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Adverse Effects of Androgen Deprivation Therapy: Defining the Problem and Promoting Health Among Men with Prostate Cancer

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Abstract

Androgen deprivation therapy (ADT) plays a central role in the management of men with locally advanced, recurrent, and metastatic prostate cancer. Because most men diagnosed with prostate cancer will die of something other than their cancer, treatment-related adverse effects are highly relevant to their long-term health. Benefits of ADT in each clinical setting must be weighed against ADT-related adverse effects. ADT is detrimental to several metabolic end points and to bone health. ADT has been prospectively shown to cause decreased lean muscle mass, increased fat mass, weight gain, increased cholesterol and triglycerides, insulin resistance, and loss of bone mineral density. In population-based analyses it has been associated with an increased incidence of diabetes, clinical fractures, and cardiovascular disease. Data-driven recommendations for managing these adverse effects are needed. Currently the authors advocate the use of adapted practice guidelines developed to prevent diabetes, fractures, and coronary heart disease in the general population.

Keywords

Prostate cancer; survivorship; GnRH agonists; osteoporosis; diabetes; obesity; coronary heart disease

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Identify clinical scenarios in which androgen deprivation therapy (ADT) is most useful in the treatment of prostate cancer
- Describe the effects of ADT on body weight and lipid metabolism
- Specify the effects of ADT on glucose metabolism and the risk for coronary heart disease
- Treat osteoporosis associated with ADT effectively

Background

Prostate cancer is the most common cancer among men, with a median age at diagnosis of 68 years.[1] The 5-year relative survival rate for all men diagnosed with prostate cancer is 98.8%.[1] Among those who present with metastatic disease, median survival is 30 months[2,3] and almost 10% live 10 years beyond diagnosis.[4] Because men often live for years to decades with their cancer, treatment-related morbidity is an important concern.

Androgen deprivation therapy (ADT) is the most effective systemic treatment for prostate cancer. Whether accomplished through bilateral orchiectomies or treatment with a gonadotropin-releasing hormone (GnRH) agonist, ADT leads to severe hypogonadism. GnRH agonists, for instance, lower serum testosterone to median levels below 20 ng/dL.[5] In the United States, practice patterns favor GnRH agonists over orchiectomy because of their reversibility, ease of administration, and acceptability to patients. GnRH agonist treatment has become increasingly common across all ages, disease stages, and tumor grades (Figure 1).[6,7]

The benefits of ADT are well established in specific clinical settings. First, GnRH agonists improve disease-free and overall survival when administered in combination with external beam radiation therapy for locally advanced or high-risk nonmetastatic disease.[8,9] Second, ADT is the primary therapy for metastatic disease. With an objective response rate of more than 80% in that setting,[10,11] ADT reduces pain and produces a small improvement in overall survival.[12] Third, adjuvant ADT is associated with improved overall survival in men with nodal-metastases after prostatectomy and pelvic lymphadenectomy.[13] Patients and clinicians must weigh the benefits of ADT against treatment-related adverse effects. In these 3 clinical settings, the benefits of therapy are well established and generally favor the use of ADT.

ADT is often used in other common clinical settings with limited data on how it impacts clinical outcomes. Two particular clinical situations lead to treatment of a large number of men. First, regular prostate-specific antigen (PSA) testing after primary therapy can diagnose PSA-recurrence. Biochemical relapses are generally identified years before disease would be clinically evident or radiographically visible.[14] Although PSA-recurrent disease often leads to initiation and long-term maintenance of ADT, this practice has not yet been shown to affect

survival.[15] Second, some men with localized disease are treated with primary ADT rather than surgery or radiation. This has not been shown to improve survival.[16]

ADT is intended to cause severe hypogonadism. Currently, more than one third of the 2 million men with prostate cancer in the United States are treated with ADT.[17] The drastic reduction in serum testosterone also causes several undesirable changes. GnRH agonists have been shown to produce detrimental changes in body composition, lipid profile, insulin sensitivity, and bone mineral density. Men treated this way experience a greater incidence of diabetes,[17,18] fracture,[19] and likely coronary heart disease.[17,20] In sum, ADT worsens the burdens of several prevalent health problems.

Aggressive prostate cancer treatments prompted by early diagnoses have increased the burden of treatment on survivors. Systematic reviews of available data on ADT adverse effects are available.[21,22] This article presents a focused summary of the scope and severity of the metabolic and skeletal adverse effects of androgen deprivation, with particular focus on obesity and sarcopenia, insulin resistance and diabetes, cardiovascular disease, and osteoporosis and fractures.

