Review Article

Adverse effects of androgen deprivation therapy in prostate cancer: Current management issues

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ABSTRACT

Prostate cancer (CaP) is the most common visceral malignancy and a leading cause of cancer death in men. Androgen deprivation therapy (ADT) is an established treatment for locally advanced and metastatic CaP, and often used as primary therapy in select patients. As ADT has continued to assume an important role in the treatment of CaP, a greater appreciation of potential adverse effects has been acknowledged in men receiving this therapy. Given that all treatments for CaP are frequently associated with some degree of morbidity and can have a negative impact on health-related quality of life (HRQOL), the potential benefits of any treatment, including ADT, must outweigh the risks, particularly in patients with asymptomatic disease. Once the choice to proceed with ADT is complete, it is imperative for the urologist to possess comprehensive knowledge of the potential adverse effects of ADT. This permits the urologist to properly monitor for, perhaps diminish, and to treat any linked morbidities. Patient complaints related to ADT such as a decrease in HRQOL, cognitive and sexual dysfunction, hot flashes, endocrine abnormalities, cardiovascular disease, and alterations in skeletal and body composition are commonly reported throughout the literature. Herein, we review the principal adverse effects linked with ADT in CaP patients and suggest various universal strategies that may diminish these potential adverse consequences associated with this therapy.

Key words: Androgen deprivation therapy, complications, prostate cancer

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INTRODUCTION

Prostate cancer (CaP) is the most common visceral malignancy in men, with an expected 218 890 new cases and 27 050 deaths estimated in 2007 in the United States alone.[1] Ever since the discovery of androgen-dependent CaP, androgen-deprivation therapy (ADT) has become an integral piece of the armamentarium for treating contemporary CaP.[2] The survival advantages have been documented with ADT when applied to patients as neoadjuvant or adjuvant therapy in combination with external-beam radiotherapy (EBRT), as well as when implemented as early adjuvant therapy in men diagnosed with lymph node metastases following radical prostatectomy.[2,3] In addition to the applications of ADT in the settings of locally advanced or metastatic CaP, significant increases have been recognized in the use of primary ADT in select patients.[4] As the role of ADT in the treatment algorithm of CaP continues to evolve, there has been increasing attention towards identifying and preventing ADT-associated morbidities in recent literature. It is essential for urologists and oncologists to have a comprehensive understanding of the major adverse effects of ADT not only in order to properly counsel patients, but also to attempt to identify, alleviate, and treat these potential morbidities during therapy. Herein, we discuss the major ADT-associated morbidities, and provide methods for identifying and treating these complaints in men receiving ADT for CaP.

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ADVERSE EFFECTS OF ADT

Quality of life

The impact on health-related quality of life (HRQOL) following ADT induction has gained significant clinical attention. Several series have documented an association between ADT and declining HRQOL.[5–10] Potosky *et al.* published a series of 661 men with localized CaP, comparing men receiving primary ADT (n = 245, 37%) to men selecting watchful waiting (WW, n = 416, 63%). Using the Medical Outcomes Study (MOS): 36-Item Health Survey, they compared HRQOL between these two groups. They found significantly higher rates of physical discomfort (P = 0.02) in men receiving primary ADT. Further, men receiving ADT reported more physical limitations and

bother from CaP, though these were not statistically significant ($P = 0.11$ and $P = 0.21$, respectively).[5] Similarly, Dacal *et al*., compared HRQOL between men undergoing short-term ADT (<6 months), long-term ADT (>6 months), and healthy controls. Again, using the MOS questionnaire, they found that men receiving any duration of ADT demonstrated significantly worsened HRQOL. In particular, ADT recipients demonstrated decreased scores in: Physical component health summary ($P < 0.001$), physical function domain ($P < 0.001$), and general health category ($P < 0.001$). Notably, a time-dependent relationship between decreased HRQOL and duration of ADT was not established.[6] Fowler *et al*. compared HRQOL between men treated with radical prostatectomy ($n = 810$) vs. radical prostatectomy in combination with adjuvant ADT ($n = 220$).[10] In this study, men receiving ADT demonstrated significantly decreased scores in all HRQOL domains studied. In particular, men receiving prostatectomy and ADT reported worse scores with respect to the effect of cancer and treatment on overall well-being ($P < 0.0001$), perception of body image ($P < 0.0001$), mental health ($P = 0.01$), general health ($P = 0.01$), activity level ($P = 0.0002$), worry about cancer and death ($P < 0.0001$), and energy level ($P < 0.0001$).[10] These findings have been supported by other studies demonstrating the negative impact of ADT on cognition, sexual function, social interaction, and role functioning, as well as an increase in the level of emotional distress.[8,9] In addition to effects on overall HRQOL, recent data investigating the association between ADT and psychiatric illness has documented an almost two-fold increase in the risk of de novo psychiatric illness following ADT induction.[7]

