

Maintaining Bone Health and Integrity During Androgen-deprivation Therapy for Prostate Cancer

a report by

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Since the early 1990s, earlier diagnosis and improved treatment options have caused a steady decline in the prostate cancer mortality rate.^{1,2} Consequently, many of the 186,000 men in the US who will be diagnosed with prostate cancer in 2008 may live for many years with the disease and any long-term treatment-related adverse effects (AEs).² Androgen-deprivation therapy (ADT) has become an accepted standard of care for prostate cancer treatment and its use is recommended in various stages of the disease.³ However, ADT is not without AEs, some of which may have long-term consequences. Of particular concern is the increased risk for fracture associated with ADT, especially in patients treated for many years.⁴⁻⁶ Clinicians who treat prostate cancer patients should be aware of the potential AEs associated with ADT and of strategies for preventing and/or treating them. This article reviews the prevalence and consequences of bone loss and fractures in men with prostate cancer and without bone metastases receiving ADT, and discusses prevention and treatment strategies.

Adverse Effects Associated with Androgen-deprivation Therapy

Non-skeletal Adverse Effects

ADT-treated patients commonly experience a range of AEs, including sexual dysfunction, hot flashes, anemia, metabolic syndrome, body composition changes, fatigue, and cognitive and mood changes.⁷⁻¹⁰ Although the focus of this article is skeletal-related AEs, a brief discussion about the increased risk for cardiovascular disease (CVD) in patients receiving ADT is warranted to increase awareness of this potential long-term AE.⁸ ADT-associated AEs that can increase the risk for CVD include metabolic syndrome and body composition changes.^{3,8,9} Metabolic syndrome is diagnosed when three or more of the following are present: abdominal obesity, hypertriglyceridemia, low levels of

high-density lipoprotein cholesterol, or elevated blood pressure. Low testosterone levels are predictive of the development of metabolic syndrome in men.^{3,8} Results of a recent cross-sectional study showed that 55% of prostate cancer patients receiving ADT for at least one year

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developed metabolic syndrome compared with 22% of age-matched eugonadal men not receiving ADT.⁸ The presence of metabolic syndrome in prostate cancer patients increases the risk for insulin resistance, diabetes mellitus, CVD, and death.³ Changes in body composition such as an increased proportion of body fat and/or weight gain are often observed in men receiving ADT, and also contribute to the risk for CVD.⁹

Compared with healthy controls, Chen and colleagues⁹ found that men receiving ADT for one to five years were 5.5 times more likely to become obese (body mass index [BMI] ≥ 30 kg/m²). Prostate cancer patients are more likely to die from CVD than from prostate cancer itself, so clinicians should be aware of the increased CVD risk in all prostate cancer patients, especially those receiving ADT, and should monitor patients for early signs of CVD.¹¹ Furthermore, before administering ADT to men with early-stage disease who are likely to receive long-term therapy (>1 year), clinicians must consider the risk for ADT-associated CVD, especially for men already at increased risk for CVD-related mortality.³

Skeletal Adverse Effects

Bone loss is the most studied ADT-associated AE. Results of multiple studies have shown that bone mineral density (BMD) of the femoral neck, lumbar spine, and total hip decreases by up to 4.6% annually in prostate cancer patients without bone metastases who receive ADT, a rate that is four to eight times higher than the normal bone loss rate (0.5–1% per year) observed in otherwise healthy aging men.^{1,10,12-21} As bone loss increases the probability of fracture, prostate cancer patients who receive ADT are at an increased risk for fracture and related morbidity and mortality.^{4-6,22} Indeed, men with prostate cancer and no bone metastases



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Table 1: Types of Androgen-deprivation Therapy and Corresponding Effects on Bone in Men with Prostate Cancer and No Bone Metastases

