

Endocrine Complications of Androgen-deprivation Therapy in Men With Prostate Cancer

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Keywords

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Abstract: Prostate cancer is one of the most common cancers in men. Androgen-deprivation therapy (ADT) is often employed in the treatment of recurrent and metastatic prostate cancer. Although its use as an adjuvant therapy has resulted in improved survival in a subset of patients, ADT also results in a multitude of endocrine complications. These complications affect quality of life and sense of well-being in these men. Some of the endocrine complications of ADT such as osteoporosis, sexual dysfunction, hot flashes, gynecomastia, and adverse body composition are well-known. Recently, insulin resistance, hyperglycemia, and metabolic syndrome have emerged as metabolic complications of castration and may be responsible for increased cardiovascular mortality in this population. In this article, we provide a detailed review of the endocrine complications of ADT, touching upon management strategies where applicable.

Prostate cancer (PC) is one of the most common malignancies in men. Statistics suggest that its incidence is on the rise, primarily due to increased detection from widespread prostate-specific antigen (PSA) screening.¹ It was in 1941 that Huggins and colleagues described the androgen-dependence of PC.² Androgen-deprivation therapy (ADT) has in recent decades become a common mode of therapy in men with recurrent or metastatic PC. The modalities of ADT are surgical (orchiectomy) or medical (gonadotropin-releasing hormone [GnRH] agonists or antagonists), with most patients choosing the medical option. The adjuvant use of ADT in men with locally advanced PC has resulted in decreasing recurrence and improved survival.³ A recent meta-analysis also found ADT to be effective for palliation in patients with advanced PC and to improve survival in high-risk patients when used in combination with radiation therapy.⁴ The aim of ADT is to achieve serum testosterone levels as low as possible, with current guidelines recommending levels below 50 ng/dL (1.7 nmol/L).⁵

Male hypogonadism (of any etiology) is associated with numerous adverse effects. These include decreased libido, impotence,

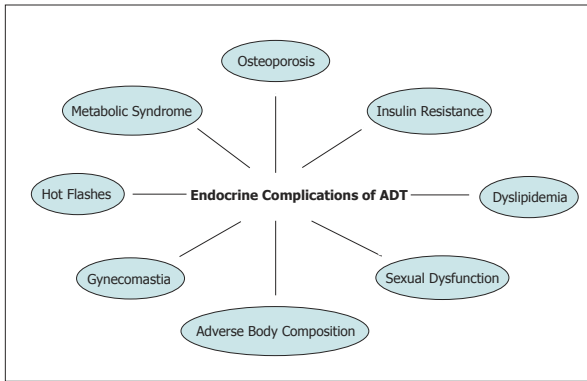


Figure 1. Endocrine complications of androgen-deprivation therapy (ADT).

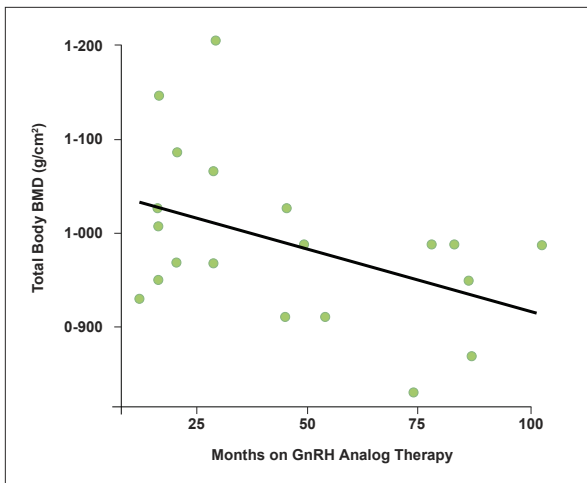


Figure 2. Association between BMD and ADT duration.⁹

ADT = androgen-deprivation therapy; BMD = bone mineral density; GnRH = gonadotropin-releasing hormone.

decreased lean body mass (LBM) and muscle strength, increased fat mass, decreased quality of life, and osteoporosis.⁶ Although these complications of hypogonadism are well known, previously unknown complications have recently been discovered. Recent population studies have shown that low testosterone levels in men are an independent risk factor in the development of diabetes and metabolic syndrome.^{7,8} Because men undergoing ADT have profound hypogonadism, they are at higher risk of developing the above-mentioned complications.

In this review, we summarize the known and newly emerging endocrine complications of ADT in men with PC (Figure 1). Where applicable, we also propose screening and management strategies for some of these complications.

