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Prostate Cancer Survivorship: Prevention and Treatment of the Adverse Effects of Androgen Deprivation Therapy

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BACKGROUND: More than one-third of the estimated 2 million prostate cancer survivors in the United States receive androgen deprivation therapy (ADT). This population of mostly older men is medically vulnerable to a variety of treatment-associated adverse effects.

MEASUREMENTS AND RESULTS: Androgen-deprivation therapy (ADT) causes loss of libido, vasomotor flushing, anemia, and fatigue. More recently, ADT has been shown to accelerate bone loss, increase fat mass, increase cholesterol and triglycerides, and decrease insulin sensitivity. Consistent with these adverse metabolic effects, ADT has also recently been associated with greater risks for fractures, diabetes and cardiovascular disease.

CONCLUSION: Primary care clinicians and patients should be aware of the potential benefits and harms of ADT. Screening and intervention to prevent treatment-related morbidity should be incorporated into the routine care of prostate cancer survivors. Evidence-based guidelines to prevent fractures, diabetes, and cardiovascular disease in prostate cancer survivors represent an important unmet need. We recommend the adapted use of established practice guidelines designed for the general population.

KEY WORDS: prostate cancer; survivorship; GnRH agonists; osteoporosis; bisphosphonates; diabetes; obesity; cardiovascular disease.

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SCOPE OF THE PROBLEM

Prostate cancer is the most common malignancy in men. The median age at diagnosis of prostate cancer is 68 years.¹ Prostate cancer does not alter life expectancy for most of these men as the 5-year relative survival for all stages combined is 98.8%.¹ Even those who present with metastatic disease have a median survival of approximately 30 months^{2,3} and a 10-year survival approaching 10%.⁴ With improvements in cancer-specific survival, treatment-related morbidity has become more relevant to the long-term health of prostate cancer survivors.

Androgens can stimulate prostate cancer growth. Lowering androgen levels with androgen deprivation therapy (ADT) is the primary systemic treatment for prostate cancer. ADT is accomplished by either bilateral orchiectomies or medical

castration with a gonadotropin-releasing hormone (GnRH) agonist. ADT achieves objective responses in over 80% of those treated.^{5,6} Most men are treated with a GnRH agonist rather than bilateral orchiectomies as GnRH agonists are easily administered, reversible, and more acceptable to patients. GnRH agonist use has risen markedly over the last 2 decades across all ages, disease stages and tumor grades.^{7,8} Currently, more than one-third of the estimated 2 million prostate cancer survivors in the United States are treated with GnRH agonists.⁹

ADT is the central treatment for metastatic prostate cancer as it improves bone pain, modestly prolongs overall survival and produces some 10-year survivors.¹⁰ GnRH agonists have been shown to improve disease-free and overall survival in combination with radiation for locally advanced or high-risk nonmetastatic disease.^{11,12} Adjuvant therapy with a GnRH agonist also improves survival in men with node-positive disease after radical prostatectomy.¹³

ADT is also used for settings where evidence of benefit is less clear. PSA monitoring after primary therapy often detects recurrences long before symptoms or imaging would have revealed them. A rising PSA after primary surgery or radiation therapy commonly leads to long-term ADT, although the effects of early ADT for "PSA-only" recurrences on mortality have not been adequately characterized.¹⁴ Additionally, some men with localized disease opt for long-term ADT instead of radiation or surgery, a practice that has not been shown to improve survival relative to observation.¹⁵

The therapeutic effect of ADT is severe hypogonadism. GnRH agonists lead to a striking reduction in serum testosterone and a number of physiologic changes. Adverse changes in bone mineral density, body composition, lipid profile and insulin sensitivity are among the effects of GnRH agonist therapy. Men receiving GnRH agonists experience elevated risks for fracture,¹⁶ diabetes and cardiovascular disease,⁹ all of which cause substantial morbidity to elderly men at baseline.

With the introduction of PSA screening, fewer than 5% of men have detectable metastases at presentation.¹⁷ Earlier diagnosis and more aggressive interventions have increased the burden of treatment for prostate cancer survivors.