Because these treatment-related hazards were described relatively recently, evidence-based guidelines for the management of ADT adverse effects do not yet exist. This article provides practical management recommendations drawn from available guidelines issued by the National Osteoporosis Foundation (NOF), American Diabetes Association (ADA), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and American Heart Association (AHA). Further efforts are needed to better define the optimal management of these adverse effects and to promote the health of men living with prostate cancer.

Obesity and Sarcopenia

Obesity is a highly prevalent problem in the general population. Currently, approximately 1 in 3 American men is obese (body mass index [BMI] $\geq$ 30.0 kg/m^2).[23] Because androgens support lean body mass over fat mass, androgen deprivation causes a shift in body composition. Specifically, prospective trials have found that the first year of ADT causes lean body mass to fall approximately 3%, fat mass to rise 10%, and weight to rise 2%.[24–26]

Cross-sectional imaging has shown that this ADT-associated redistribution of weight favors the accumulation of subcutaneous abdominal fat (Figure 2).[24,27] Significant increases in fat mass have been shown just 3 months after initiation of GnRH-agonist treatment.[28] In the general population, a large prospective cohort study showed that abdominal circumference was strongly associated with mortality even after adjustment for BMI.[29]

No evidence-based prevention or treatment strategies currently exist for ADT-associated changes in body composition. A study examining use of exercise randomized 155 men receiving ADT to either a control or treatment arm that featured resistance exercise 3 times a week.[30] Although the treatment cohort experienced significantly less fatigue, higher quality of life, and improved muscular fitness, body composition did not differ between the groups. Further work is needed to define effective strategies for managing ADT-associated changes in body composition.

Lipid Alterations

GnRH agonist treatment causes several changes in serum lipid profile. Triglycerides rise by approximately 26% and total cholesterol approximately 10%.[24,31,32] In addition, high-density lipoprotein (HDL) rises approximately 8% to 11%. The net effect of these changes on

cardiovascular risks is unknown. Significant changes can be observed within the first 3 months of treatment, with more modest subsequent change.[28,31]

In the general population, there is a continuous, graded relationship between serum cholesterol and cardiovascular mortality.[33,34] Robust data support the appropriate use of cholesterol-lowering drug therapy as primary prevention for heart disease. Adherence to the NCEP ATP III guidelines is the standard of care in the general population.[35] Diet and lifestyle changes are recommended as first-line interventions to achieve target low-density lipoprotein (LDL) concentration. If these fail to achieve target LDL, drug therapy with statins reduces all-cause mortality.[36] Among men receiving ADT, the authors recommend measurement of fasting lipoproteins at baseline, within 1 year of ADT initiation, and as clinically indicated thereafter.

Selective estrogen receptor modulators (SERMs) have been tested for their effects on bone mineral density (BMD) and fracture risk but also have been found to affect serum lipids. In a randomized, placebo-controlled phase III trial of toremifene for fracture prevention among men on ADT, planned interim analysis at 1 year showed that it decreased LDL and triglycerides and increased HDL relative to the placebo group.[37] The effect of toremifene or other SERMs on cardiovascular outcomes is not known.

Insulin Resistance and Diabetes

Insulin resistance is an independent risk factor for diabetes and cardiovascular disease. In the general population, the prevalence of insulin resistance is approximately 25%.[38,39] Prospective trials have shown that GnRH agonists decrease insulin sensitivity.[28,31,40] This adverse metabolic effect appears early; significant diseases in insulin sensitivity are observed in non-diabetic men within 12 weeks after ADT initiation.[28]

Insulin resistance and obesity are both associated with type 2 diabetes.[41] Given that insulin resistance emerges early in the course of GnRH agonist therapy, diabetes is a treatment-related concern. In the general population, diabetes is a substantial and rapidly growing burden. The incidence is now twice what it was 30 years ago[42] and is anticipated to continue to climb.[43] More than a quarter of the United States population is believed to have impaired fasting glucose. The 1999–2002 National Health and Nutrition Examination Survey estimated the prevalence of diabetes to be 6.5% diagnosed and another 2.8% undiagnosed.[44] Even before initiation of ADT, a large proportion of men have diabetes or prediabetes.

Two large population-based analyses reported that GnRH-agonist treatment is associated with greater incidence of diabetes. The first study examined 73,196 men in a Surveillance, Epidemiology and End Results (SEER)-Medicare database aged 66 years and older diagnosed with locoregional prostate cancer (Figure 3).[17] More than a third of that group (36%) received GnRH agonists and an additional 7% underwent bilateral orchiectomies (median follow-up, 4.55 years). The adjusted hazard ratio (HR) for a new diagnosis of diabetes was higher among men treated with a GnRH agonist (HR, 1.44; $P < .001$). An analysis of a Canadian database included nearly 20,000 men aged 66 years or older treated with either bilateral orchiectomies or 6 months or more of GnRH agonist.[18] When these men were matched with others not treated with ADT, a statistically significant ADT-associated elevation in the risk for diabetes was observed (HR, 1.16; 95% CI, 1.11–1.21).