As an increasing evidence base is collected regarding the negative psychosocial impacts of ADT, it is paramount that urologists discuss the potential adverse effects that ADT may pose to a patients' general mental and physical sense of well-being. Currently, no Level I evidence exists that clearly demonstrates association of ADT with a decreased HRQOL, and no consensus recommendations are published to minimize HRQOL-related adverse effects. As demonstrated in the above studies, though, a relationship between ADT use and decreased quality of life is beginning to surface in Level II/III evidence. Experts agree that patients must be advised that the potential for an overall or domain-specific decrease in HRQOL exists when the decision is made to initiate androgen suppression. A mental health history should be obtained prior to initiating androgen ablative treatment, and patients should be carefully followed for the onset of depressive symptoms during and after treatment. Further, since QOL is best thought of as the sum total of all adverse effects associated with ADT, culminating into how the patient actually perceives their existence, it is imperative that urologists and oncologists discuss this most important topic when deciding whether or not to begin ADT. The component parts to a potentially decreased HRQOL that are associated with ADT will now be discussed, and more specific recommendations to screen for, prevent, and minimize them will be provided.

Sexual dysfunction

Impotence and loss of libido were among the first described adverse effects of ADT. The relationship between androgen ablation and sexual function has been studied in several contemporary series.[2,5,10-12] Fowler *et al*., compared HRQOL outcomes in androgen-deprived ($n = 298$) and non-androgen-deprived men ($n = 1095$) following radical prostatectomy in a survey-based study using Medicare Provider and Analysis and Review (MedPAR) files. Overall, 166 men in the ADT group and 886 men in the non-ADT group responded to the survey questions regarding erectile dysfunction (ED). Patient receiving ADT reported higher rates of post-prostatectomy impotence (72 vs. 55%), but similar rates of impotence over the month prior to the survey (23 vs. 22%). Regarding the quality of erections, 3% (vs. 11%) of androgen-deprived men reported erections insufficient for intercourse, and only 2% (vs. 12%; $P < 0.0001$) reported erections firm enough for intercourse. With regards to libido, 69% (of the 170 responders) in the ADT group reported no sexual drive over the 30 days prior to the survey compared to 29% (of the 888 responders) in the non-ADT group ($P < 0.0001$).[10] In a Level I study, Potosky *et al*., analysed sexual and erectile outcomes in men receiving either orchiectomy ($n = 132$) or GnRH agonists ($n = 299$) as part of the Prostate Cancer Outcomes Study. Pretreatment, sexual function, and libido were similar between groups; however, patients undergoing orchiectomy reported slightly worse overall sexual function, though not statistically significant. Additionally, changes in sexual outcomes were similar between both ADT groups with reports of impotence increasing from 35.0 to 78.6% in the orchiectomy group, and from 37.9 to 73.3% in the GnRH analog group. Despite these similarities, 38.4% of men receiving GnRH agonist therapy reported a big/moderate problem in overall sexual function compared to only 25.6% in the orchiectomy group ($P = 0.04$).[13]

In another Level I evidence series, Potosky *et al*., compared men selecting WW (n = 416) with men selecting ADT ($n = 245$) during the first year following CaP diagnosis.[5] Patients completed sexual and QOL surveys at baseline, 6 months, and 12 months post-diagnosis. Among men reporting some sexual interest at baseline, 54% of the ADT group vs. 13% of the WW group reported no interest in sexual activity at approximately 12 months post-diagnosis ($P < 0.001$). Among men that were potent at baseline, 80% of the ADT group compared to 60% of the WW reported impotence at one-year follow-up ($P < 0.001$).

