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Androgen deprivation therapy for prostate cancer: new concepts and concerns

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Abstract

Purpose of review—The aim of this review is to summarize new concepts and concerns regarding treatment-related osteoporosis, diabetes, and cardiovascular disease in men receiving androgen deprivation therapy for prostate cancer.

Recent findings—Gonadotropin-releasing hormone agonists increase bone turnover, decrease bone mineral density, and increase fracture risk. Bisphosphonates, selective and estrogen receptor modulators significantly increase bone mineral density during androgen deprivation therapy. Ongoing randomized controlled trials will assess efficacy of denosumab, toremifene, and zoledronic acid to prevent fractures in this setting. Gonadotropin-releasing hormone agonists also increase fat mass, decrease insulin sensitivity, and increase serum lipoproteins. In contrast to the classical metabolic syndrome, however, the phenotype of men during androgen deprivation therapy is characterized by increased high-density lipoprotein cholesterol and preferential accumulation of subcutaneous fat. Gonadotropin-releasing hormone agonists are associated with greater risk of incident diabetes and cardiovascular disease in men with prostate cancer.

Summary—Androgen therapy increases risk of fractures, diabetes mellitus, and cardiovascular disease in men with prostate cancer. Current and planned studies will evaluate strategies to prevent these treatment-related adverse effects.

Keywords

cardiovascular disease; diabetes; gonadotropin-releasing hormone agonists; obesity; osteoporosis; prostate cancer

Introduction

About one-third of the estimated two million prostate cancer survivors in the United States currently receive treatment with a gonadotropin-releasing hormone (GnRH) agonist. Chronic administration of a GnRH agonist is the mainstay of treatment for metastatic prostate cancer. In addition, GnRH agonists are now a routine part of the management for many men with nonmetastatic prostate cancer [1,2]. GnRH agonists improve survival in men with locally advanced prostate cancer [3–6]. The benefits and harms of GnRH agonists in other settings, including primary therapy for early stage prostate cancer and salvage therapy for rising levels of serum prostate specific antigen as the only indication of disease recurrence ('PSA-only' prostate cancer), have not been adequately defined [7]. The increased use of GnRH agonists has increased the importance of understanding and preventing treatment-related morbidity.

The intentional consequence of treatment with a GnRH agonist is hypogonadism. GnRH agonists decrease serum concentrations of testosterone by over 95% and estrogen by approximately 80% [8,9]. Speed of onset and severity of gonadal steroid deficiency distinguishes GnRH agonist treatment from age-related andropause.

GnRH agonists have a variety of adverse effects related to gonadal steroid deficiency, including vasomotor flushing, loss of libido, osteoporosis, increased fat mass, and decreased muscle mass [7]. This review focuses on new concepts and concerns regarding treatment-related osteoporosis, diabetes, and cardiovascular disease in men with prostate cancer.

Osteoporosis in men

Osteoporosis is common in men. In the United States, osteoporosis is prevalent in more than 2 million men and another 12 million men are at risk [10]. Men experience one-third of all hip fractures and mortality after hip fractures is higher in men than women [11].

Hypogonadism, alcohol abuse, and chronic glucocorticoid therapy are the major causes of acquired osteoporosis in men [12]. These three causes account for approximately one-half of all cases of male osteoporosis. Hyperparathyroidism and hyperthyroidism are less common causes of osteoporosis in men. Smoking, low dietary calcium intake, vitamin D deficiency, and sedentary lifestyle also contribute to risk for osteoporosis in men [13]. Because of marked changes in patterns of care over the past decade, androgen deprivation therapy for prostate cancer is now a major cause of hypogonadism and a leading cause of osteoporosis in American men.

Androgen deprivation therapy and fracture risk

Three large claims-based studies provide the best evidence that GnRH agonists increase the risk of clinical fractures [14–16].

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 (hazard ratio 1.4; 95% CI 1.16–1.70; $P < 0.001$) [14]. After controlling for age, race, geographic location, and comorbidity, GnRH agonist treatment independently predicted fracture risk.

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 ($P < 0.001$) [15]. 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% CI 1.36–1.56).

Increased fracture risk was also observed in a study using a database of medical and pharmacy claims from 16 large companies in the United States [16]. 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 [17–20]. Bilateral orchiectomies are also associated with increased fracture risk in men with prostate cancer [21,22].