The observed greater risk for diabetes in these analyses argues for diabetes screening among men on ADT. Diabetes is the sixth leading cause of death in the United States[45] and is considered an equivalent to coronary heart disease.[35] In the absence of evidence-based recommendations in this specific population, the authors recommend risk-adapted screening and intervention according to guidelines from the ADA.[46] Because insulin resistance emerges after just 3 months of GnRH agonist treatment, the authors recommend screening men at

baseline and again within 1 year for those treated with long-term ADT. Fasting plasma glucose and hemoglobin A1c are both reasonable screening tests.[41,47] Individuals with hemoglobin A1c between 6.0% and 6.5% or impaired fasting glucose (fasting glucose, 100–125 mg/dL) should be considered to be at high risk for developing diabetes and counseled to pursue 5% to 10% weight loss and 150 minutes or more per week of moderate physical activity.

Coronary Heart Disease

More than one fourth of all deaths in the United States are the result of heart disease. It is the most common cause of mortality and affects men proportionally more than women.[45] GnRH agonist therapy causes elevations in triglycerides and total cholesterol, weight gain, and insulin resistance. GnRH agonist therapy is also associated with increased incidence of diabetes in population-based studies. Although this combination of ADT-associated side effects suggests an elevated risk for cardiovascular disease, data on this topic have been inconsistent.

First, a large SEER-Medicare–based analysis of 73,196 men aged 66 years and older with prostate cancer identified significant GnRH agonist-associated elevations in risk for myocardial infarction (HR, 1.11; $P = .03$), sudden cardiac death (HR, 1.16; $P = .004$), and new diagnosis of coronary heart disease (HR, 1.16; $P < .001$; Figure 3).[17] Similarly, a second SEER-Medicare–based study of 23,000 men with prostate cancer found a 20% ADT-attributable rise in cardiovascular morbidity at 1 year.[20]

In contrast, a recently reported matched cohort analysis of approximately 20,000 men in an On-tario database found no association between ADT and acute myocardial infarction (HR, 0.91; 95% CI, 0.84–1.00).[18]

A smaller population-based observational study of 3262 men who had undergone prostatectomy for prostate cancer found that ADT was significantly associated with cardiovascular mortality, although only in the subset of men aged 65 years and older.[48] This analysis failed to validate baseline coronary artery disease and diabetes as risk factors for cardiovascular mortality. Finally, combined analysis of 3 randomized trials involving men with localized prostate cancer found that in the subset of men aged 65 years and older, 6 months of treatment with a GnRH agonist led to earlier onset of fatal myocardial infarction.[49] Some have called this conclusion into question primarily because of the exceedingly low number of events (16 in the control group and 18 in the ADT group).[50]

Three large randomized, controlled trials by the Radiation Therapy Oncology Group (RTOG) have been retrospectively analyzed for an association between neoadjuvant/concomitant/adjuvant ADT and cardiovascular mortality. These analyses have not found convincing evidence of an association.[51–53] Secondary analyses of a randomized controlled trial from the EORTC found no association between ADT and cardiovascular mortality. The RTOG and EORTC trials were randomized, featured large enrollments, and had long-term follow-up.

Data on ADT-attributable risk for cardiovascular events and mortality are inconsistent. Because prospective studies in the general population have convincingly shown that individuals with fewer known risk factors for cardiovascular disease have a lower incidence of heart disease and stroke,[54,55] the authors recommend emphasizing primary prevention in accordance with NCEP ATP III and the AHA guidelines (Table 1). According to those guidelines, primary prevention should feature universal tobacco cessation and appropriate management of hypertension. Low-dose aspirin is recommended for men with a 10% or greater 10-year risk for coronary heart disease. Lifestyle should feature weight control, regular physical activity, and low intake of saturated fat and cholesterol. If lifestyle fails to achieve target LDL, statins should be used as first-line drug treatment of hyperlipidemia.