Nevertheless, despite the pronounced effects that ADT has on libido and erectile function, successful therapy outcomes have also been reported.[11,12] Sexual dysfunction should actually be addressed prior to ADT initiation, so that physicians have a working idea of baseline sexual function

and can then individually tailor treatments. Experts agree that patients should routinely be asked about changes in sexual function over the course of therapy. Level III evidence suggests that penile injections and phosphodiesterase-5 inhibitors (PDE-5 inhibitors) have demonstrated some success in treating the sexual side effects associated with ADT; however, diminished libido in men receiving ADT and the partial dependence of PDE-5 inhibitors on the presence of circulating androgens can attenuate their efficacy.[11] Nonetheless, reasonable treatment response outcomes have been reported. In a recent series of 395 men receiving ADT, DiBlasio *et al*., identified 57 men (14.4%) reporting post-ADT ED who went on to receive targeted therapy; 40 (70.2%) of which experienced new-onset ADT-associated ED. Overall, treatment success was reported in 33.3–47.4% of men receiving single-modality medical therapy, and 80% of men receiving combination medical therapy.[12] This Level III evidence suggests that combination medical therapy with PDE-5 inhibitors, prostaglandin E1 analogs, and vacuum erection devices, seem to provide a promising approach to treating ADT-induced ED, as they appear to have synchronistic properties that act through different biochemical and mechanical pathways. Higher level evidence is lacking largely due to difficulty in uniformly assessing baseline sexual dysfunction and treatment efficacy following initiation of targeted therapy. Randomized clinical trials are necessary to investigate which erectile dysfunction treatment or combination therapies are best suited for patients with ADT-induced ED.

Vasomotor symptoms

Vasomotor flushing, commonly referred to as 'hot flashes', are a well-described phenomenon in perimenopausal women manifesting as the sudden sensation of heat over the upper body, cutaneous flushing, and sometimes by drenching sweating or shivering at the conclusion of the event. These vasomotor symptoms are noted to occur at relatively high frequencies in men undergoing androgen ablation, and are one of the most frequently reported adverse consequences of ADT.[2,14,15] Spetz *et al*., performed a Level I prospective analysis comparing the incidence of hot flashes in men receiving complete androgen blockade (CAB) to men receiving estrogen therapy for treatment of CaP.[15] In their cohort of 915 patients with metastatic disease, 458 were treated with polyestradiol phosphate while 457 received CAB. Of men receiving CAB, 74.3% reported hot flashes compared to 30.1% in men receiving estrogen therapy ($P < 0.001$). Further, a significantly greater percentage of men treated with CAB were 'greatly distressed' by the hot flashes (11.3 vs 2.6%, $P < 0.01$) and reported at least four hot flashes per day (33.7 vs. 2.7%, $P < 0.001$).

Androgen deprivation therapy-associated vasomotor flushing remains a common complaint reported by men receiving this therapy, and this side effect should be thoroughly discussed prior to ADT initiation and closely monitored following treatment induction. Patients should be educated about hot flashes, which are reported in up to 80% of men receiving ADT, so they will understand what they are experiencing if they have one. In follow-up interviews after initiating ADT, patients should be asked about the constellation of hot flash symptoms described above. If patient are having vasomotor symptoms and are interested in active therapy for treating hot flashes (many men are reluctant to take medications for vasomotor symptoms), therapeutic options should be discussed. Megestrol acetate, estrogens, clonidine, progesterone, lifestyle changes, increased dietary soy and flaxseed, and host of other complementary medicines have demonstrated some success in treating ADT-related hot flashes.[16] These interventions are largely based on anecdotal reports or small series but increasing resources are being dedicated to further research in this area. Megestrol acetate is the most extensively studied treatment for vasomotor symptoms. At doses between 20 and 40 mg/day, Level I evidence demonstrates that the drug can reduce hot flash symptoms by up to 85%. Chills, weight gain, and carpal tunnel-like pain are reported side effects of megestrol acetate.[16] Preliminary studies have shown that certain antidepressants including venlafaxine and paroxetine may relieve vasomotor symptoms in men receiving ADT.[14] Level I evidence is lacking since only placebo-controlled pilot studies have been conducted to this point; however, all show a decrease in vasomotor symptoms, and these drugs may be particularly effective in patients with hot flashes and symptoms of depression.