Decreased Bone Mineral Density

Osteopenia and osteoporosis are well-recognized complications of hypogonadism. Men treated with ADT frequently experience bone loss. In cross-sectional studies, men undergoing ADT have significantly lower bone mineral density (BMD) at all skeletal sites compared to disease- and age-matched controls.^{9,10} They have higher concentrations of urinary N-telopeptides, a marker of bone resorption,⁹ and their average BMD is 6.5–17.3% lower than age-matched eugonadal counterparts.¹⁰ Furthermore, the severity of bone loss increases with the duration of ADT (Figure 2).⁹ Longitudinal studies of ADT showed that the decline in BMD is seen as early as 6 months into therapy. Mean lumbar spine and femoral neck BMD decreased by 3% and 2.7% at 6 months, 4.6% and 3.9% at 12 months, and 7.1% and 6.6% at 18 months, respectively.¹¹ Another report showed mean bone loss of 3.3% at total hip and 5.3% at distal radius after 1 year of ADT.¹² This issue is compounded by the fact that over 63% of men have low BMD on dual-energy x-ray absorptiometry (DEXA) scan even before starting ADT.¹³ Because spinal osteophytes and calcification of paravertebral structures (including large vessels) falsely elevate BMD on DEXA, this prevalence is even higher on quantitative computed tomography (QCT). Decreased vitamin D and calcium intake and age-related hypogonadism are the main etiologies of low BMD in hormone-naïve men.¹⁴

As low BMD entails a risk for fractures, they are expected in this population. Patients on ADT are three times more likely to experience fractures compared to age-matched controls.¹⁵ Men undergoing orchiectomy have a 7-year cumulative fracture incidence of 13.6% versus 1.1% in men who are not androgen-deprived.¹⁶ A recent retrospective analysis of 50,613 men showed fracture rates of 19.4% in men receiving ADT and 12.6% in men not on ADT.¹⁷ This study also showed that the number of doses of GnRH agonist given correlated with the subsequent risk of fracture. The relative risk of fracture was 1.45 and 1.54 among patients treated with GnRH agonist and orchiectomy, respectively. Slender (body mass index [BMI] <25 kg/m²) white men are at greatest risk of fracture.¹⁸ Because ADT also results in decreased LBM and muscle strength,⁹ men may also be predisposed to falls that may result in fracture. As a history of fracture is an independent negative predictor of survival in men with PC,¹⁹ preservation of bone health in this population is paramount.

Fortunately, prevention and treatment of osteoporosis in this patient population can be achieved by various agents, the most potent being bisphosphonates. A recent open-label study randomized 47 hormone-naïve men with locally advanced or recurrent PC to receive GnRH

agonists alone or GnRH agonists plus the second-generation bisphosphonate pamidronate (Aredia, Novartis) 60 mg intravenously every 12 weeks for 48 weeks.²⁰ Men not receiving bisphosphonates experienced a significant decline in spinal and hip BMD, but bone loss was prevented in the pamidronate group. A randomized, double-blind crossover study of 21 men with metastatic PC treated with ADT and a single intravenous infusion of 90 mg pamidronate or placebo resulted in a 7.8% increase in mean lumbar spine BMD and a 2% increase in femoral neck BMD at 6 months after pamidronate administration, whereas men lost bone while on placebo.²¹ Another prospective study randomized 106 men about to begin ADT to the third-generation bisphosphonate zoledronic acid (Zometa, Novartis) 4 mg intravenously every 3 months or placebo and followed them for 12 months.²² Men on zoledronic acid experienced a significant increase in spinal and hip BMD, whereas the bone loss continued in the placebo group. Recently, selective estrogen receptor modulators have been used in men undergoing castration. A recent 12-month trial of raloxifene (Evista, Eli Lilly) 60 mg/day in men receiving GnRH agonists resulted in a significant decrease in markers of bone turnover and a significant increase in hip BMD, whereas the control group showed continuous decline in BMD.²³ Though the studies using bisphosphonates and raloxifene are positive, fracture data are not yet available and are eagerly awaited.

Despite the fact that medications are available to prevent or treat osteoporosis, the majority of the patients undergoing ADT are neither screened nor treated for it. A recent retrospective review showed that 75% of men on ADT had either osteoporosis or osteopenia and only 8.7% had received a DEXA scan.²⁴ Similarly, just 5% of men were on a bisphosphonate and less than 10% were prescribed calcium or vitamin D supplementation. This suggests that men on ADT are not aggressively screened for bone loss.

Management of men on ADT requires a multidisciplinary approach, with collaboration between oncologists, urologists, endocrinologists, and internists.²⁵ Prior to initiation of ADT, secondary causes of male osteoporosis should be identified (Table 1) and treated (except hypogonadism). Ideally, all men should be screened for osteoporosis with a DEXA scan or QCT. The DEXA scan should be performed at all sites (including distal radius) because spinal BMD alone may not be reliable in elderly men. Though QCT is more accurate in determining spinal trabecular bone mass, it is not widely available. Markers of bone resorption should be measured at baseline and during the course of ADT. All patients should take calcium 1,500 mg/day and vitamin D 800 IU/day and be encouraged to perform weight-bearing exercises. In men with existing osteopenia or osteoporosis at baseline, treatment

Table 1. General and ADT-specific Risk Factors for Osteoporosis in Men

General Risk Factors
<ul style="list-style-type: none"> • Hypogonadism • Thyrotoxicosis • Hyperparathyroidism • Vitamin D deficiency • Hypercalciuria • Medications (glucocorticoids, antiepileptics, long-term heparin) • Smoking • Alcoholism • Family history of osteoporosis • Immobilization
Risk Factors Already Identified in Men on ADT
<ul style="list-style-type: none"> • White race • Body mass index <25 kg/m² • Duration of ADT

ADT = androgen-deprivation therapy.

with bisphosphonates should be initiated. Although long-term efficacy and fracture data are needed, administration of bisphosphonates has resulted in a significant increase in BMD at all sites. A strategy for following the bone health of patients receiving ADT is summarized in Figure 3. Lastly, guidelines for the prevention and treatment of osteoporosis in men on ADT need to be developed to guide the physicians caring for these patients.