Here we provide a focused review of the recently recognized complications of ADT: osteoporosis and fractures, obesity and sarcopenia, insulin resistance and diabetes, and cardiovascular disease. Readers are referred elsewhere for systematic reviews about these and other adverse effects of ADT.^{18,19} We also provide our recommendations for prevention and treatment of fractures, diabetes and cardiovascular disease in men treated with ADT. Our recommendations, detailed in Table 1, are adapted from broadly accepted practice guidelines from the National Osteoporosis Foundation (NOF), the American Diabetes Association (ADA), the

Table 1. Recommendations for Men Receiving ADT for Prostate Cancer***Osteoporosis**

Screening: BMD testing for all men on ADT given the NOF recommendation for adults receiving a medicine associated with bone loss; test at baseline, repeat after 1 year of ADT, then repeat every 2 years or as clinically indicated

Treatment: Supplemental calcium ($\geq 1,200$ mg daily) and vitamin D (800–1,000 IU daily) for all and consideration of drug treatment if age ≥ 50 and any of:

- Personal history of hip or vertebral fracture
- T-score ≤ -2.5 at the femoral neck or spine (secondary causes evaluated)
- Low T-score at femoral neck or spine (-1.0 to -2.5) and by US-adapted WHO algorithm:
 - 10-year probability of a hip fracture $\geq 3\%$ or
 - 10-year probability of a major osteoporosis-related fracture $\geq 20\%$

Diabetes and pre-diabetes

Screening:

- Consider testing in all men treated with ADT at baseline and yearly thereafter while receiving ADT
- Recommended test: fasting plasma glucose (FPG)
- Impaired Fasting Glucose (IFG) = FPG 100–125 mg/dl
- The use of hemoglobin A1C for the diagnosis of diabetes is not recommended

Treatment of pre-diabetes/IFG:

- For those identified with pre-diabetes, treat other CHD risk factors
- For those diagnosed with pre-diabetes, repeat testing at least yearly and counsel lifestyle interventions (with follow-up counseling):
 - 5–10% weight loss
 - ≥ 150 min/week of moderate physical activity

Hyperlipidemia and CHD risk factors

Screening:

- Fasting lipoproteins at baseline, within 1 year of ADT initiation, then every 5 years or as clinically indicated
- Assign target LDL based on major CHD risk factors as outlined in NCEP ATP III

Treatment:

- Emphasis on primary prevention
- Tobacco cessation for all
- Treatment of hypertension per AHA guidelines
- Lifestyle interventions:
 - Reduce intake of saturated fat and cholesterol
 - Increase physical activity
 - Weight control
- Low-dose aspirin in men with 10-year CHD risk $\geq 10\%$
- Statins are first line for hyperlipidemia if lifestyle fails to meet target LDL

Key: ADT, androgen deprivation therapy; BMD, bone mineral density; LDL low density lipoprotein; CHD, coronary heart disease; FPG, fasting plasma glucose; IFG, impaired fasting glucose

*Our recommendations are adapted for the clinical situation from practice guidelines published by the National Osteoporosis Foundation (NOF), the American Diabetes Association (ADA), the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) and the American Heart Association (AHA)

National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) and the American Heart Association (AHA).

Evidence-based guidelines for men on ADT are lacking. This is due in part to the fact that these ADT-specific hazards were identified relatively recently and are still being fully defined. Moreover, few studies of various strategies to screen for and/or manage prostate cancer patients on ADT have been completed to date. Further clinical investigation is needed to better define the most effective strategies to promote health among prostate cancer survivors.

OSTEOPOROSIS AND FRACTURES

Fractures cause significant morbidity in men worldwide.²⁰ One in three hip fractures occur in men.²¹ Hypogonadism,

chronic glucocorticoid therapy and alcohol abuse are the most common causes of acquired osteoporosis in men.²²

ADT accelerates bone turnover,^{23,24} decreases bone mineral density^{23–28} and contributes to fracture risk.^{16,29,30} Analysis in the Surveillance, Epidemiology and End Results (SEER) Medicare database of over 50,000 older men with prostate cancer revealed that among those surviving 5 years beyond diagnosis, fracture rates were 19.4% in men who received ADT and 12.6% in men who did not.¹⁶ A second claims-based analysis in men with nonmetastatic prostate cancer similarly showed a significant association between GnRH agonist use and fractures (RR 1.21; $P < 0.001$).²⁹

Bisphosphonates including pamidronate,^{31,32} zoledronic acid^{33,34} and alendronate³⁵ have been shown to improve bone mineral density and decrease markers of bone metabolism in men on ADT. Notably, none of the completed studies was designed to prevent fracture.