Several factors may account for the high fracture rates 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. Although the relative contributions of each of these factors have not been adequately characterized, treatment-related changes in bone mineral density appear sufficient to explain the increase in fracture risk in men with prostate cancer.

Changes in bone mineral density during androgen deprivation therapy

GnRH agonists significantly decrease bone mineral density in men with prostate cancer [23–28]. Most studies report 2–3% decrease per year in bone mineral density of the hip and spine during initial therapy. Notably, high rates of bone loss were observed despite concurrent administration of supplemental calcium and vitamin D and careful exclusion of secondary causes of osteoporosis [26,28]. Bone mineral density appears to decline steadily during long-term treatment [29,30].

Some but not all men develop osteoporosis during androgen deprivation therapy for prostate cancer. Pretreatment bone mineral density varies between men because of individual differences in peak bone mass and the rates of adult bone loss. Accordingly, men begin androgen deprivation therapy with different relative risks for developing osteoporosis. Rates of treatment-related bone loss and duration of GnRH agonist treatment also vary between individuals.

Mechanisms of hypogonadal bone loss

GnRH agonists increase bone turnover in men with prostate cancer [24,26]. Biochemical markers of osteoclast and osteoblast activity rise progressively after treatment with a GnRH agonist and appear to reach a plateau after approximately 6 months [26]. GnRH agonists increase parathyroid hormone-mediated osteoclast activation [31] suggesting that 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 normal men. Estrogen receptors are expressed in osteoblasts and osteoclasts [32,33]. In older men, serum estradiol levels are positively associated with spinal bone mineral density and negatively associated with vertebral fracture risk [34–36]. Estrogens contribute to the regulation of both bone formation and bone resorption in men [37,38]. In addition, medical castration with estrogens does not decrease bone mineral density [39] or increase biochemical markers of osteoclast activity [40] in men with prostate cancer.

Prevention and treatment of osteoporosis in hypogonadal men

Table 1 summarizes the results of randomized controlled trials to prevent bone loss in men receiving androgen deprivation therapy.

Calcium and vitamin D—The National Institutes of Health Food and Nutrition Board recommends supplemental vitamin D (400 IU/day) and supplemental calcium to maintain a total dietary calcium intake between 1200 and 1500 mg/day [12]. In men and women aged 65 years or more, dietary supplementation with calcium and vitamin D moderately reduces bone loss in the hip and spine and decreases fracture incidence [41]. Calcium and vitamin D are recommended but not sufficient to prevent bone loss during GnRH agonist therapy.

High dietary calcium intake (>2000 mg/day) is associated with increased risk of prostate cancer [42,43]. 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 [44]. The link between dietary calcium and prostate cancer risk has led to concern about the potential impact 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 1200–1500 mg/day influences prostate cancer progression. Moreover, treatment with the combination of supplemental calcium and vitamin D during androgen deprivation therapy increases serum levels of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D [26].

Bisphosphonates—Intermittent administration of either intravenous pamidronate or zoledronic acid prevents treatment-related bone loss in men with prostate cancer [26,28,45].

In a prospective study of 47 men with nonmetastatic prostate cancer, pamidronate (60 mg intravenously every 12 weeks) significantly increased bone mineral density of the lumbar spine, total hip, and trochanter. Similar significant improvements in bone mineral density were reported in another controlled trial of pamidronate in 21 men with prostate cancer [45].

In a multicentered prospective study, 106 men with locally advanced or recurrent prostate cancer and no bone metastases were randomly assigned to receive androgen deprivation therapy and zoledronic acid (4 mg intravenously every 12 weeks) or androgen deprivation therapy plus placebo for 12 months [28]. Zoledronic acid significantly increased bone mineral density of the hip and lumbar spine. The between-group differences were 3.9% and 7.3% for the hip and lumbar spine, respectively. In a recently reported randomized placebo-controlled, zoledronic acid (zoledronic acid 4 mg once) also significantly increased bone mineral density of the hip and spine after 1 year [46]. The between-group differences were similar to that reported in a prior multicentered study, suggesting that annual zoledronic acid is as effective as more frequent treatment.

