120762]
13. Leder BZ, LeBlanc KM, Schoenfeld DA, Eastell R, Finkelstein JS. Differential effects of androgens and estrogens on bone turnover in normal men. J Clin Endocrinol Metab 2003;88:204–10. [PubMed: 12519853]
14. Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M, Johnston CC. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. J Clin Invest 1997;100:1755–9. [PubMed: 9312174]
15. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 1998;83:2266–74. [PubMed: 9661593]
16. Greendale GA, Edelstein S, Barrett-Connor E. Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. J Bone Miner Res 1997;12:1833–43. [PubMed: 9383688]

17. Eriksson S, Eriksson A, Stege R, Carlstrom K. Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. Calcif Tissue Int 1995;57:97–9. [PubMed: 7584882]
18. Scherr D, Pitts WR Jr, Vaughn ED Jr. Diethylstilbestrol revisited: androgen deprivation, osteoporosis and prostate cancer. J Urol 2002;167:535–8. [PubMed: 11792913]
19. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer 1998;83:1561–6. [PubMed: 9781950]
20. Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. J Urol 2000;163:181–6. [PubMed: 10604342]
21. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy X-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 2002;167:2361–7. discussion 2367. [PubMed: 11992038]
22. Smith MR, Eastham J, Gleason D, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men undergoing androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 2003;169:2008–12. [PubMed: 12771706]
23. Smith MR, Fallon MA, Lee H, Finkelstein JS. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:3841–6. [PubMed: 15292315]
24. Lee H, McGovern K, Finkelstein JS, Smith MR. Changes in bone mineral density and body composition during initial and long-term gonadotropin-releasing hormone agonist treatment for prostate cancer. Cancer 2005;104:1633–7. [PubMed: 16116596]
25. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154–64. [PubMed: 15647578]
26. Smith M, Boyce S, Moyneur E, Duh M, Raut M, Brandman J. Risk of clinical fracture after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol 2006;175:136–9. discussion 139. [PubMed: 16406890]
27. Daniell HW. Osteoporosis after orchiectomy for prostate cancer [see comments]. J Urol 1997;157:439–44. [PubMed: 8996327]
28. Townsend MF, Sanders WH, Northway RO, Graham SD Jr. Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. Cancer 1997;79:545–50. [PubMed: 9028366]
29. Hatano T, Oishi Y, Furuta A, Iwamuro S, Tashiro K. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer [in process citation]. BJU Int 2000;86:449–52. [PubMed: 10971270]
30. Oefelein MG, Ricchuiti V, Conrad W, et al. Skeletal fracture associated with androgen suppression induced osteoporosis: the clinical incidence and risk factors for patients with prostate cancer. J Urol 2001;166:1724–8. [PubMed: 11586210]
31. Melton LJ III, Alothman KI, Khosla S, Achenbach SJ, Oberg AL, Zincke H. Fracture risk following bilateral orchiectomy. J Urol 2003;169:1747–50. [PubMed: 12686824]
32. Dickman PW, Adolfsson J, Astrom K, Steineck G. Hip fractures in men with prostate cancer treated with orchiectomy. J Urol 2004;172:2208–12. [PubMed: 15538233]
33. Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 1998;58:442–7. [PubMed: 9458087]
34. Chan JM, Giovannucci E, Andersson SO, Yuen J, Adami HO, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). Cancer Causes Control 1998;9:559–66. [PubMed: 10189041]
35. Giovannucci E. Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control 1998;9:567–82. [PubMed: 10189042]

36. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older [see comments]. N Engl J Med 1997;337:670–6. [PubMed: 9278463]
37. Diamond TH, Winters J, Smith A, et al. The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study. Cancer 2001;92:1444–50. [PubMed: 11745221]
38. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423:337–42. [PubMed: 12748652]
39. Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res 2004;19:1059–66. [PubMed: 15176987]
40. Taxel P, Fall PM, Albertsen PC, et al. The effect of micronized estradiol on bone turnover and calciotropic hormones in older men receiving hormonal suppression therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:4907–13. [PubMed: 12414849]
41. Balfour JA, Goa KL. Raloxifene. Drugs Aging 1998;12:335–41. discussion 342. [PubMed: 9571395]
42. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in post-menopausal women. N Engl J Med 1997;337:1641–7. [PubMed: 9385122]
43. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637–45. [PubMed: 10517716]
44. Steiner MS, Patterson A, Israeli R, Barnette KG, Boger R, Price D. Toremifene citrate versus placebo for treatment of bone loss and other complications of androgen deprivation therapy in patients with prostate cancer [abstract 4597]. Proc Am Soc Clin Oncol 2004;22:4597.
45. Verhelst J, Denis L, Van Vliet P, et al. Endocrine profiles during administration of the new non-steroidal anti-androgen Casodex in prostate cancer. Clin Endocrinol (Oxf) 1994;41:525–30. [PubMed: 7525125]
46. Smith MR, Goode M, Zietman AL, McGovern FJ, Lee H, Finkelstein JS. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol 2004;22:2546–53. [PubMed: 15226323]
47. Sieber PR, Keiller DL, Kahnoski RJ, Gallo J, McFadden S. Bicalutamide 150 mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. J Urol 2004;171:2272–6. quiz 2435. [PubMed: 15126801]
48. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer 2004;100:892–9. [PubMed: 14983482]
49. Bae DC, Stein BS. The diagnosis and treatment of osteoporosis in men on androgen deprivation therapy for advanced carcinoma of the prostate. J Urol 2004;172:2137–44. [PubMed: 15538219]

Table 1

Bone mineral density during initial androgen deprivation therapy for prostate cancer

Study	*n*	Androgen deprivation therapy	Change in BMD at 1 y (%)	
			Hip	Spine
Eriksson et al. (17)	11	Orchiectomies	−9.6	ND
Maillefert et al. (6)	12	GnRH agonist	−3.9	−4.6
Daniell et al. (20)	26	Orchiectomies or GnRH agonist	−2.4 to −3.7	ND
Smith et al. (7)	47	GnRH agonist	−3.3	−1.8
Berutti et al. (21)	35	GnRH agonist	−2.3	−0.6
Smith et al. (22)	106	Orchiectomies or GnRH agonist	−2.1	−2.8

Abbreviations: BMD, bone mineral density; ND, not done.

Table 2

Randomized controlled trials to prevent bone loss in GnRH agonist–treated men with prostate cancer

Study	*n*	Arms	Results	Treatment effect at 12 mo (95% CI)
Smith et al. (7)	47	Pamidronate vs no pamidronate	Pamidronate increased BMD of hip and spine	Lumbar spine: 3.8% (1.8–5.7%) Total hip: 2.0% (0.7–3.4%)
Diamond et al. (37)	21	Pamidronate vs placebo	Pamidronate increased BMD of hip and spine	Not reported
Smith et al. (22)	106	Zoledronic acid vs placebo	Zoledronic acid increased BMD of hip and spine	Lumbar spine: 7.3% (5.3–8.8%) Total hip: 3.9% (2.4–5.0%)
Smith et al. (23)	48	Raloxifene vs no raloxifene	Raloxifene increase BMD of hip	Lumbar spine: 2.0% (−0.2–4.0%) Total hip: 3.7% (2.0–5.4%)
Steiner (44)	46	Toremifene vs placebo	Toremifene increased BMD of hip and spine	Not reported

Table 3

Randomized controlled trials to prevent fractures in GnRH agonist–treated men with prostate cancer

Study	*n*	Arms	Primary end points	Status
Acapodene	1,335	toremifene versus placebo	Incident vertebral fractures, BMD	Completed accrual 10/2005
HALT PC	1,468	AMG162 versus placebo	Incident vertebral fractures, BMD	Completed accrual 4/2005

Abbreviation: HALT PC, Hormone Ablation Bone Loss Trial in Prostate Cancer.