Changes in Body Composition

Male hypogonadism results in a decline in LBM and an increase in fat mass, and testosterone replacement reverses this unfavorable body composition.²⁶ Both cross-sectional and longitudinal studies have confirmed that men undergoing ADT have this adverse profile. A cross-sectional study showed that men undergoing ADT (duration 12–101 months) had increased fat mass in the trunk and all extremities (measured by DEXA) compared to eugonadal men with PC not undergoing ADT (these men had undergone prostatectomy and/or radiation therapy) and age-matched eugonadal controls.⁹ A longitudinal study of ADT in 22 men newly diagnosed with PC showed an increase in fat mass of 1.7% and a decrease in LBM of 1.7% at 3 months.²⁷ These measures were obtained with bioelectric impedance analysis. These findings were confirmed by a long-term prospective study in which 40 men were followed for 48 weeks.²⁸ As a result of ADT, both average body weight and BMI increased by 2.4%. At the end of the study, body fat mass had increased by 9.4% and LBM decreased by 2.7%. The cross-sectional area

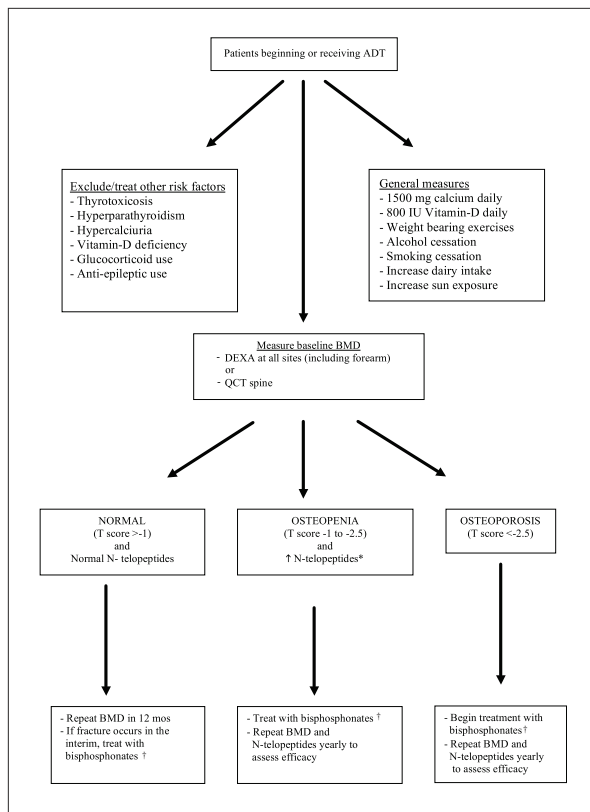


Figure 3. Strategy for the prevention and treatment of bone loss in men undergoing ADT.²⁵

* Secondary to ADT only and after exclusion/treatment of other causes (including bone metastases).

† Zoledronic acid and pamidronate have shown benefit (trials of oral bisphosphonates are ongoing).

ADT = androgen-deprivation therapy; BMD = bone mineral density; DEXA = dual-energy x-ray absorptiometry; QCT = quantitative computed tomography

of the abdomen increased by 3.9% and this increase was mainly due to increase in subcutaneous fat with no major changes in intra-abdominal fat.

Only limited studies have measured muscle strength in this patient population. We have previously reported that men undergoing ADT have reduced upper body strength compared to men with PC not undergoing ADT.⁹ Although lower body strength was also decreased in these men, the results did not reach statistical significance. These studies clearly demonstrate that ADT results in an unfavorable body composition. This decline in LBM and muscle strength may result in increased frequency of falls in this population. Because these men have low bone mass, falls may lead to fractures.

Insulin Resistance, Hyperglycemia, and Metabolic Syndrome

In recent years, it has become evident that one complication of hypogonadism is insulin resistance and type-2 diabetes. Epidemiologic studies have shown that low testosterone levels in men predict the development of insulin resistance, type-2 diabetes, and metabolic syndrome.^{7,29,30} Studies have confirmed a direct relationship between serum testosterone concentration and insulin sensitivity.³¹ Interventional studies have also shown that testosterone replacement in obese men improves insulin sensitivity.³² Hence, men undergoing ADT with castrate levels of androgens are at particular risk of developing these metabolic complications. This topic needs to be addressed in patients with PC, as reports show that noncancer-related deaths now exceed cancer-related mortality in men with PC, with cardiovascular disease being the single most common cause.³³ Hence, it is conceivable that this high incidence of cardiovascular problems may be more prevalent in men on ADT. Thus, these metabolic complications deserve exploration.