An ongoing study from the Radiation Therapy Oncology Group will evaluate the effects of zoledronic acid on fracture risk with men with prostate cancer (Table 2). A total of 1272 men receiving neoadjuvant therapy with a GnRH agonist in combination with radiation therapy for early stage prostate cancer will be randomly assigned to zoledronic acid (4 mg intravenously every 3 months) or placebo. The primary study endpoints are incident clinical fractures and change in bone mineral density.

There is less information about the efficacy of oral bisphosphonates to prevent osteoporosis in men receiving androgen deprivation therapy for prostate cancer although the available evidence suggests that oral bisphosphonates also significantly increase bone mineral density. In a preliminary report of randomized controlled trial of men with prostate cancer, for example, oral alendronate significantly increased bone mineral density of the hip and spine [47].

RANKL inhibition—The RANK signaling pathway regulates the activation, differentiation, proliferation, and apoptosis of osteoclasts [48]. The pathway consists of receptor activator of NF- κ B ligand (RANKL), its receptor RANK, and its decoy receptor osteoprotegerin (OPG). RANKL binds and activates RANK, a transmembrane receptor expressed on hematopoietic stem cells 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 RANKL by bone stromal cells and osteoblasts.

Denosumab is a human monoclonal antibody that binds and neutralizes human RANKL. In postmenopausal women, a single administration of denosumab resulted in marked (>80%) and sustained (6-month) suppression of osteoclast activity [49]. AMG162 is in development

for the treatment and prevention of postmenopausal osteoporosis, treatment-related osteoporosis in men with prostate cancer and women with breast cancer, and bone metastases. In an ongoing phase III study termed HALT PC, 1468 men who are receiving a GnRH agonist for prostate cancer were randomly assigned to either denosumab subcutaneously every 6 months or placebo. 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 estrogen is not associated with treatment-related osteoporosis. In a small nonrandomized study of men with prostate cancer, changes in bone mineral density were compared between men who underwent castration by either bilateral orchiectomies or treatment with estrogen [39]. 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. In a phase II single arm study, androgen deprivation therapy with transdermal estrogen also increased bone mineral density [50].

Estrogen replacement therapy may prevent osteoporosis in GnRH agonist-treated men although information about the efficacy and safety of estrogens in castrate men with prostate cancer is limited. In a randomized controlled trial of 25 castrate men with nonmetastatic prostate cancer, estradiol (1 mg/day) decreased significantly biochemical markers of osteoclast activity after 9 weeks [51]. A small cross-sectional study reached similar conclusions [40].

To date, no controlled study has assessed the effects of medical castration with estrogen on bone mineral density or fracture risk in men with prostate cancer. Similarly, there have been no controlled trials to assess estrogen replacement therapy on clinical outcomes in castrate 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 [52]. Raloxifene prevents early postmenopausal bone loss in women and reduces the rate of vertebral fractures in women with postmenopausal osteoporosis [53,54]. 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/day) or no raloxifene [55]. Bone mineral density of the posteroanterior lumbar spine and proximal femur were measured by dual energy X-ray absorptiometry. Raloxifene significantly increases bone mineral density of the hip and tended to increase bone mineral density of the spine (Table 1). Raloxifene decreased biochemical markers of bone turnover, suggesting that raloxifene increases bone mineral density by similar mechanisms 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 androgen deprivation 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 [56]. Toremifene (60 mg/day) significantly increased bone mineral density and reduced hot flashes. In an ongoing phase III study, 1392 men who are receiving a GnRH agonist for prostate cancer will be randomly assigned to either toremifene or placebo (Table 2). Study outcomes include changes in bone mineral density and incident fractures. Because toremifene may have additional nonskeletal benefits in this setting, the study will also evaluate changes in lipids and hot flashes.

Treatment-related changes in body composition

Androgens are important determinants of body composition in men. Serum testosterone concentrations correlate positively with muscle mass and negatively with fat mass [57]. Testosterone replacement therapy increases lean body mass in men with hypogonadism due to aging, HIV infection, and other chronic diseases [58–60]. Some but not all studies have reported that testosterone replacement therapy decreases fat mass in hypogonadal men [58,61,62].