Osteoporosis and Fracture Risk

Men commonly experience hip or vertebral body (Figure 4) fragility fractures with advancing age.[56] The consequences of osteoporosis are not confined to women, as one third of all hip fractures occur in men.[57] The 3 most common causes of osteoporosis in men are alcohol abuse, chronic glucocorticoids, and hypogonadism.[58]

Available evidence convincingly shows that ADT is detrimental to bone health. Prospective trials have shown that ADT causes accelerated bone turnover[59,60] and decreases BMD.[59–64] Retrospective population-based analyses have shown that ADT is associated with elevated fracture risk as a continuous function of treatment duration. Among more than 50,000 men with prostate cancer in a SEER-Medicare database, incidence of fracture 5 years after diagnosis of prostate cancer was higher among those treated with ADT (19.4% vs. 12.6%).[19] A separate but similar claims-based analysis also found a significant association between GnRH agonist treatment and clinical fractures (relative risk [RR], 1.21; $P < .001$).[65]

Bisphosphonates, including pamidronate,[66,67] zoledronic acid,[68,69] alendronate,[70] and risedronate,[71] have consistently been found to increase BMD and decrease markers of bone turnover among men during ADT. Notably, however, no bisphosphonate study has been large enough to evaluate impact on treatment-related fractures. Two additional classes of drugs, however, were recently found to prevent clinical fractures in randomized phase III studies exclusively involving men treated with ADT.

Receptor activator of nuclear factor κ-B ligand (RANKL) regulates osteoclast differentiation, function, and survival.[72–76] Denosumab is a fully human monoclonal antibody against RANKL that was studied for the prevention of osteoporotic fractures in a recently reported, randomized, placebo-controlled phase III trial that enrolled 1468 men receiving ADT and at high risk for fracture because of history of fracture, age of 70 years or older, or low BMD. When given subcutaneously every 6 months, denosumab significantly increased BMD at all measured sites and reduced the incidence of new vertebral fractures by 62% ($P = .006$), fractures at any site by 28% ($P = .10$), and multiple fractures at any site by 72% ($P = .006$).[77] Ongoing trials are evaluating denosumab for the prevention and treatment of prostate cancer bone metastases.

SERMs raloxifene and toremifene have both been shown to improve BMD and markers of bone turnover among men on ADT.[78,79] Toremifene was studied for its ability to prevent fractures in a randomized, placebo-controlled, phase III trial enrolling 1389 men aged 50 years or older treated with ADT and at elevated facture risk because either their age was 70 years or older or they had low BMD. The primary analysis was positive because the toremifene arm experienced fewer vertebral fractures (2.5% vs. 4.9%; RR, 0.50; $P < .05$ by modified intent to treat analysis).[80] The toremifene arm also had superior BMD (lumbar spine and hip), lower LDL, lower triglycerides, higher HDL, less breast pain, and less frequent hot flashes among men who had at least 6 hot flashes each day at baseline.

Accurate assessment of fracture risk is essential to guide clinicians to treat only those most likely to benefit from drug therapy to prevent fractures. Historically, risk assessment centered on dual-energy radiograph absorptiometry scan measurement of BMD. Reliance on this measurement alone, however, is inadequate because most fractures occur in men who do not have osteoporotic-range BMD.[81]

Screening and treatment recommendations can reasonably be drawn from the NOF guidelines for the general population (Table 2). Screening with BMD testing should be performed in high-risk populations, such as men receiving ADT. The authors recommend BMD testing at baseline, after 1 year of ADT, then every 2 years or as clinically indicated. Guidelines recommend that

all men aged 50 and older take supplemental calcium (≥ 1200 mg/d) and vitamin D (800–1000 IU/d). They also recommend drug therapy for those who have low T-score (−1.0 to −2.5) and a 10-year risk for hip fracture of at least 3%, or at least 20% for any osteoporosis-related fracture, according to the United States–adapted Fracture Risk Assessment Tool (FRAX) model.[82] Existing data support ADT as a cause of secondary osteoporosis when using the FRAX tool.

FRAX is an online fracture risk-assessment tool (http://www.shef.ac.uk/FRAX/) that uses age, BMI, and a group of clinical risk factors to estimate 10-year fracture risks in individual patients.[83] Meta-analyses have shown that each risk factor independently contributes to risk. These risk factors include family history of hip fracture, personal history of fragility fracture, ongoing tobacco smoking, history of chronic glucocorticoid use, daily alcohol consumption of 3 units or more, rheumatoid arthritis, and other causes of secondary osteoporosis.[84–91] The algorithm can be used with or without BMD data.