Type of ADT	Effect on Bone	Mechanism of Bone Effect
Orchiectomy ^{16,27}	Decrease in FN BMD during first year of therapy: -2.4; -7.6 decrease observed in second year	Testosterone-deficiency-induced decrease in osteoblasts and estrogen-deficiency-induced increase in osteoclast and decrease in osteoblast activity
GnRH agonist ^{10,14,16,19,20,27,30}	LS: -1.9 to -4.6 TH: -1.9 to -2.8 FN: -0.1 to -3.9	Testosterone-deficiency-induced decrease in osteoblasts and estrogen-deficiency-induced increase in osteoclast and decrease in osteoblast activity by downregulating GnRH receptors
Antiandrogen monotherapy ²⁹	NTX, BSAP, osteocalcin levels similar to those observed in hormone-naïve patients	Selectively inhibits androgen receptors; increases serum testosterone and estradiol concentrations
GnRH antagonist ^{27,30}	Studies are lacking; however, effects on bone expected to be similar to those observed with GnRH agonists (studies are warranted)	Testosterone-deficiency-induced decrease in osteoblasts and estrogen-deficiency-induced increase in osteoclast and decrease in osteoblast activity by directly inhibiting GnRH receptors
GnRH agonist ± antiandrogen ^{16,17,27,29,30}	LS: -2.0 to -2.7 TH: -2.1 to -2.8 FN: -2.1 ^a	GnRH agonist: testosterone-deficiency-induced decrease in osteoblasts and estrogen-deficiency-induced increase in osteoclast and decrease in osteoblast activity by downregulating GnRH receptors Antiandrogen: selectively inhibits androgen receptors; increases serum estrogen concentration
Estrogen ^{25,28,31}	Orch versus estrogen: decrease BMD with orch, but not estrogen DES versus GnRH versus orch: increased uNTX levels with GnRH and orch, but not DES	Maintains estrogen-induced bone resorption
Ketoconazole ³⁰	NR	Inhibits cytochrome P450 enzymes involved in the synthesis of precursors to testosterone
Intermittent ADT + antiandrogen ^{12,27,29,30}	LS: -4.5 TH: -2.5 FN: NR	Testosterone-deficiency-induced decrease in osteoblasts and estrogen-deficiency-induced increase in osteoclast and decrease in osteoblast activity by downregulating GnRH receptors Antiandrogen: selectively inhibits androgen receptors; increases serum estrogen concentration

ADT = androgen-deprivation therapy; BMD = bone mineral density; BSAP = bone-specific alkaline phosphatase; DES = diethylstilbesterol; FN = femoral neck; GnRH = gonadotropin-releasing hormone; LS = lumbar spine; NR = not reported; NTX = cross-linked N-telopeptide; orch = orchiectomy; TH = total hip; uNTX = urinary cross-linked N-telopeptide; a = not reported in Israeli 2007.

receiving ADT are up to 37% more likely to experience a fracture than patients not receiving ADT; fracture-related hospitalizations are also more common in patients receiving ADT compared with patients not receiving ADT (4.9 versus 2.2%; $p < 0.001$).⁶ The personal and economic consequences of fractures are significant. Studies evaluating the effects of ADT-related fractures on quality of life (QOL) are lacking, but results from studies that evaluate QOL in the general population indicate that QOL is substantially diminished in men who experience osteoporotic fractures.²³ In one study, men who had experienced an osteoporotic hip fracture had decreased role-physical domain scores (a standard QOL measure) compared with men who had not experienced a fracture (-35.7; 95% confidence interval [CI] -60.4 to -11.1).²³ While the study was not specific to the ADT-related fracture population, the results are likely relevant. Also, while no prospective studies have been developed to investigate the economic burden of ADT-related fractures in men with prostate cancer and no bone metastases, one recent retrospective claims database study evaluated healthcare system costs over a three-year period.²⁴ In this study, ADT-treated prostate cancer patients who had experienced a fracture cost the healthcare system more than double ADT-naïve prostate cancer patients who had not experienced a fracture (adjusted costs using a multivariate general linear model: \$29,044 versus \$68,647).²⁴

Types of Androgen-deprivation Therapy and Corresponding Bone Effects

Orchiectomy and gonadotropin-releasing hormone (GnRH) agonists (± an antiandrogen) are the most common modalities used to achieve androgen suppression in prostate cancer patients. Shortly after therapy

initiation, either method causes an increase in markers of bone turnover and/or accelerated bone loss.^{13–16,18,20,25} Furthermore, orchiectomy and GnRH agonists (± an antiandrogen) increase the risk for fracture (see Table 1).^{10,12,14,16,17,19,20,25–31} The mechanism by which orchiectomy and GnRH agonists (± an antiandrogen) induce bone loss is directly related to the decrease of levels of both testosterone (by up to 95%) and estrogen (by up to 80%) achieved with these therapies.¹