Endocrine dysfunction (ED)

Male hypogonadism is recognized as an independent risk factor for the development of endocrine dysfunction (ED).[17–22] In particular, there is increasing evidence supporting an association between ADT and increased risk of the metabolic syndrome and its associated adverse endocrine and end-organ effects.[18] Metabolic syndrome is diagnosed when three of five criteria proposed by the Adult Treatment Panel III are met, including: Fasting plasma glucose >100 mg/dl, serum triglyceride level >150 mg/dl, serum high-density lipoprotein (HDL) <40 mg/dl, waist circumference >102 cm, and blood pressure >130/85. A recent cross-sectional study by Braga-Basaria *et al*., assessed differences in the overall prevalence of the metabolic syndrome in men receiving ADT, as well as various components constituting this syndrome.[18] In men receiving ADT, the authors noted a significantly higher overall prevalence of abdominal obesity ($P = 0.007$), hyperglycemia ($P = 0.007$), and hypertriglyceridemia ($P = 0.06$) – all factors that contribute to the diagnosis of metabolic syndrome. Further, the prevalence of the metabolic syndrome was found to be significantly higher in the men receiving ADT (55%) compared to both the non-ADT group (22%) and eugonadal controls (20%, $P = 0.03$).

Development of insulin resistance, a major constituent of the metabolic syndrome, has also been associated with the receipt of ADT.[17,19-22] In a Level II prospective 12-week

study by Smith *et al*., 25 men with locally advanced or recurrent CaP and no evidence of metastasis or diabetes were studied for ADT-related effects on insulin resistance. Patients received a 12-week course of CAB (leuprolide depot and bicalutamide) and baseline, and follow-up comparisons were made between the following parameters: Plasma glucose, plasma insulin, hemoglobin A1c, lipid profiles, and percentage of fat body. Mean percent fat body mass increased 4.3 ± 1.3% (P = 0.002) after three months, while percent lean body mass decreased 1.4 ± 0.5% (P = 0.006). Further, ADT demonstrated significant effects on all of the lipid indices assessed, with rises in total cholesterol (9.4 ± 2.4%, P < 0.001), HDL cholesterol (9.9 ± 2.9%, P = 0.01), LDL cholesterol (8.7 ± 4.7%, P = 0.09), and triglycerides (23 ± 8.0%, P = 0.04). No changes in fasting blood glucose were seen during the study; however, significant rises were seen in plasma insulin levels (P = 0.04) and mean serum HbA1c levels (P < 0.001). Further, insulin sensitivity significantly decreased by nearly 13% (P = 0.02) and one patient was diagnosed with diabetes mellitus (DM) at the completion of the study.[22]

Basaria *et al*., performed a cross-sectional study of 53 men: 18 with CaP who received more than 12 months of ADT, 17 age-matched patients with CaP treated with radical prostatectomy or external-beam radiotherapy (but no ADT), and 18 age-matched men with no history of CaP (control group). The authors identified significant increases in fasting serum glucose levels (P < 0.01) and serum insulin levels (P = 0.02) in the ADT group, which remained significant after adjusting for age and BMI on multivariate analysis. Further, the ADT group exhibited a significantly higher insulin resistance (P = 0.01).[17]

More recently, Keating *et al*., published a Level II large series of 73 196 men with local and regional CaP from the Surveillance, Epidemiology, and End Results (SEER) database. Of the 36.3% of patients in the cohort receiving medical castration, they identified a significant increase in the incidence of DM (P < 0.001) when compared to those not receiving ADT. Further, the duration of ADT was identified as a predictor for increased risk of subsequent diabetes, even in patients receiving only short courses of ADT. Lastly, the authors also found orchiectomy to be associated with increased rates of incident DM.[20]