Conclusions and Recommendations

Because prostate cancer–specific mortality is remarkably low overall, many men live for years to decades with their disease. Given that the disease process is often chronic, treatment-related adverse effects are relevant to the general health of these men. ADT is commonly prescribed and is supported by strong evidence of benefit in several clinical settings. However, it is now known to cause gain of fat, loss of muscle, weight gain, insulin resistance, undesirable changes in the lipid profile, and loss of BMD. It is consequently associated with increased risk for diabetes, fractures, and likely coronary heart disease. The potential for therapeutic benefits and the potential for harm must each be considered.

ADT causes adverse changes in body composition and the development of insulin resistance. Although these effects were prospectively shown, effective strategies for prevention and treatment have not been developed. This is an important un-met clinical need. Some insight was provided by the Diabetes Prevention Trial in the general population. Physical activity and weight loss led to a 58% reduction in the incidence of diabetes relative to control subjects; far greater than the reduction provided by metformin.[92] Multiple ongoing randomized trials are anticipated to provide additional information about the potential value of lifestyle interventions in this clinical setting.

Coronary heart disease and type 2 diabetes cause an enormous amount of morbidity and mortality in the general population and are among the most common causes of noncancer death in patients with cancer.[93] Given that ADT worsens several markers of risk for heart disease and is associated with an increased incidence of diabetes, the authors believe that proactive screening and interventions are essential. Practice guidelines for the general population provide substantial guidance for the management of hyperlipidemia,[35] the detection and management of prediabetes and diabetes,[46] and primary and secondary prevention of cardiovascular disease.[94] Because ADT has been clearly associated with elevated fracture risk, men receiving ADT should be carefully evaluated. The authors recommend using the NOF guidelines for screening and treatment of the general male population. Regardless of risk, all men should be encouraged to take supplemental calcium (≥ 1200 mg/d) and vitamin D (800–1000 IU/d). Drug therapy should be started if the T-score is −2.5 or less or if the patient has a history of hip or vertebral fracture. Additionally, drug therapy should be started for those who have a low T-score (−1.0 to −2.5) and a 10-year risk for hip fracture of 3% or greater, or 20% or greater for major osteoporotic fracture according to the United States–adapted FRAX model.[82] The authors encourage the use of the WHO/FRAX online fracture risk assessment tool (http://www.shef.ac.uk/FRAX/index.htm) in accordance with the NOF guidelines to risk-stratify patients and identify men likely to benefit from drug therapy. Two recently-reported

phase III trials provide level 1 evidence that denosumab and toremifene are each effective for fracture prevention.

Prostate cancer survivors represent a large and growing population of medically vulnerable older men. Because many of them receive long-term treatment with ADT, they are at elevated risk for fractures, diabetes, and likely cardiovascular disease. Careful attention to screening and treatment guidelines can likely improve overall health within this population. Further clinical investigation is needed to develop strategies to better combat the treatment-related hazards.

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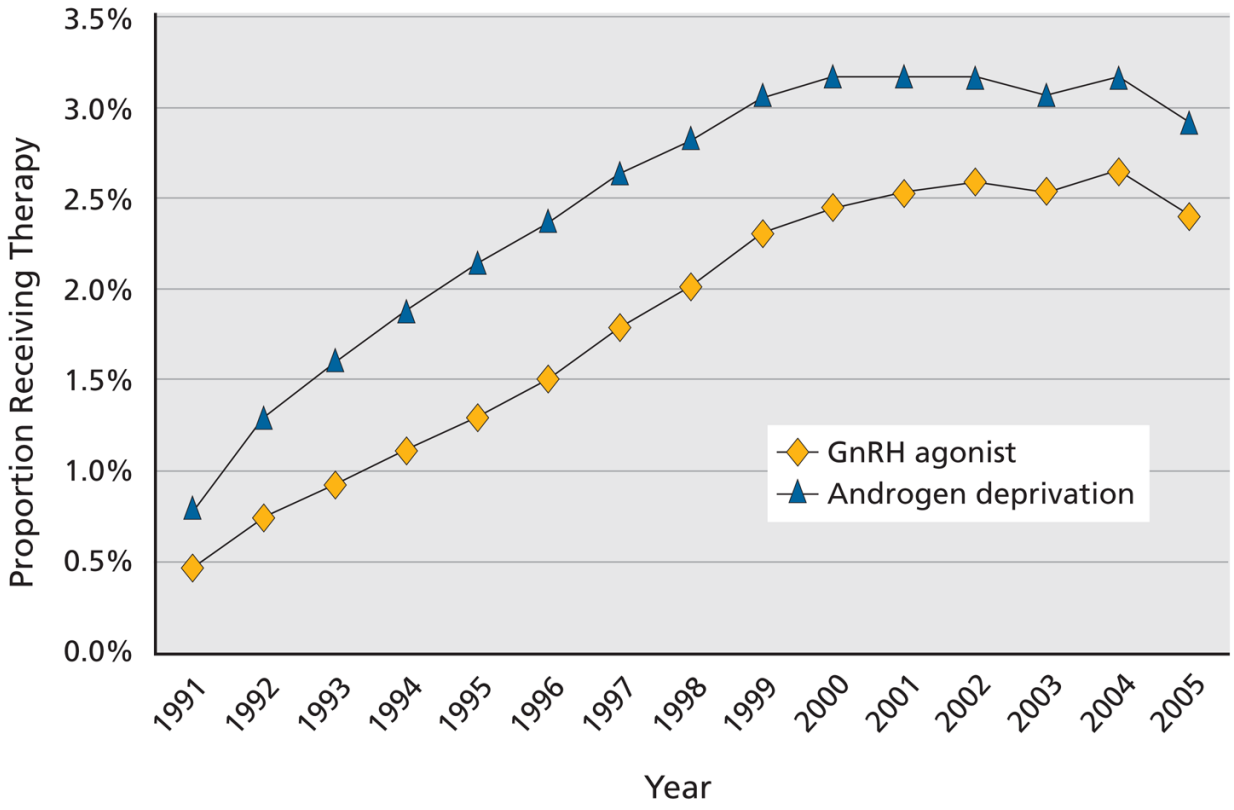