Bone remodeling is dependent on a balance of osteoblasts (bone formation cells) and osteoclasts (bone resorption cells); testosterone and estrogen play key roles in this balance.²⁷ Testosterone stimulates

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osteoblast proliferation and inhibits osteoblast and osteoclast apoptosis; therefore, a deficiency in testosterone causes a decrease in the number of osteoblasts and osteoblast function.²⁷ Estrogen is the primary hormone responsible for regulating bone resorption, and estrogen deficiencies

Ketoconazole inhibits cytochrome P450 enzyme-induced synthesis of testosterone precursors and is sometimes used as second-line therapy when disease progression occurs after conventional ADT.³⁰ Although studies that evaluate the bone effects of ketoconazole in prostate cancer patients are lacking, bone loss has been observed in renal transplantation patients receiving ketoconazole during the first six months post-transplant.³⁴ Whether these results are solely a result of ketoconazole's effect on calcitriol or due to its inhibition of the metabolism of corticosteroids that also have detrimental effects on bone is yet to be determined.³⁴ Ongoing studies are evaluating the use of ketoconazole as ADT in patients who are unresponsive to conventional ADT, and ADT with GnRH antagonists is currently under investigation for use in prostate cancer patients who progress while receiving a GnRH agonist. If GnRH antagonists prove to prolong survival time (similar to GnRH agonists) and are found to be safe for use in these patients, studies evaluating bone effects of these agents will be needed; currently, GnRH antagonists are reserved for palliative therapy in patients with advanced symptomatic disease who are not candidates for GnRH agonists or refuse orchiectomy.³⁰

Maintaining Bone Health and Integrity During Androgen-deprivation Therapy

Various factors, including baseline BMI <25kg/m², hyperthyroidism, hyperparathyroidism, liver disease, and calcium or vitamin D malabsorption/deficiencies, place prostate cancer patients at risk for bone loss even before ADT is initiated.⁷ Although studies to date have not been designed to show whether minimizing bone loss prevents fractures in prostate cancer patients without bone metastases, loss of BMD is a proven reliable surrogate marker for fracture risk.²² Therefore, all prostate cancer patients should be evaluated for underlying causes of bone loss, as well as counseled on the importance of lifestyle modifications (i.e. smoking cessation, minimizing

Fracture risk also appears to increase with the duration of androgen-deprivation therapy; however, studies evaluating the long-term incidence in patients without bone metastases are needed.

alcohol consumption, routine weight-bearing exercise) and daily calcium (500–1,500mg) and vitamin D (400–800IU) supplementation to help prevent bone loss.^{1,3,35} Clinicians should consider pharmaceutical intervention (bisphosphonate therapy, estrogens, selective estrogen receptor modulators [SERMs]) for patients at greatest risk for bone loss, especially those receiving ADT. Furthermore, national guidelines now recommend that all patients receive a baseline BMD scan before beginning ADT.³ Routine follow-up BMD scans (every six to 12 months) should also be considered in patients receiving ADT.¹

Bisphosphonates

Bisphosphonates inhibit osteoclast activity.⁷ Both oral and intravenous (IV) formulations have demonstrated efficacy in preventing and, in the case of

zoledronic acid, reversing bone loss (see *Table 2*).^{10,15–17,19,21,25,36–39} Intravenous bisphosphonate formulations are the most studied; however, recent results suggest that oral alendronate and risedronate maintain or significantly increase BMD in patients receiving ADT (see *Table 2*).^{10,15–17,19,21,25,36–39}

Both of the IV bisphosphonates—pamidronate and zoledronic acid—have demonstrated efficacy in preventing bone loss in men with prostate cancer and no bone metastases receiving ADT (see *Table 2*).^{10,15–17,19} Pamidronate

Both of the intravenous bisphosphonates—pamidronate and zoledronic acid—have demonstrated efficacy in preventing bone loss in men with prostate cancer and no bone metastases receiving androgen-deprivation therapy.

appears to maintain BMD during ADT, while several studies show that zoledronic acid increases BMD.^{10,15–17,19} Whether bisphosphonates prevent fractures in prostate cancer patients without bone metastases, as has been observed in patients with metastatic disease and in other cancer and non-cancer populations at risk for bone loss, is unknown.^{1,40}