GnRH agonist significantly decrease lean body mass and increase fat mass in men with prostate cancer [27,63–66]. In two prospective studies of men with nonmetastatic prostate cancer, for example, we demonstrated that GnRH agonists decreased lean body mass by 2.7 to 3.8% and increase fat mass by 9.4 to 11.0% from baseline to 1 year [65,66]. Treatment-related increases in fat mass appear to result from accumulation of primarily subcutaneous fat because abdominal subcutaneous fat area increased but intra-abdominal fat area does not change significantly [65].

In a 3-month study of 22 men with nonmetastatic prostate cancer, GnRH agonist treatment increased mean fat mass by 8.5% ($P = 0.008$) and decreased lean body mass by 2.6% ($P = 0.003$) [64]. In another 3-month prospective study of men with nonmetastatic prostate cancer, mean fat mass increased by 4.3% ($P = 0.002$) and lean body mass decreased by 1.4% ($P = 0.006$) [67]. The similarity of results between these prospective 3-month and 12-month studies suggests that body composition changes are an early adverse effect and may be clinically important even with short-term therapy. Analyses of prospective changes in body composition during initial and long-term GnRH agonist treatment also suggests that fat mass increases and lean body mass decreases mostly during initial GnRH agonist therapy [30].

Androgen deprivation therapy and insulin resistance

Insulin resistance is a common metabolic abnormality that characterizes individuals with type 2 diabetes and is prevalent in about 20–25% of nondiabetic adults. Insulin resistance is an independent risk factor for cardiovascular disease. Insulin resistance is also linked to a variety of abnormalities associated with increased cardiovascular disease risk including obesity, hypertension, elevated triglyceride levels, decreased high density lipoprotein cholesterol levels, and impaired vascular endothelial function. This constellation of abnormalities is collectively known as the insulin resistance syndrome or the metabolic syndrome [68,69]. Patients with the metabolic syndrome have substantially higher rates of cardiovascular disease than other patients [69–71].

The phenotype of men receiving GnRH agonists appears to share some features with the insulin resistance syndrome. In addition to increasing fat mass, GnRH agonists also increase fasting plasma insulin levels, a marker of insulin resistance [64]. To better characterize the short-term effects of GnRH agonist treatment on insulin sensitivity, we prospectively evaluated 25 non-diabetic men with nonmetastatic prostate cancer [72• •]. Oral glucose tolerance tests and body composition assessments by dual energy X-ray absorptiometry were performed before and 12 weeks after initiation of GnRH agonist treatment. The primary study outcome was change in composite whole-body insulin sensitivity index [73]. Fasting plasma insulin levels increased by 26% ($P = 0.04$). Whole-body insulin sensitivity index decreased by 11% ($P = 0.04$). Fasting plasma glucose did not change although glycosylated hemoglobin increased significantly.

GnRH agonists also alter serum lipoproteins in men with prostate cancer. In a study of 26 elderly men receiving treatment with a GnRH agonist, for example, mean total cholesterol levels increased by 10.6% ($P = 0.003$), high-density lipoprotein (HDL) cholesterol increased by 8.2% ($P = 0.05$) and triglycerides increased by 26.9% ($P = 0.050$); low-density

lipoprotein (LDL) cholesterol levels were unchanged [74]. In another prospective study of men with nonmetastatic prostate cancer, we reported that serum total cholesterol, HDL cholesterol, and low-density lipoprotein cholesterol increased significantly by 9.0, 11.3, and 7.3%, respectively, after 12 months [65]. Serum triglycerides increased significantly by 26.5%.

Consistent with the results of these prospective studies demonstrating significant treatment-related increases in fat mass, insulin resistance, and serum lipoproteins, several small cross-sectional studies have reported greater prevalence of features of the metabolic syndrome in men receiving GnRH agonist therapy for prostate cancer [75,76].

There is less information about the effects of GnRH agonists on other components of the metabolic syndrome. In a small study of men with prostate cancer, medical castration with estrogen (intramuscular polyestradiol phosphate) significantly increased high-sensitivity C-reactive protein (hsCRP) concentrations [77]. There have been no controlled prospective studies to assess the effects of GnRH agonists on biomarkers of inflammation or fibrinolysis.