Figure 1.
Rising prevalence of androgen deprivation therapy (ADT) in the United States. The estimated prevalence of ADT among male Medicare beneficiaries in the United States rose steadily during the 1990s. GnRH agonist use accounts for most ADT. By 2000 to 2002, 44.8% of men with incident prostate cancer were exposed to ADT during the first year after diagnosis. From Gilbert SM, Kuo YF, Shahinian VB. Prevalent and incident use of androgen deprivation therapy among men with prostate cancer in the United States. Urol Oncol 2009; in press.

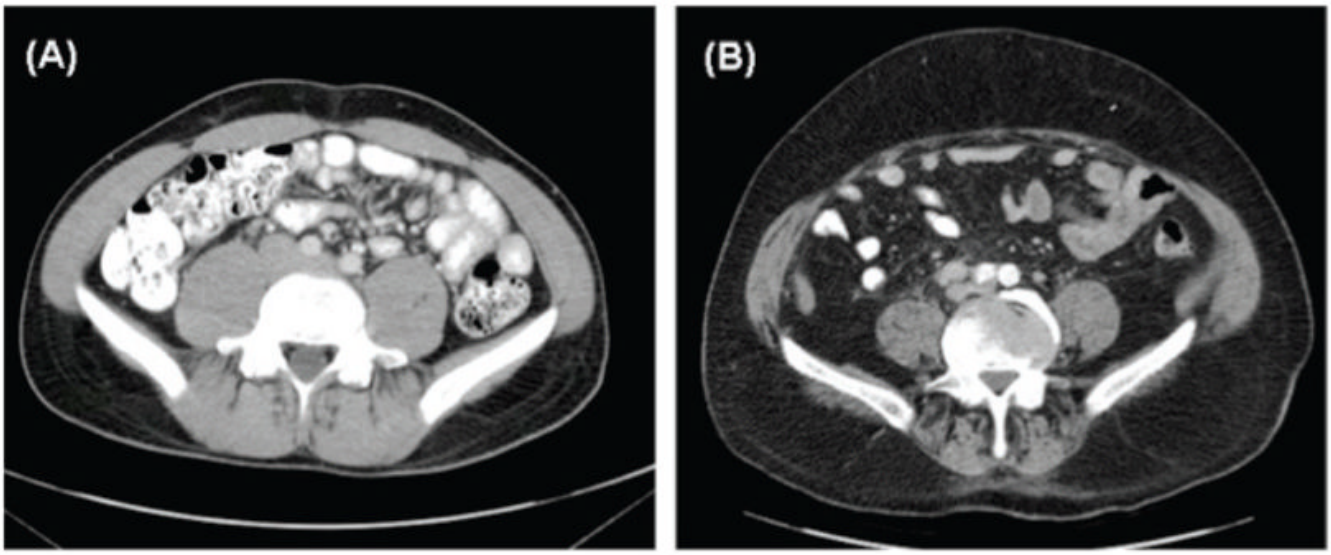

Figure 2.

Androgen deprivation therapy (ADT)–related sarcopenic obesity. Gonadotropin-releasing hormone (GnRH) agonists cause the accumulation of abdominal subcutaneous fat and loss of lean muscle mass. Cross sectional images of (A) a young healthy man and of (B) a man with ADT-associated sarcopenic obesity caused by long-term GnRH agonist therapy. Panel B is notable for a collection of subcutaneous fat and sparse abdominal and paraspinal musculature. From Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol 2009;181:1998–2006; with permission.