In another Level II retrospective cohort study, Derweesh *et al*. reported on 396 men receiving ADT for CaP. Overall, 319 were nondiabetics at ADT initiation and 36 (11.3%) were diagnosed with new-onset DM and received appropriate medical management. Additionally, the authors found that in the 77 patients with pre-existing diabetes, ADT was associated with a rise in serum HbA1c and fasting blood glucose levels of >10% in 15 (19.5%) and 22 (28.6%) patients, respectively.[19]

Thus, there is increasing evidence supporting a link between ED and ADT. Experts agree that patients who are to receive more than 6 months of ADT therapy should meet a nutritionist to discuss a healthy diet and weight-loss strategies. Further, exercise regimens should be planned, as Level II evidence suggests that exercise helps minimize insulin resistance, decrease weight gain, and improve fatigue and overall QOL.[16] No Level I recommendations to monitor for diabetes currently exist; however, Level III evidence promotes close monitoring of HbA1c and fasting blood glucose levels in patients with pre-existing diabetes and obese patients (BMI > 30 kg/m^2) without a history of diabetes.[19]

Cardiovascular phenomena

In addition to ADT-associated endocrinopathy, the association between hypogonadism and cardiovascular disease continues to be elucidated. Haffner *et al*., assessed the relationship between serum sex hormone levels and lipid indices in a cohort of 178 nondiabetic men. After adjustments for age, BMI, waist-to-hip ratios, and glucose and insulin concentrations, free serum testosterone levels were significantly correlated with lipid profiles, including triglyceride levels (r = 0.15) and HDL concentrations (r = 0.15). The authors concluded that a relatively hypogonadal state may confer increased risk of cardiovascular events as it is associated with a decrease in cardioprotective HDL cholesterol and an increase in serum triglyceride levels.[23] Khaw *et al*., demonstrated the relationship between serum testosterone and hypertension, another well-described cardiac risk factor, linking low endogenous serum testosterone levels to a higher incidence of hypertension.[24] This study also identified an inverse relationship between serum testosterone levels and both systolic (r = 0.17, P < 0.001) and diastolic (r = 0.15, P < 0.001) blood pressure. Further, this study on 1132 men demonstrated a stepwise decrease in mean systolic and diastolic blood pressure per increasing quartile of testosterone when adjusting for obesity.[24]

A more recent study by Dockery *et al*., identified arterial stiffness (an inverse of vascular compliance and cardiac risk factor) to be significantly increased in men receiving GnRH analogs.[25] This study compared central and peripheral arterial compliance in 16 men receiving ADT induction vs. 15 matched controls. Arterial compliance measures were recorded at baseline and again at 12-weeks post-ADT induction in this Level II study. A significant decrease in systemic arterial compliance, or increase in arterial stiffness, was observed in the ADT group but not in the controls (P = 0.03), with a potential for associated adverse cardiovascular effects.

In a Level II study by Malcolm *et al*., 395 men receiving ADT were reviewed for incidence of cerebrovascular accident or myocardial infarction. Logistic regression demonstrated a time-dependent relationship between risk of myocardial infarction [hazards ratio (HR) = 2.12, P = 0.03) and cerebrovascular accident (odds ratio = 3.22, P = 0.001)

and increasing duration of ADT administration.[26] Further in another Level II study, Keating *et al*. identified a higher incidence of coronary heart disease (HR = 1.16, $P < 0.001$), myocardial infarction (HR = 1.11, $P = 0.03$), and sudden cardiac death (HR = 1.16, $P = 0.004$) in men receiving ADT when compared to a control group. Additionally, the increased risk of coronary heart disease remained significantly increased even in men receiving ADT for as few as 1-4 months (HR = 1.29, $P < 0.001$). Myocardial infarction and sudden cardiac death also occurred at higher frequencies in the ADT group when stratified by duration of therapy, though this did not demonstrate statistical significance.[20]