The issue has been evaluated in several cross-sectional and short-term longitudinal studies. A prospective study of 22 men with PC undergoing ADT showed a significant increase in serum insulin levels, from 11.8 mU/L at baseline to 19.3 mU/L at 3 months of ADT; however, there was no significant change in plasma glucose levels.²⁷ Another 3-month prospective study showed that ADT results in a 63% increase in fasting insulin levels without any changes in fasting glucose.³⁴ A recent 12-week prospective study using combined androgen blockade showed a 26% increase in insulin from baseline, suggesting insulin resistance.³⁵ Interestingly, this study also showed a significant increase in glycosylated hemoglobin; however, there was no significant increase in glucose values. These observations suggest that insulin resistance (manifested by hyperinsulinemia) develops within a few months of initiating androgen deprivation; however, this hyperinsulinemia is sufficient to prevent the development of diabetes.

We recently conducted a cross-sectional study to evaluate the long-term metabolic complications of ADT. We evaluated a total of 53 men, 18 with PC undergoing ADT for at least 12 months prior to the onset of the study (ADT group), 17 who were age-matched and eugonadal with nonmetastatic PC who were postprostatectomy and/or postradiotherapy and were not androgen-deprived (non-ADT group) and 18 age-matched eugonadal controls (control group).³⁶ None of the men had a known

history of diabetes mellitus. The mean duration of androgen deprivation in the ADT group was 45 months (range 12–101 months). The evaluation of the non-ADT group allowed us to account for the influence of PC on any of these metabolic parameters, and the control group was recruited to account for insulin resistance that occurs with aging. We found that men in the ADT group had significant hyperinsulinemia and insulin resistance (measured by homeostasis model of assessment of insulin resistance) compared to the other two groups. Importantly, the key finding of the study was the prevalence of hyperglycemia in the ADT group. The mean glucose in the ADT group was 131 ± 7.43 mg/dL compared to 103 ± 7.42 mg/dL and 99 ± 7.58 mg/dL in the non-ADT and controls groups, respectively (Figure 4). Interestingly, 44% of men in the ADT group had fasting glucose levels over 126 mg/dL (one criterion for the diagnosis of diabetes mellitus) compared to 12% and 11% in the non-ADT and control groups, respectively (Figure 5).³⁶ We suggested that the higher prevalence of hyperglycemia in the ADT group was due to the longer duration of ADT compared to previous reports. A 6-month prospective study of 49 men undergoing ADT also showed significant increase in fasting glucose; however, serum insulin levels were not checked in this study.³⁷ Hence, it can be concluded that insulin resistance develops within a few months after initiation of ADT, but the resulting hyperinsulinemia prevents the development of hyperglycemia. However, this hyperinsulinemia ultimately fails to control glucose levels in men on prolonged treatment, resulting in hyperglycemia or frank diabetes.

In the past decade, a great deal of work has been done on the association of metabolic syndrome with various cardiovascular endpoints. According to the Adult Treatment Panel-III criteria,³⁸ a male is considered to have metabolic syndrome if he has three of the following five criteria: fasting plasma glucose level over 110 mg/dL, serum triglyceride level at least 150 mg/dL, serum high density lipoprotein (HDL) level below 40 mg/dL, waist circumference over 102 cm, and blood pressure of at least 130/85 mm Hg. Subjects on antihypertensives and lipid-lowering medications are also occasionally classified as positive for the respective criterion. Recently, male hypogonadism has emerged as an independent risk factor in the development of metabolic syndrome. Cross-sectional studies showed that men with low testosterone levels have a higher prevalence of metabolic syndrome after adjusting for confounders.⁸ Similarly, longitudinal studies indicated that lower testosterone levels in men independently predict the development of metabolic syndrome.³⁰ We recently performed a cross-sectional study to evaluate the prevalence of metabolic syndrome in men with PC undergoing long-term ADT and compared it with age- and