Taken together, these studies demonstrate that GnRH agonists are associated with some changes consistent with the metabolic syndrome including increased fat mass, increased fasting plasma insulin levels, decreased insulin sensitivity, and increased serum triglycerides. Other treatment-related changes, including preferential accumulation of subcutaneous rather than visceral fat and increases in both HDL and LDL cholesterol are distinct from the classic metabolic syndrome. The distinct metabolic changes associated with GnRH agonist treatment suggest that additional research is warranted to better characterize the metabolic effects of GnRH agonist treatment and to assess their relationship to clinical outcomes including diabetes and cardiovascular disease.

Diabetes and cardiovascular disease after androgen deprivation therapy

Cardiovascular disease and diabetes are leading causes of noncancer death in cancer survivors, and men with prostate cancer have higher rates of noncancer mortality than the general population [78]. In a large population-based study, we recently demonstrated that GnRH agonists are associated with increased risk of diabetes mellitus and cardiovascular disease [79••]. We studied the records of 73 196 men in the linked database of the Surveillance, Epidemiology, and End Results program and Medicare (SEER-Medicare) diagnosed with local or local-regional prostate cancer in the period from 1992 through 1999. The primary outcomes were incident diabetes mellitus, incident cardiovascular disease, and admission for myocardial infarction. Cox proportional hazards models with time varying treatment variables and time varying covariates were used to assess the relationship between GnRH agonist or orchiectomy and primary study outcomes.

One-third of men received a GnRH agonist during follow-up. Using a Cox proportional hazards model that adjusted for patient and tumor characteristics, current use of a GnRH agonist was associated with a significantly increased risk of incident diabetes (adjusted hazard ratio 1.42, $P < 0.001$), coronary heart disease (adjusted HR 1.16, $P < 0.001$), and admission for myocardial infarction (adjusted HR 1.11; $P = 0.03$) compared with men receiving no androgen deprivation therapy. Similar results were obtained using propensity score methods to match treated with similar untreated patients, suggesting that potential differences in baseline characteristics between the groups is unlikely to explain the observed associations.

Conclusion

In men with prostate cancer, GnRH agonists increase bone turnover, decrease bone mineral density, and increase fracture risk. Bisphosphonates and selective androgen receptor modulators significantly increase bone mineral density during androgen deprivation therapy. GnRH agonists also increase fat mass, decrease insulin sensitivity, and increase serum lipoproteins. Consistent with these adverse metabolic effects, GnRH agonists are associated with greater risk of incident diabetes and cardiovascular disease in men with prostate cancer.

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Abbreviations

GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 260–261).

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Table 1

Randomized controlled trials to prevent bone loss in gonadotropin-releasing hormone agonist-treated men with prostate cancer

Study	<i>n</i>	Arms	Results	Between-group differences at 12 months (95% CI)
Smith <i>et al.</i> [26]	47	Pamidronate versus 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 <i>et al.</i> [45]	21	Pamidronate versus placebo	Pamidronate increased BMD of hip and spine	Not reported
Smith <i>et al.</i> [28]	106	Zoledronic acid versus placebo	Zoledronic acid (4 mg every 12 weeks) increased BMD of hip and spine	Lumbar spine: 7.3% (5.3, 8.8%) Total hip: 3.9% (2.4, 5.0%)
Michaelson <i>et al.</i> [46]	44	Zoledronic acid versus placebo	Annual zoledronic acid increased BMD of hip and spine	Lumbar spine: 7.1% (4.2, 10.0%) Total hip: 2.6% (0.9, 4.3%)
Smith <i>et al.</i> [29]	48	Raloxifene versus no raloxifene	Raloxifene increased BMD of hip	Lumbar spine: 2.0% (30.2, 4.0%) Total hip: 3.7% (2.0, 5.4%)
Steiner [56]	46	Toremifene versus placebo	Toremifene increased BMD of hip and spine	Not reported

BMD, bone mineral density.

Table 2

Randomized controlled trials to prevent fractures in gonadotropin-releasing hormone agonist-treated men with prostate cancer

Study	<i>n</i>	Arms	Endpoints	Status
Amgen	1468	Denosumab versus placebo	Incident fractures, BMD	Completed accrual 4/2005
GTx	1391	Toremifene versus placebo	Incident fractures, BMD	Completed accrual 11/2005
RTOG	1272	Zoledronic acid versus placebo	Incident fractures	Accrual ongoing

BMD, bone mineral density; RTOG, Radiation therapy oncology group.