Tsai *et al*., directly examined the relationship between ADT and cardiac-related death in an analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor database (CaPSURE).[27] In this Level II study of 4892 patients with organ-confined CaP, 1015 received either neoadjuvant or adjuvant ADT, with median therapy duration of 4.1 months, in conjunction with local surgical or radiation treatment. Competing regression analyses that controlled for age, ADT administration, and a history of heart disease or diabetes mellitus at baseline, were used to compare cardiac-related mortality rates between men receiving ADT or treated without castration.[27] The authors found that in men treated with radical prostatectomy ($n = 3262$), age (HR = 1.07, $P = 0.003$) and ADT use (HR = 2.6, $P = 0.002$) were significantly associated with an increased risk of cardiac-related death. Moreover, 5-year cumulative incidence estimates of cardiac death were higher in men receiving ADT when stratified by age ($P = 0.02$ for <65 years, $P = 0.01$ for >65).[27]

A relationship between ADT therapy and cardiovascular disease has only recently been described as increasing data suggests that ADT use increases the incidence of known risk factors for cardiovascular disease, including DM, hypertension, and dyslipidemia. There is a paucity of screening guidelines on this topic though numerous general health and prostate cancer-specific recommendations exist. As for all patients, men that are to receive ADT should be counseled against smoking, maintaining a healthy diet, and exercising regularly. Cardiovascular risk should be assessed before initiating ADT and then routinely, with blood pressure monitoring and analysis of serum lipid profiles. Currently no specific recommendations are made for patients with hypertension that are on ADT therapy and it can be assumed that goals should be systolic < 140 mm Hg and diastolic < 90 mm Hg, or <130/90 for patients with diabetes of chronic kidney disease. No Level I recommendations are made specifically for treating dyslipidemia in androgen-ablated men. However, statins are found to have potential anti-cancer effects and are promoted in treating high cholesterol in men receiving ADT.[16]

In addition to cardiac-related death, the relationship between all-cause mortality and ADT use has also been examined.[27] Tsai *et al*., utilized the CaPSURE database to study this survival endpoint. In this study, significant prognostic factors for all-cause mortality identified for men undergoing radical prostatectomy included: ADT administration (HR = 2.2, $P < 0.001$), older age (HR = 1.07, $P < 0.001$), higher Gleason grade sum (HR = 2.3, $P = 0.002$), and baseline DM (HR = 1.9, $P = 0.03$). However, ADT was not predictive of increased all-cause mortality in men selecting other primary treatment modalities ($P = 0.7$).[27] Again, this must be discussed globally with patients prior to initiating ADT therapy.

Skeletal composition and fractures

Osteoporosis in men has gained significant clinical attention over the last decade, and concerted efforts are underway to more completely delineate the disease process in males. T-score criteria for a diagnosis of osteoporosis and osteopenia are still evolving; however, it is estimated that using fractures as a clear endpoint for the disease in males have a 13–25% lifetime risk of developing osteoporosis.[28] Hypogonadism is well-described as one of the major causes of osteoporosis in men along with alcohol abuse, glucocorticoid excess, low-dietary calcium, vitamin D deficiency, and sedentary lifestyle. The increasing use of ADT in current practice patterns for the treatment of local and advanced CaP has made ADT one of the leading causes of hypogonadism, and thus osteoporosis in men.[29]

In a contemporary series of 395 men receiving ADT (Level II evidence), Malcolm *et al*., identified ADT as an independent risk factor for the development of osteoporosis and nonpathologic fractures. In this series, 23% of men receiving ADT developed osteoporosis, while 7% were diagnosed with nonpathologic fractures. Further, duration of ADT was identified to be an independent predictor for development of osteoporosis ($P < 0.001$), and was on average, 49% longer in patients diagnosed with fractures ($P < 0.001$). Importantly, the development of osteoporosis was positively associated with the development of nonpathologic fractures in this cohort ($P < 0.001$).[30]