While ongoing studies are evaluating the effect of bisphosphonates on fracture rate in prostate cancer patients without bone metastases, the National Comprehensive Cancer Network (NCCN) recommends that all prostate cancer patients with baseline osteopenia or osteoporosis receive bisphosphonate therapy while undergoing ADT.³ Whether patients with other osteoporotic risk factors (e.g. low BMI, inadequate vitamin D and/or calcium intake) at baseline should receive bisphosphonate therapy to prevent the development of osteopenia or osteoporosis is unknown. However, results of studies indicate that if initiated during the first year of ADT, when ADT-related bone loss is greatest, zoledronic acid prevents and often reverses bone loss in patients with a variety of risk factors.^{13,17}

Bisphosphonates are generally well tolerated. Although serious AEs such as renal dysfunction and osteonecrosis of the jaw (ONJ) are rare in prostate cancer patients, clinicians should monitor their patients, especially men who are at the highest risk for developing them. In the case of zoledronic acid, grade 3 or 4 renal AEs appear to be related to the dose and infusion rate, and have not been observed in studies evaluating 4mg doses administered over 15 minutes.^{16,17,19} However, the dose may be adjusted for patients who are at risk for or with underlying renal dysfunction.⁴¹ ONJ with bisphosphonate treatment is most commonly reported in multiple myeloma and breast cancer patients.⁴¹ No cases of ONJ have been reported in clinical trials evaluating zoledronic acid (4mg q three months) in patients with prostate cancer without bone metastases.^{16,17,19} Patients who undergo dental procedures (e.g. tooth extraction) within one year prior to or during bisphosphonate therapy and/or are receiving chemotherapy or corticosteroid therapy are at a higher risk for ONJ.⁴² To avoid the requirement for dental procedures during bisphosphonate therapy, clinicians should counsel all bisphosphonate-therapy patients on the

Table 2: Pharmaceutical Interventions for the Prevention of Bone Loss in Men with Prostate Cancer and No Bone Metastases Receiving Conventional Androgen-deprivation Therapy^a

Drug	Duration of Anti-bone-loss Therapy	Mean Percentage Change in BMD ^{b,c}			Reference(s)
		Lumbar Spine	Total Hip	Femoral Neck	
Alendronate 70mg/wk PO versus placebo	1 year	3.7 -1.4 (p<0.001)	0.7 -0.7 (p=0.002)	1.6 -0.7 (p<0.001)	Greenspan, 2007, Greenspan, 2008 ^{21,36}
Risedronate 2.5mg/day PO	6 months	4.9%	NR	No change	Ishizaka, 2007 ³⁷
Pamidronate 60mg IV q 12 weeks versus control group	48 weeks	No change -3.3 (p<0.001)	No change -1.8 (p=0.005)	No change No change (p=0.56)	Smith, 2001 ¹⁵
Zoledronic acid 4mg IV q 3 months versus placebo	48 weeks–1 year	4.6–5.6 -2.2 to -2.0 (p<0.001)	1.1–1.6 -2.8 to -2.1 (p<0.001)	1.2–1.3 (NR in Israeli) -2.4 to -2.1 (p<0.001)	Smith, 2003, Ryan, 2006, Isreali, 2007 ^{16,17,19}
Zoledronic acid 4mg IV x 1 dose versus placebo	1 year	4 -3.1 (p<0.001)	0.7 -1.9 (p=0.004)	2 -0.1 (p=0.06)	Michaelson, 2007 ¹⁰
Estrogen ^d versus orchiectomy	1 year	NR NR	NR NR	-1.2% -9.6% (p=NR)	Eriksson, 1995 ²⁵
Raloxifene 60mg/day PO versus control group	1 year	1 -1 (p=0.07)	1.1 -2.6 (p<0.001)	0.3 -1.7 (p=0.06)	Smith, 2004 ³⁸
Toremifene 80mg/day PO versus placebo	1 year	1.6 -0.7 (p<0.001)	0.7 -1.3 (p=0.001)	0.2 -1.3 (p=0.009)	Smith, 2008 ³⁹