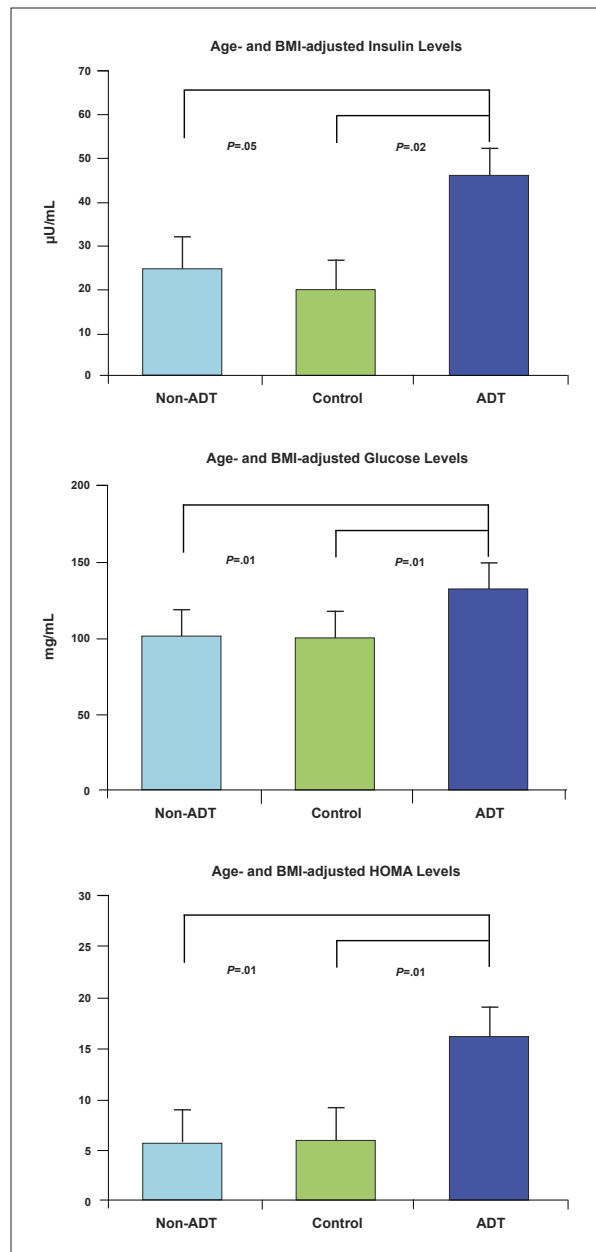


Figure 4. Fasting insulin, glucose, and HOMA_{IR} levels in men undergoing long-term ADT (comparison is made to eugonadal non-ADT group and age-matched eugonadal controls).³⁶

ADT = androgen-deprivation therapy; BMI = body mass index; HOMA_{IR} = homeostasis model of assessment of insulin resistance

disease-matched controls.³⁹ We found that 55% of men in the ADT group had metabolic syndrome, compared to 22% and 20% of men in the non-ADT and control groups, respectively. Hyperglycemia and abdominal obesity were the major determinants of the higher prevalence of metabolic syndrome in this group.

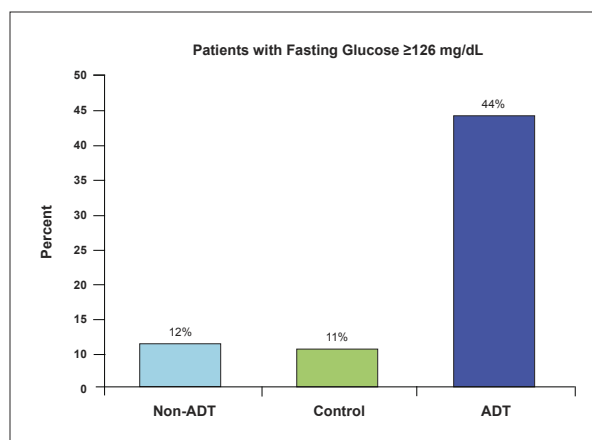


Figure 5. A comparison of the prevalence of fasting glucose value >126 mg/dL (a criterion for the diagnosis of diabetes) in the three groups.³⁶

ADT = androgen-deprivation therapy.

Based on these observations, long-term prospective studies are needed to determine the time of onset of various metabolic alterations in men undergoing ADT. These studies should be followed by interventional studies to treat insulin resistance and metabolic syndrome in this patient population. We currently recommend that men receiving ADT for at least 12 months be screened for diabetes by measuring fasting glucose values (or in some cases performing an oral glucose tolerance test).

Dyslipidemia

Hyperlipidemia is a known risk factor for cardiovascular disease. Recent epidemiologic research suggests that low serum testosterone levels in men are associated with an adverse lipid profile, especially elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.^{8,40} Furthermore, testosterone replacement in hypogonadal men has resulted in an improvement in lipid profile.⁴¹ The effect of ADT on lipid profiles in men with PC has been evaluated in both cross-sectional and prospective trials. A recent cross-sectional study evaluated lipid profiles of 16 men undergoing long-term ADT (at least 12 months) and compared it with two control groups: 14 age-matched eugonadal men with PC who had previously undergone local therapy and 14 eugonadal controls.⁴² None of the men in the study had known diabetes or dyslipidemia (and none was on antilipid medications). The study found that men on ADT had significantly higher fasting levels of total and LDL cholesterol compared to eugonadal controls. Prospective studies have revealed similar information. A prospective study of 16 men undergoing short-term (3 months) ADT resulted

in a significant increase in total and HDL cholesterol, whereas no changes were seen in LDL cholesterol and triglyceride levels.³⁴ Similarly, a long-term prospective trial of 40 men undergoing ADT for 48 weeks showed increases of 9%, 7.3%, and 26.5% in total cholesterol, LDL cholesterol, and triglycerides, respectively.²⁸ However, HDL cholesterol also increased by 11.3%. Another 6-month prospective study of 49 men showed a significant increase in total cholesterol, whereas no effects were seen on other lipid parameters.³⁷ However, these findings are not universal, and a prospective study of 22 men did not show any change in lipid profiles after 3 months of ADT.²⁷

In summary, ADT in men with PC leads to an increase in total cholesterol, LDL cholesterol, and triglycerides. In some studies, HDL cholesterol is also increased. Hence, the long-term cardiovascular consequences of these changes in lipid profiles are currently unknown and will be clarified only by conducting long-term follow-up studies. We currently recommend that baseline lipid profiles be measured in all patients with PC who are starting ADT, with regular follow-up to evaluate the development of dyslipidemia. A low-saturated fat diet and exercise should be emphasized. Initiation of cholesterol-lowering medications may be warranted in patients whose lipid profiles are adversely affected by ADT.