Selective Estrogen Receptor Modulators (SERMs) have been tested for their effects on bone mineral density and markers of bone metabolism in men receiving ADT. Raloxifene³⁶ and toremifene³⁷ are both SERMs that increase bone mineral density and decrease markers of bone metabolism in men treated with ADT. Recently, toremifene has been evaluated in a multicenter phase III study powered to demonstrate fracture prevention (see Table 2). The trial enrolled 1,389 men with low bone mineral density and/or age ≥ 70 and randomized them to receive daily toremifene or placebo for 24 months. In a preliminary report, toremifene significantly decreased new vertebral fractures and increased bone mineral density at all measured skeletal sites.³⁸

Receptor activator of nuclear factor-kappa-B ligand (RANKL) is a critical regulator of osteoclast differentiation, function and survival.^{39–43} Denosumab is a subcutaneously administered fully human monoclonal antibody against RANKL. It is in broad clinical development for postmenopausal osteoporosis, osteoporosis in cancer survivors and the prevention and treatment of bone metastases. Denosumab has been studied in a randomized, placebo-controlled fracture prevention trial that enrolled over 1,400 men at high risk for fracture due to ongoing ADT, older age and/or low bone mineral density (see Table 2). The study was completed in 2008; final results are pending.

Accurate assessment of fracture risk is necessary to identify which men are most likely to benefit from treatment. The World Health Organization/FRAX model improves fracture risk

Table 2. Completed Phase III Fracture Prevention Trials

Study drug	N	Population	Arms	Endpoint(s)
Denosumab (RANK-L inhibitor)	>1,400	Current ADT, high risk due to old age and/or low BMD	Denosumab vs. placebo	New vertebral fractures, bone mineral density
Toremifene (SERM)	1,392	Current ADT, ≥ 50 years old	Toremifene vs. placebo	Incident vertebral fractures within 24 months, bone mineral density, lipid profile

assessment by incorporating a group of clinical risk factors in addition to femoral neck bone mineral density (<http://www.shef.ac.uk/FRAX/index.htm>).^{44–46} These clinical risk factors are based on large meta-analyses and include prior fragility fracture, family history of hip fracture, current tobacco smoking, chronic use of glucocorticoids, daily consumption of alcohol, rheumatoid arthritis and other conditions associated with secondary osteoporosis.^{41–54} Men receiving GnRH agonists are a high-risk population and should be screened for fracture risk with bone mineral density testing at baseline, after 1 year of ADT, then every 2 years or as clinically indicated (see Table 1).

The 2008 NOF guidelines recommend calcium ($\geq 1,200$ mg daily) and vitamin D (800–1,000 IU daily) supplementation for all men age 50 or over. The guidelines also recommend drug therapy for those who have low T-score (-1.0 to -2.5) at the femoral neck or spine and 10-year risk of at least 3% for hip fracture or at least 20% for any osteoporosis-related fracture according to the US-adapted FRAX model.⁵⁵ We believe that existing data clearly support considering ADT as a cause of secondary osteoporosis when using the FRAX tool. Although the ability of pharmacologic therapy to prevent fracture among men on ADT remains preliminary, the results of two phase III fracture prevention trials are anticipated soon.

OBESITY AND SARCOPENIA

Approximately one in three American men are obese [body mass index (BMI) ≥ 30.0 kg/m²].⁵⁶ Androgens are important determinants of body composition as they promote lean body mass over fat mass.⁵⁷ Conversely, ADT increases fat mass and decreases lean body mass.^{25,58}

Prospective clinical trials have shown that 1 year of ADT causes approximately a 10% increase in fat body mass, a 3% fall in lean body mass and 2% increase in overall weight.^{58–60} Cross-sectional imaging has revealed that abdominal girth increases during GnRH agonist therapy because of subcutaneous rather than intra-abdominal fat.^{58,61} Abdominal adiposity is a particular concern, as a very large prospective European cohort study found that waist circumference was strongly associated with risk of death even after adjustment for BMI.⁶² ADT-associated changes in body composition occur early in treatment, with significant rises in fat body mass⁶³ as well as accompanying increases in plasma insulin^{63,64} occurring within 3 months of GnRH agonist therapy.

The optimal strategy to prevent or reverse these adverse changes in body composition during GnRH therapy is unknown. One study randomized 155 men to three-times-per-week resistance exercise or to a waiting list control group and found no difference in body composition between the groups at 3 months.⁶⁵ Resistance training did provide some benefit in the form of less fatigue, higher quality of life and higher levels of muscular fitness. Further research on the treatment and prevention of ADT-associated changes in body composition is needed.