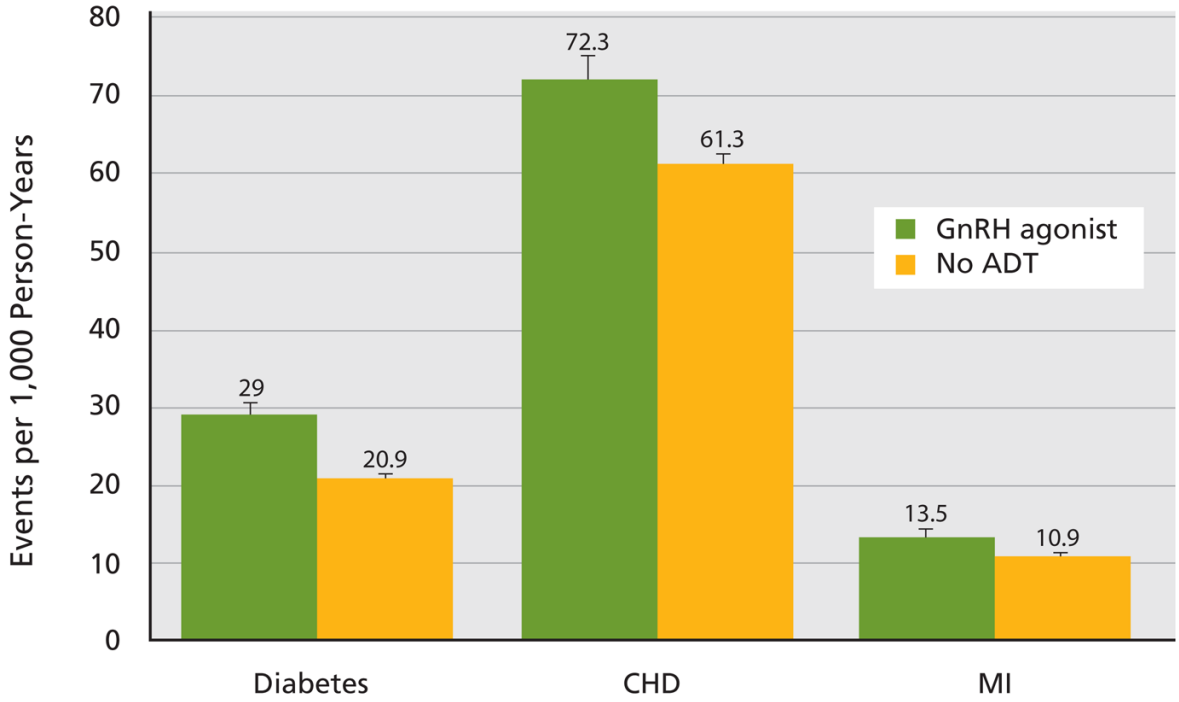

Figure 3.

Unadjusted event rates among men with prostate cancer. Unadjusted event rates (per 1,000 person-years) for diagnosis of diabetes, coronary heart disease (CHD), and myocardial infarction (MI) are from a database analysis of more than 73,000 Medicare enrollees with prostate cancer. Diabetes, CHD, and MI were all significantly more common in men treated with a gonadotropin-releasing hormone (GnRH) agonist ($P < .001$ for all 3 comparisons). Error bars denote upper end of the 95% CI.

Data from Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–4456.