Hot Flashes

Although not life-threatening, hot flashes in men receiving ADT can significantly affect quality of life. Hot flashes, which are a manifestation of vasomotor instability, are generally described as a sudden perception of heat located within the upper body and can be accompanied by a change in skin color to pink or red, a feeling of warmth in the arms and soles, or sudden sweating (which may be accompanied by chills), lasting for seconds to hours.⁴³ Hot flashes can be mild or severe, the latter can be incapacitating and could result in the inability to work or function normally. Some men also experience psychological consequences of hot flashes including anxiety, agitation, and impaired cognition.

The exact pathophysiology of these hot flashes remains elusive. However, it is believed that the main etiology of these symptoms in men is the same as in postmenopausal women (ie, deficiency of estrogen). Indeed, estrogen is well-known to exert direct, nongenomic effects on the blood vessels.⁴⁴ Some have speculated that the decline in estradiol results in changes in the hypothalamic “thermoregulatory zone,” which triggers the heat-loss mechanism, resulting in a hot flash.⁴⁵ The phenomenon of hot flashes in men is not limited to subjects undergoing ADT. Even men who suffer from mild hypogonadism (of any etiology) also experience hot flashes. One example is elderly

men undergoing age-related decline in testosterone levels, also called “andropause” or “late-onset hypogonadism.”⁴⁶ In men, estradiol is mainly produced via aromatization of testosterone; thus, estradiol levels also decline in hypogonadal men. However, because men undergoing ADT experience an abrupt and significant decline in testosterone (and estradiol) levels, the symptoms experienced by these men are drastic and more pronounced. The evidence that estradiol is the main culprit in the pathophysiology of hot flashes comes from the fact that treatment with estradiol (without testosterone replacement) leads to resolution of these hot flashes.

Hot flashes in men receiving ADT are common. Recently, 55 patients with PC undergoing ADT were surveyed to examine the influence of hot flashes on quality of life.⁴⁷ Among these men, 15 received ADT only and 40 men were on combined androgen blockade. Mean duration of ADT was 21 months. Hot flashes were documented in frequency and severity (mild, moderate, and severe). About 58% of the men suffered from hot flashes, resulting in a deterioration in physical well-being (as measured by a quality-of-life questionnaire). This study showed that hot flashes adversely influence patients’ physical status and quality of life. Another study evaluated the prevalence and duration of hot flashes after surgical or medical castration in men with PC.⁴⁸ The evaluation was performed using a questionnaire inquiring about vasomotor symptoms. Hot flashes were reported by 68% of the subjects. About 70% of these symptomatic men had flashes even 5 years into treatment, and only 30% of men reported relief 5 years after ADT initiation. This study disproved the notion that hot flashes disappear with time and showed that they may persist long after castration. Indeed, in our group of men undergoing long-term ADT (12–101 months), hot flashes were present in 95% of the subjects compared to no symptoms in the age- and disease-matched controls (Basaria et al, unpublished observations, 2002).

Recently, the role of estrogen as a means of castration and its effects on hot flashes were evaluated by the Scandinavian Prostatic Cancer Group.⁴⁹ In this study, 458 men were randomized to castration with polyestradiol phosphate while 457 men underwent complete androgen blockade (orchiectomy or GnRH analogs + flutamide). Median follow-up was 18.5 months. About 74% of men undergoing complete androgen blockade reported hot flashes during the trial compared to only 30% in the polyestradiol phosphate group. Furthermore, only 21% of men in the polyestradiol phosphate group reported distress due to hot flashes compared to 55% of men in the androgen ablation group. During follow-up, 50% of men in the polyestradiol phosphate group reported complete relief from hot flashes compared to none undergoing androgen ablation. Hence, it appears that

estradiol-induced castration could be one way of reducing the frequency of and distress due to hot flashes; however, long-term cardiovascular adverse effects with this therapy should be investigated.

Many agents have been tried to treat hot flashes in men on ADT. As expected, transdermal estrogen is one of those modalities. Low-dose estrogen (0.05 mg) resulted in decreased severity of hot flashes, and high-dose estrogen (0.10 mg) resulted in decreased severity as well as decreased daily frequency. Twelve men with moderate to severe hot flashes were randomized to either low-dose (0.05 mg) or high-dose (0.10 mg) estrogen patches, which were applied twice weekly for 4 weeks.⁵⁰ After a 4-week washout period, the men received the alternative dose for 4 more weeks. There was a significant reduction in the overall severity of hot flashes in both the low- and high-dose groups, with 83% of men reporting some degree of improvement. Painless gynecomastia was seen in 17% and nipple tenderness in 42% of men. This was a short-term study; thus, the long-term cardiovascular safety of estrogens remain unclear.