LIPID ALTERATIONS

GnRH agonists cause increases in total cholesterol (approximately 10%), triglycerides (approximately 26%) and high-

density lipoprotein (HDL) (approximately 8–11%),^{58,66,67} and these changes have been observed after just 3 months of therapy.^{63,66} Clinician awareness of the potential for these changes can facilitate appropriate monitoring and management. We recommend fasting lipoproteins at baseline, within 1 year of ADT initiation and as clinically indicated thereafter.

Existing data strongly support a continuous, graded relationship between serum cholesterol and cardiovascular mortality.^{68,69} In the general population, the NCEP ATP-III guidelines define the standard-of-care.⁷⁰ Diet and lifestyle are first line interventions to achieve target low-density lipoprotein (LDL). When this is not successful, statins reduce all-cause mortality and are the first-line pharmacologic intervention.⁷¹

SERMs such as toremifene may benefit men with hyperlipidemia during ADT. A recently completed randomized placebo-controlled phase III trial was designed to primarily evaluate daily toremifene for fracture prevention in men receiving ADT. Planned interim analysis at 1 year demonstrated that toremifene decreases LDL cholesterol and triglycerides and increases HDL cholesterol compared to placebo.³⁷ The effect of SERMs on cardiovascular outcomes is not yet known.

INSULIN RESISTANCE

Insulin resistance is associated with obesity and is an independent risk factor for diabetes and cardiovascular disease. Its prevalence in the general adult population is about 25%.^{72,73} Several small prospective studies have shown that GnRH agonists increase fasting insulin levels early in the course of GnRH agonist treatment.^{63,64,66} In a prospective study of nondiabetic men, ADT significantly decreased insulin sensitivity after 12 weeks.⁶³ ADT did not significantly alter fasting plasma glucose levels, but did modestly increase glycated hemoglobin levels.

DIABETES

The incidence of diabetes has doubled in the last 30 years⁷⁴ and is projected to rise further.⁷⁵ The National Health and Nutrition Examination Survey (NHANES) from 1999–2002 estimated the prevalence of diabetes in the population at 6.5%, with another 2.8% undiagnosed.⁷⁶ When these percentages are added to the 26.0% prevalence of impaired fasting glucose, more than a third of the US population either has diabetes or is at high risk for developing it.

Among 73,196 men in a SEER-Medicare database who were age 66 or older with locoregional prostate cancer,⁹ 36% were treated with a GnRH agonist and 7% underwent bilateral orchiectomy during follow-up (median of 4.55 years). The adjusted hazard ratio for incident diabetes was significantly higher among the men treated with GnRH agonists during follow-up (HR 1.44; $P < 0.001$). A preliminary report from a population-based study of Canadian men with prostate cancer confirmed the association between ADT and greater incidence of diabetes.⁷⁷

Based on the prevalence of occult diabetes in older men and the observed association between ADT and greater incidence of diabetes, we recommend screening and intervention to reduce diabetes in line with guidelines from the ADA.⁷⁸ Given the alterations in insulin sensitivity and the association of ADT

with diabetes, we recommend testing of all men receiving long-term ADT at baseline and within 1 year of initiation (see Table 1). Fasting plasma glucose is the preferred diagnostic test and should be repeated yearly while on ADT. The use of A1C for the diagnosis of diabetes is not recommended. The ADA recommends counseling 5–10% weight loss and at least 150 min/week of moderate physical activity to prevent or delay diabetes in those with impaired fasting glucose (fasting glucose 100–125 mg/dl).

CARDIOVASCULAR DISEASE

Cardiovascular disease is the leading cause of death in the US and its prevalence rises with age. Obesity, insulin resistance and elevated triglycerides are all associated with ADT. Studies of ADT and cardiovascular disease are mixed. One analysis of the SEER-Medicare data demonstrated that men receiving GnRH agonists were more likely to develop incident coronary heart disease (HR 1.16; $P < 0.001$), myocardial infarction (HR 1.11; $P = 0.03$) and sudden cardiac death (HR 1.16, $P = 0.004$).⁹ Another population-based study of 23,000 men with prostate cancer demonstrated a 20% rise in 1-year cardiovascular morbidity.⁷⁹ A population-based observational study with relatively short follow-up (3.9 years) and few events (61) reported greater cardiovascular mortality in a subset of older men who underwent prostatectomy.⁸⁰ Notably, this increase in cardiovascular mortality was not apparent in the overall study population and traditional cardiovascular disease risk factors, including prevalent cardiovascular disease and diabetes, were not associated with cardiovascular mortality. A pooled analysis of three small randomized controlled trials of men with clinically localized prostate cancer suggested that 6 months of ADT led to earlier onset of fatal myocardial infarction in the subset of men at least 65 years old.⁸¹ This article's statistical methods have been criticized for the low number of observed events (16 in the control group and 18 in the ADT group).⁸²