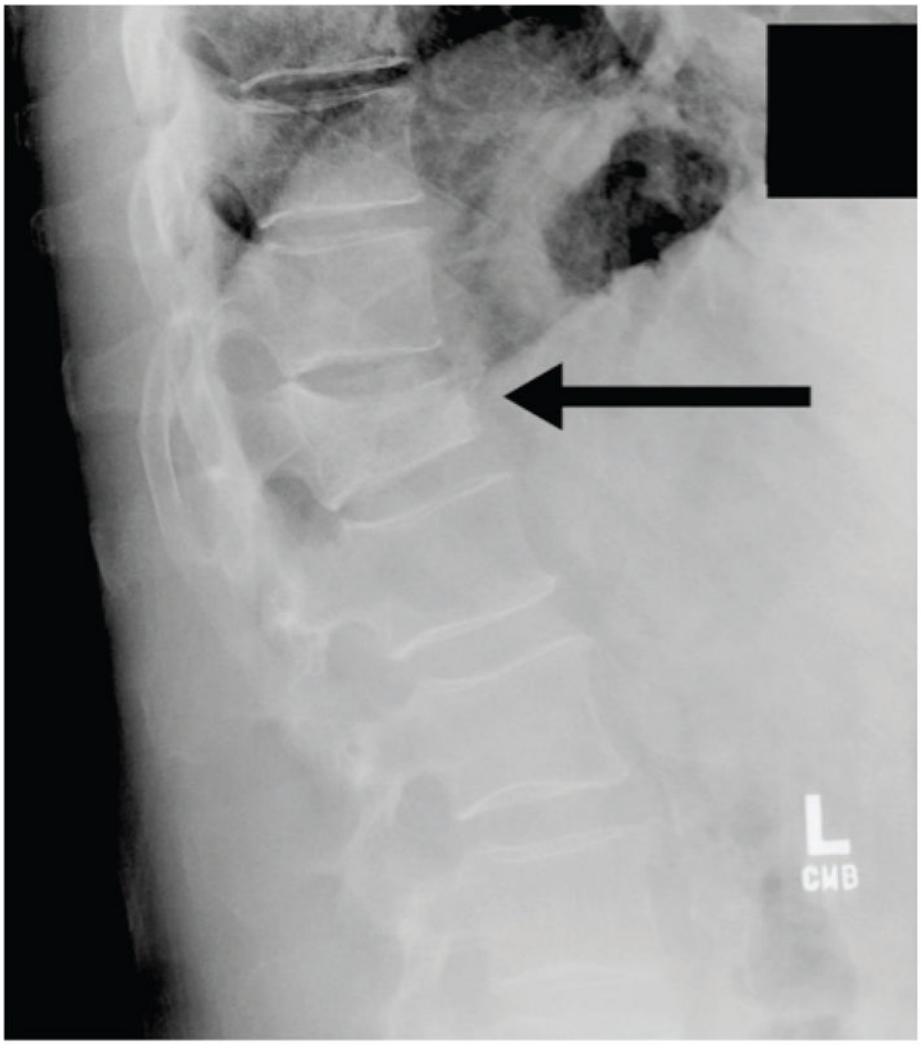

Figure 4.
Vertebral compression fracture. Vertebral body compression fracture (arrow) is a potential complication of therapy-related osteoporosis. These fractures can lead to pain, loss of height, and decreased quality of life. Denosumab and toremifene have now been shown in randomized phase III trials to significantly reduce the incidence of vertebral fractures among men treated with ADT.

Table 1

Metabolic Adverse Effects: Recommendations for Screening and Treatment

Hyperlipidemia and CHD Risk Factors

Screening:

- Fasting lipoproteins at baseline, after 1 year of ADT, and then 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 = 10%
- Statins are first-line treatment for hyperlipidemia if lifestyle interventions fail to achieve target LDL

Diabetes and Prediabetes

Screening:

- Consider testing in all men treated with ADT at baseline and yearly thereafter
- Recommended tests: hemoglobin A1c or FPG
- Diabetes: hemoglobin A1c = 6.5% or FPG = 126 mg/dL
- High risk to develop diabetes (prediabetes):
  - Hemoglobin A1c 6.0%–6.5%
  - IFG = FPG 100–125 mg/dL

Treatment of high-risk individuals:

- For those identified with prediabetes, identify and 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 minutes of moderate physical activity per week

Recommendations are adapted for the clinical situation from practice guidelines published by the NCEP ATP III, the AHA, and the American Diabetes Association (ADA).

Abbreviations: ADT, androgen deprivation therapy; AHA, American Heart Association; CHD, coronary heart disease; FPG, fasting plasma glucose; IFG, impaired fasting glucose; LDL, low-density lipoprotein; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 2

Fracture Risk: Recommendations for Screening and Treatment

Screening:

- Estimate fracture risk using online WHO/FRAX fracture risk assessment tool
- BMD testing for all men treated with ADT given the NOF recommendation for adults receiving a medicine associated with bone loss
- Test BMD at baseline, repeat after 1 year of ADT, and repeat as clinically indicated

Treatment:

- Supplemental calcium (≥ 1200 mg/d) and vitamin D (800–1000 IU/d) for all
- Consideration of drug treatment if age ≥ 50 years and any of the following:
  - 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 either of the following by US-adapted WHO algorithm:
    - 10-year probability of a hip fracture ≥ 3% or
    - 10-year probability of a major osteoporosis-related fracture ≥ 20%

Recommendations are adapted for the clinical situation from published NOF practice guidelines.

Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density; NOF, National Osteoporosis Foundation.