ADT = androgen-deprivation therapy, BMD = bone mineral density; NR = not reported. a = ADT consisted of GnRH agonist, GnRH agonist ± antiandrogen, estrogen, or orchiectomy; b = BMD measured by dual-energy X-ray absorptiometry; c = p value provided for between-group comparison; d = polyestradiol phosphate 160mg intramuscularly q four weeks x three months then 80mg q four weeks thereafter and ethinyl estradiol 1mg per oral (po) once-daily (qd) x two weeks followed by 0.15mg po qd either concomitantly or after three months of polyestradiol phosphate intramuscular injections.

appear to play a larger role in the AEs of ADT than testosterone deficiencies.³² Estrogen deficiencies cause osteoclast activation, decrease osteoclast apoptosis, and possibly decrease osteoblast formation, proliferation, and function.²⁷ Ultimately, the net result of this imbalance is bone loss. Although the greatest degree of bone loss tends to occur during the first year of ADT, the prevalence of osteopenia/osteoporosis appears to increase with prolonged duration of ADT.^{13,33} Results of one study found that after only two years of GnRH agonist (± bicalutamide) therapy, approximately 40% of bone-metastases-free prostate cancer patients developed osteoporosis; this rate doubled to approximately 80% after 10 years of therapy, and no patients had a normal BMD beyond 10 years.³³ Fracture risk also appears to increase with the duration of ADT; however, studies evaluating the long-term incidence in patients without bone metastases are needed.⁴

Little is known about the extent to which other forms of ADT such as estrogen and antiandrogen monotherapy, intermittent GnRH agonists (± antiandrogen), GnRH antagonists, and ketoconazole affect bone health. However, results of studies indicate that some of the less

conventional modalities may have less of a negative impact on BMD, and some may actually prevent bone loss (see *Table 1*).^{12,17,25,28,29} For example, Scherr and colleagues²⁸ found that markers of bone resorption (N-telopeptide [NTX]) did not increase from baseline in prostate cancer patients receiving diethylstilbesterol (DES) monotherapy compared with controls; in contrast, NTX levels increased in men who had undergone an orchiectomy or were receiving GnRH monotherapy. Similarly, in another study evaluating the bone effects of antiandrogen (bicalutamide) monotherapy, NTX and deoxyypyridinoline (biochemical markers of osteoclast activity) levels were significantly higher in men receiving a GnRH agonist compared with patients receiving bicalutamide monotherapy.²⁹ Bone turnover marker levels were similar between the hormone-naïve and bicalutamide groups.²⁹ These results suggest that antiandrogen monotherapy may prevent bone loss in men requiring long-term ADT, likely as a result of uninhibited estrogen activity. Larger studies to confirm these results are needed. BMD loss may also be minimized with intermittent GnRH agonist therapy, allowing for BMD stabilization to occur during the off-treatment period, although the long-term effects of intermittent ADT on BMD are unknown.¹²

importance of good oral hygiene, and the patient should receive a dental examination before bisphosphonate initiation.

Estrogens and Selective Estrogen Receptor Modulators

Both estrogen and SERMs (raloxifene and toremifene) have demonstrated efficacy in preventing bone turnover or loss in prostate cancer patients without bone metastases (see *Table 2*).^{25,28,32} Estrogen has also been shown to prevent increases in biochemical markers of bone turnover in these patients relative to patients receiving conventional ADT and no estrogen.^{25,28} Due to its positive effects on bone resorption, a resurgence of estrogen use in the treatment of prostate cancer has been observed. However, because oral estrogen has known cardiovascular and thromboembolic toxicities in prostate cancer patients, more studies evaluating the efficacy and safety of other estrogen formulations (e.g. transdermal) are warranted. SERMs mimic the effects of endogenous estrogen on bone resorption by selectively binding to skeletal estrogen receptors.³⁸ Results of recent studies have shown that both raloxifene and toremifene increase BMD and prevent bone loss in men receiving ADT

(see *Table 2*).^{38,39} Whether estrogen therapy or SERMs prevent fractures in prostate cancer patients, as has been observed in post-menopausal women, is unknown; however, an ongoing study is evaluating toremifene's effects on fracture rate in this population.^{39,43}

Conclusions

Bone loss and fractures in prostate cancer patients are significant AEs of ADT. Lifestyle changes, calcium/vitamin D intake, and bisphosphonate therapy are currently recommended strategies for preventing ADT-related bone loss, and should be part of the overall treatment plan in men with prostate cancer receiving ADT. Further studies are under way to evaluate SERMs and other therapies for preventing bone loss in these patients. ■

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