In contrast, a preliminary report from a population-based study of Canadian men with prostate cancer found no significant association between ADT and acute myocardial infarction.⁷⁷ Secondary analyses of three large randomized controlled trials from the Radiation Therapy Oncology Group (RTOG) of men with locally advanced prostate cancer reported no association between neoadjuvant/adjuvant ADT and cardiovascular mortality.^{83–85} Similarly, secondary analyses of a randomized controlled trial from the European Organization for Research and Treatment of Cancer (EORTC) reported no association between ADT and cardiovascular mortality. Major strengths of the RTOG and EORTC studies include randomized study design, large sample size, long follow-up and a relatively large number of events.

Given the uncertain association between ADT and myocardial infarction, we recommend a standard emphasis on primary prevention as guided by NCEP ATP III and the American Heart Association (AHA) guidelines. Tobacco cessation and aggressive management of hypertension should be pursued for all. Low-dose aspirin is appropriate for men with at least 10% 10-year risk of CHD. Lifestyle interventions should include weight control, regular physical activity, and reduced intake of saturated fat and cholesterol. Statins are first line for the treatment of hyperlipidemia if lifestyle interventions fail to bring LDL cholesterol to goal.

CONCLUSIONS AND RECOMMENDATIONS

For many men, prostate cancer is a chronic disease. As prostate cancer specific mortality has fallen to low levels, internists and oncologists commonly manage men with prostate cancer for years and sometimes for decades. ADT, the mainstay of treatment for recurrent and metastatic prostate cancer, has a variety of recently recognized adverse metabolic effects including osteoporosis, obesity, insulin resistance and lipid alterations. Recently, ADT has also been associated with greater risk for fractures, diabetes and cardiovascular disease. Recognition and prevention of these potential treatment-related harms are essential to promoting the health of prostate cancer survivors.

ADT increases the incidence of clinical fractures in prostate cancer survivors. All such men should be encouraged to take supplemental calcium ($\geq 1,200$ mg daily) and vitamin D (800–1,000 IU daily). We advocate the use of the online WHO/FRAX fracture risk tool (<http://www.shef.ac.uk/FRAX/index.htm>) to estimate fracture risk in individual patients and identify candidates for pharmacologic intervention. The results of recently completed large phase III fracture prevention studies (see Table 2) will help establish evidence-based guidelines for fracture prevention for men receiving ADT.

Although insulin resistance and changes in body composition are both substantial burdens to men receiving ADT and associated with increased risk of diabetes, effective management strategies have not yet been established. In men and women at high risk for diabetes in the general population, the Diabetes Prevention Trial found that physical activity and weight loss reduced the incidence of diabetes by 58% compared with controls. This was almost twice the reduction achieved with metformin.⁸⁶ A randomized trial of intensive lifestyle intervention in men treated with GnRH agonists is ongoing. This trial is designed to detect improvements in insulin sensitivity and markers of cardiovascular disease.

Cardiovascular disease and diabetes are two of the leading causes of non-cancer death among all patients with cancer⁸⁷ and are particular concerns among men treated with GnRH agonists. We believe the best available management strategy is to employ broadly accepted practice guidelines for patients in the general population, including recommendations for management of hyperlipidemia,⁷⁰ the detection and management of pre-diabetes and diabetes,⁷⁸ and primary and secondary prevention of cardiovascular disease.⁸⁸

Internists work with radiation oncologists, urologists and medical oncologists to promote the health of the growing population of medically vulnerable older men with prostate cancer. Survivorship research has defined many risks unique to this population. Awareness of the recently described adverse effects of GnRH agonists allows clinicians to educate, motivate and manage their patients to combat these changes. We anticipate that recently completed and ongoing trials will further guide our efforts to reduce treatment-related morbidity.

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