Recently, several large Level II series have reported evidence that GnRH agonists increase the risk of fractures in men receiving ADT when compared to controls.[31-33] Shahinian *et al*., analysed men with CaP from the SEER database to assess osteoporosis and fracture risk in the ADT population. For men surviving at least five years from CaP diagnosis, the incidence of fractures was 19.4% for patients treated with GnRH agonists vs. 12.6% for men treated with other modalities ($P < 0.001$). Further, Cox proportional-hazards regression analyses identified a statistically significant relationship between the number of GnRH injections in the first year following diagnosis and the risk for developing fractures, after adjusting for other clinicopathologic variables.[31]

Smith *et al*., assessed the risk for fracture development in men with non-metastatic disease who were treated with

ADT.[33] Nearly 4000 men with a history of ADT receipt were matched to men receiving no form of castration therapy (n = 7774). Their comparison study demonstrated a significantly higher clinical fracture risk in the GnRH agonist group (7.88/100 vs. 6.51/100 person-years at risk, $P < 0.001$). Further, ADT independently predicted future fracture risk in multivariate analyses, and longer treatment duration conferred a greater risk for subsequent fractures.[33] These results were corroborated and demonstrated to be remarkably reproducible in another study by Smith *et al*., which utilized claims information from 16 large American insurance companies. This study identified a higher incidence of bony fractures in patients with non-metastatic CaP treated with GnRH agonists than in matched controls (7.91/100 vs. 6.5/100 person-years at risk, RR = 1.21, 95% CI 1.09-1.34). Again, ADT therapy was identified as an independent risk factor for fracture risk on multivariate analysis.[32]

The increased fracture rates in patients receiving hormonal therapy are multifactorial, including higher incidence of metastatic bony lesions, fragility from disease and disease-related treatment, and decreased bone mineral density (BMD) associated with ADT.[34] Several mechanisms linking decreased BMD with GnRH agonists have been proposed since it has been observed that ADT decreases BMD at a rate of approximately 4-5% per year, and increases urinary and serum concentrations, markers of osteoclastic and osteoblastic activity.[34] Leder *et al*., reported increased skeletal responsiveness to the bone-resorbing effects of parathyroid hormone (PTH) in men treated with ADT by comparing metabolic indicators of skeletal activity during PTH infusion prior to the initiation of ADT and after serum-confirmed GnRH-induced hypogonadism.[35] Further, 17b-estradiol levels, which have been shown to have a significantly positive relationship with BMD measurements, have also been demonstrated to with ADT.[36] A more thorough understanding of the mechanisms contributing to osteoporosis in men and specifically in males receiving ADT is driving clinical solutions.

Currently no consensus clinical guidelines exist for monitoring bone loss in chemically castrate patients. However, it has been proposed that these patients be monitored similarly to peri-and postmenopausal women, with a baseline dual energy X-ray absorptiometry (DEXA) scan or quantitative computerized tomography (qCT) scan and then at various intervals dictated by the baseline measurements. Patients already receiving ADT should receive a baseline scan and be routinely followed. Practically, DEXA scan may be better than the more sensitive qCT, as it is relatively cost effective and minimizes radiation exposure.[37] Recently, an expert panel (Level V evidence) has provided specific recommendations for this patient population.[38] The group proposed that men with CaP at increased risk for fracture (i.e. those receiving ADT or with a prior history of fractures) should have routine BMD screens every two years for T-score > 1 and every 6-12 months for T-score between 1.0 and 2.5.[38]

Treatment for increased fracture risk and osteoporosis in chemically castrate men starts with nonmedical therapy and overlapping strategies that are used in males without malignancies and postmenopausal females. Weight-bearing exercise regimens to preserve BMD, muscle mass, and total body weight should be implemented. Men with metastatic disease or established osteoporosis are to be counseled to refrain from heavy lifting.[37] All men at increased risk for fractures are advised to maintain a diet with adequate calcium (1200-1500 mg/day) and vitamin D intake (400-800 IU per day).[29] Bisphosphonate therapy is recommended for males with a diagnosis of osteoporosis or radiographically confirmed fractures following minimal trauma.[38] Pamidronate and zoledronic acid have both been shown to prevent bone loss in men receiving ADT in well-designed clinical trials (Level II evidence).[39-41] Optimal dosing regimens are still under investigation, but efficacy has been demonstrated with 60 mg pamidronate every 12 weeks, or a single 90 mg infusion every 6 months.[39,41] Intravenous zoledronic acid, 4 mg every three months, has been shown not only to prevent bone loss, but actually to increase BMD in men receiving ADT.[40] Preliminary data suggests that other bisphosphonates may prevent osteoporosis and fractures in men on ADT; however, more data is requisite.