Megestrol acetate has been used in men receiving ADT. In a double-blind, placebo-controlled trial, 66 men on ADT with a median of 8.4 hot flashes per day were randomized to megestrol acetate 20 mg twice daily for 4 weeks followed by placebo for 4 weeks, or vice versa.⁵¹ Megestrol acetate decreased frequency of hot flashes by 80% compared to 19% with placebo. Similarly, severity of hot flashes significantly decreased in the megestrol acetate group compared to placebo. Although efficacious, however, increased PSA levels have been associated with the use of megestrol acetate at similar dosage, though normalizing after its discontinuation.⁵² Therefore, caution should be exercised. Among other agents, antidepressants such as venlafaxine (Effexor, Wyeth; 12.5 mg bid for 4 weeks) has shown efficacy with 63% of men experiencing a decrease of over 50% in hot flash score.⁵³ In a pilot study, acupuncture treatment also decreased the number of hot flashes by 70%.⁵⁴

In summary, a number of modalities have become available in the treatment of hot flashes in androgen-deprived men. Long-term studies are now needed to determine their efficacy and safety.

Sexual Dysfunction

Testosterone plays a key role in male sexual function, including both desire (libido) and performance. Male hypogonadism is associated with a decrease in sexual desire, early morning erections, and potency.⁴⁶ These effects can have a significant effect on quality of life. Although a minority of men undergoing ADT still maintain their libido, the majority of men experience sexual dysfunction.

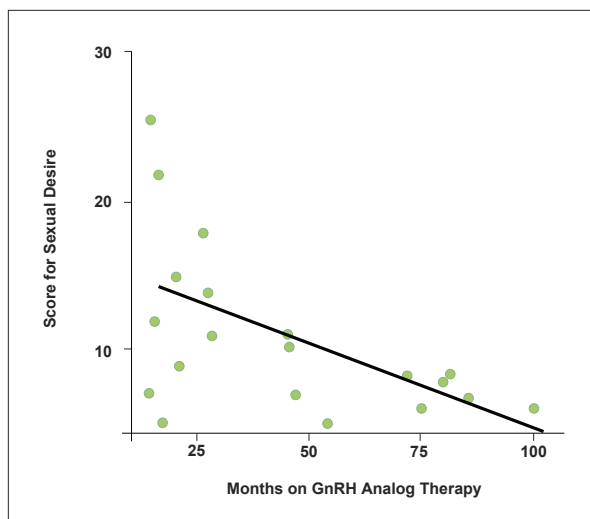


Figure 6. Relationship between the duration of ADT and sexual desire.⁹

ADT = androgen-deprivation therapy; GnRH = gonadotropin-releasing hormone.

The maintenance of sexual function in some of these men may be related to factors such as pre-ADT sexual function and testosterone levels, general well-being, age, and social circumstances. Serum androgen levels (and libido) are somewhat reversible once ADT is discontinued; however, many of these men are on long-term ADT and continue to have sexual dysfunction.

Studies have shown that ADT results in decreased sexual desire and performance. A cross-sectional study showed that men undergoing ADT had significantly lower scores on Watts Sexual Function Questionnaire compared to eugonadal men with PC who had undergone local therapy (surgery and/or radiotherapy) and age-matched eugonadal controls.⁹ The castrated men had decreased desire to engage in sexual activity, decreased arousal, fewer early morning erections, and difficulty attaining or maintaining erections during sexual relations compared to men in the other two groups. Interestingly, sexual desire was inversely related to the duration of GnRH analog therapy (Figure 6). In another study, the authors compared measures of health-related quality of life, including sexual function, in men who received ADT after radical prostatectomy with those who only had surgery.⁵⁵ Men who had undergone radical prostatectomies were identified by reviewing Medicare files and the data were used to select men who subsequently were androgen deprived and those who were not. Approximately 69% of men undergoing ADT reported no sexual drive during the preceding 30 days compared to only 29% of men who had undergone only surgery. Similarly, only 2% of androgen-deprived men were able to have intercourse in

the previous month compared to 12% of surgery-only patients. The Prostate Cancer Outcomes Study compared health-related quality-of-life outcomes in 431 men undergoing ADT with orchiectomy or GnRH agonists.⁵⁶ Overall, 73% of men stopped engaging in sexual activity after starting ADT. Similarly, 69% of men developed impotence. The evaluation of mode of ADT revealed that the percentage of men with no sexual interest increased from 27.6% to 63.6% before and after orchiectomy and from 31.7% to 58% before and after treatment with GnRH agonists. Similarly, the percentage of men with impotence increased from a baseline of 47.9% to 82.8% with orchiectomy and from 45% to 80.2% with GnRH agonists. This study confirms that both medical and surgical ADT result in worsening of sexual function.