CONCLUSION

Androgen deprived therapy remains a widely utilized therapy for treatment of both localized and advanced CaP. Evidence suggests that ADT is accompanied by a host of pervasive adverse effects—from diminished quality of life to decreased bone mineral density—that involve nearly all physiologic systems with varying incidences [Table 1]. Physicians must

Table 1: Estimated incidences of major adverse effects of androgen-deprivation therapy

Adverse effect	Estimated incidence or increased risk	Reference
Poorer health-related quality of life	-	5-10
Decreased libido	54–97.5	5,10,12
Erectile dysfunction	72–80	5,10,12
Hot flashes	68–74	14,15
Diabetes mellitus	10.9–11.3	19,20
Coronary heart disease	72.3[a]	20
Myocardial infarction	13.5[a]	20
Sudden cardiac death	12.9[a] Age < 65: 2.9-3.6%[b] Age > 65: 5.5-8.4%[b]	20,27
Osteoporosis	23–27%	30,38
Clinical fractures	7-19.4% 7.88-7.91[c]	32,33

[a]Events per 1000 person-years; [b]5-year cumulative incidence; [c]Events per 100 person-years at risk

Table 2: Management of complications of androgen-deprivation therapy

Complication	Management strategy
Decreased HRQOL	Advise patients for potential decrease in HRQOL when initiating ADT Obtain mental health history prior to commencing ADT Screen for depressive symptoms in follow-up visits
Sexual dysfunction	Evaluate baseline sexual function prior to ADT Monitor for changes in sexual function during treatment Targeted therapy with PDE-5 inhibitors ± combination treatment with prostaglandin E1 analogs and vacuum erection devices
Vasomotor symptoms	Educate patients about hot flash symptoms before ADT Screen for hot flash symptoms in follow-up Level I treatment: Megestrol acetate (20–40 mg/day) Other options: Venlafaxine and Paroxetine, estrogens, clonidine, progesterone, lifestyle changes, increased dietary soy and flaxseed
Endocrine dysfunction	Meet with a nutritionist to discuss healthy diet, exercise regimens, and weight-loss strategies prior to ADT Close monitoring of HbA1c and fasting blood glucose levels in patients with pre-existing diabetes and obese patients
Cardiovascular risk factors and disease	Counsel against smoking, maintaining a healthy diet, and exercising regularly Blood pressure monitoring before and after ADT initiation (Goal: <140/90 or <130/90 if diabetic or chronic kidney disease) Analysis of serum lipid profiles before and after therapy (Statins-class drugs for dyslipidemia)
Osteoporosis and fractures	Initial baseline DEXA scan or quantitative qCT scan BMD screens every two years for T-score >−1 and every 6–12 months for T-score between −1.0 and −2.5 Nonpharmacologic management: a) Weight-bearing exercise, b) diet with adequate calcium (1200-1500 mg/day) and vitamin D intake (400-800 IU per day) Bisphosphonate therapy: Pamidronate (60 mg every 12 weeks or single 90 mg infusion every 6 months) or Zoledronic acid (4 mg IV every 3 months)

counsel and educate patients on the effects of ADT prior to initiating treatment and should continually screen for adverse outcomes over the course of therapy [Table 2]. Moreover, urologists must be aware of pharmacologic and non-pharmacologic interventions that are available to mitigate the undesirable effects of ADT. As demonstrated in this review, continued research into identifying, ameliorating, and treating the adverse effect of ADT are becoming increasingly important as the number of patients diagnosed with CaP continues to grow. Intermittent ADT and lifestyle alterations offer promising avenues for those more broadly ameliorating the effects of an androgen-deprived state.

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