Because testosterone treatment is contraindicated in men with PC,⁵⁷ there is no other means of increasing libido in these men. However, for men on ADT who have intact libido and suffer only from erectile dysfunction, treatment modalities are available. Recent studies have shown that sildenafil citrate (Viagra, Pfizer) improves erectile function in men in whom erectile dysfunction develops following radiation therapy for PC.⁵⁸ Future studies should carefully evaluate various modalities of treatment for erectile dysfunction in men undergoing ADT.

Gynecomastia

Gynecomastia is a common complication of ADT in men with PC. Gynecomastia is defined as a benign proliferation of glandular breast tissue, initially appearing in the subareolar region of the breast and then expanding laterally. An increase in the ratio of estrogen to testosterone is considered the main underlying etiology.⁵⁹ Gynecomastia may be accompanied by mastodynia in some patients. When present for more than 6–12 months, the ductal tissue can undergo hyalinization, leading to irreversible fibrosis. The incidence of gynecomastia in men undergoing ADT varies with the modality of castration. Orchiectomy and GnRH agonist therapy are associated with an incidence of gynecomastia of approximately 1–16%.⁶⁰ These modalities result in castrate levels of testosterone while estrogen continues to be produced via aromatization of adrenal androgens, hence the altered ratio of estrogen to androgen. Men receiving antiandrogens (eg, flutamide, bicalutamide [Casodex, AstraZeneca]) have a 16–80% higher incidence of gynecomastia. This higher incidence is based on the fact that antiandrogens also block the androgen receptors on the pituitary gland, resulting in loss of negative feedback by circulating androgens. This leads to an increase in luteinizing hormone and testosterone levels, ultimately resulting in higher estradiol levels. As expected, men undergoing combined androgen blockade have an intermediate incidence of 13–22%.

Although an in-depth review of treatment options of gynecomastia is beyond the scope of this article, we will summarize various available modalities. Recent reviews have been published on the prevalence and treatment of gynecomastia in this population.^{61,62} Surgical treatment is often employed in the prophylaxis and treatment of gynecomastia in men on ADT. Previously, subcutaneous mastectomy via periareolar incision was the most common procedure; however, liposuction techniques are currently being employed in the removal of the proliferating ductal tissue. Prophylactic radiation therapy (especially in men planning to undergo ADT with androgen receptor antagonists) has resulted in good success. A large Scandinavian study showed that men receiving prophylactic radiation therapy prior to starting flutamide had a significantly lower incidence of gynecomastia and mastodynia compared to nonirradiated groups.⁶³ However, the efficacy of radiation therapy is significantly reduced once the gynecomastia has set in. In terms of medical treatment, tamoxifen at a dose of 10 mg/day for 24 weeks resulted in a significantly higher rate of prevention of gynecomastia in men on bicalutamide compared to radiation therapy.⁶⁴ Tamoxifen was also effective in the treatment of patients who had already developed gynecomastia on bicalutamide monotherapy. Another study showed that tamoxifen was superior to anastrozole (an aromatase inhibitor) in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy.⁶⁵

It thus appears that tamoxifen and radiation therapy are effective in the prevention of gynecomastia in men undergoing ADT with antiandrogens. In terms of treatment of gynecomastia that has already developed, tamoxifen and surgery remain the main modalities.

Conclusions

Though ADT is beneficial in a subset of patients with PC, it is associated with many endocrine complications and physicians administering this therapy need to be cognizant of these adverse effects. Decrease in BMD is a common occurrence, but it is responsive to prevention and treatment with bisphosphonates. Hence, monitoring of BMD should be performed in all patients. Furthermore, patients with established osteoporosis/osteopenia prior to starting ADT should be started on a regimen of calcium and vitamin D supplementation, weight-bearing exercises, and bisphosphonates. Decreased LBM and muscle strength and increased fat mass resulting from ADT may interfere with normal daily activities and independence and may predispose to falls. Because anabolic steroids are contraindicated in this patient population, patients should be encouraged to continue good nutrition and physical activity as much as possible to prevent further deterioration. Insulin resistance, hyperglycemia, and metabolic

syndrome are recently recognized complications of ADT and may be responsible for imparting increased cardiovascular complications in these men. The development of diabetes mellitus should be monitored in men on long-term ADT. Long-term studies are needed to determine the timing of onset of these metabolic complications. Hot flashes and sexual dysfunction have significant effect on patients' quality of life and should not be underestimated simply because they are not life-threatening. Gynecomastia is a common complication of ADT. Radiation therapy remains an effective prophylactic treatment in men who are about to undergo ADT with androgen receptor antagonists. Tamoxifen and surgery remain effective treatment modalities in men with established gynecomastia.

The approach to patients with PC undergoing ADT should be multidisciplinary, with collaboration between endocrinologists, oncologists, radiation oncologists, urologists, and internists. This will ensure that patients are appropriately educated regarding the complications of ADT and are treated when these complications occur.

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