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Metabolic Consequences of Androgen Deprivation Therapy for Prostate Cancer

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Abstract

Purpose of Review—To summarize the metabolic alterations associated with androgen deprivation therapy (ADT) for prostate cancer and to evaluate the evidence linking ADT with an increased risk of diabetes and cardiovascular disease.

Recent Findings—ADT by either bilateral orchiectomy or treatment with gonadotropin-releasing hormone agonists causes changes in body composition, alterations in lipid profiles, and decreased insulin sensitivity. The spectrum of metabolic changes during ADT are distinct from classically described metabolic syndrome. Population-based, linked cancer registry studies have consistently reported significant associations between ADT and greater risk for diabetes mellitus. Some but not all studies have reported a link between ADT and cardiovascular disease risk. Most studies have reported no increase in cardiovascular mortality following ADT.

Summary—ADT appears causally associated with diabetes mellitus. ADT is also linked to cardiovascular morbidity, although there is less evidence that this relationship is causal.

Keywords

androgen deprivation therapy; gonadotropin-releasing hormone agonists; diabetes; cardiovascular disease; prostate cancer

Introduction

Androgen deprivation therapy (ADT) is the cornerstone of treatment for metastatic prostate cancer. Androgen deprivation can be achieved by surgical castration (bilateral orchiectomy) or via chronic treatment with a gonadotropin-releasing hormone (GnRH) agonist. GnRH agonists are also commonly used to treat non-metastatic prostate cancer in the United States, and its use is increasing in prevalence [1–3]. GnRH agonists reduce serum testosterone by >95% and estradiol by 80% [4, 5]. ADT increases survival in men with high risk and locally advanced prostate cancer [6–11]. The impact of ADT on survival has not been established in

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other settings, including primary therapy for localized disease, neoadjuvant therapy for low risk disease, or for biochemical recurrence after prior surgery or radiation therapy. The deaths of many men with prostate cancer are unrelated to their malignancy. In one large population-based cohort of nearly 2000 patients diagnosed with prostate cancer, for example, less than 40% of the deaths were secondary to their underlying malignancy [12]. The use of ADT causes several side effects, including fatigue, vasomotor symptoms, loss of libido, erectile dysfunction, gynecomastia, and weight gain [13]. ADT has also been linked to osteoporosis with increased fracture risk [14–16] and anemia [17–20]. In prospective studies, ADT has been demonstrated to cause changes in body composition and metabolic parameters, including loss of muscle mass, gain of fat mass, changes in lipid profiles and development of insulin resistance. In addition, a large SEER/Medicare study linked ADT to an increased risk of diabetes and cardiovascular disease [21] **. Accordingly, the potential benefit patients may receive from ADT must be balanced against the likelihood and severity of adverse events related to treatment, particularly in settings where there is no known survival benefit. In this review, we critically examine the relationship between ADT and risks for diabetes and cardiovascular disease in men with prostate cancer and summarize the potential mechanism(s) of treatment-related morbidity.

Metabolic Changes of ADT

The major metabolic effects of ADT are decreased muscle mass and increased fat mass (together known as sarcopenic obesity), alterations in lipids, and decreased insulin sensitivity.

Sarcopenic Obesity

Sarcopenic obesity was first defined by Baumgartner, describing a group of patients who demonstrated loss of muscle mass in conjunction with obesity, with resultant implications for functional status [22]. Sarcopenic obesity has been estimated to occur in up to 12% of the general population [23].

Androgens play an important role in regulation of body composition. Fat mass is increased and lean body mass is decreased in men with idiopathic and acquired hypogonadism [24]. Testosterone supplementation has been demonstrated to increase lean body mass in hypogonadal men [25–28].

Similar to the phenomenon observed in hypogonadal men, the use of ADT for prostate cancer decreases lean body mass and increases body fat [29–35]. In three prospectively designed studies of men with locally advanced, node-positive, or biochemical recurrent prostate cancer treated with leuprolide, weight increased by 1.8–3.1% and body fat by 9.4–11.2%, while lean body mass decreased by 2.7–3.8% [34, 36, 37]. The increase in fat mass was primarily subcutaneous fat [36, 37]. These effects are not limited to the characteristically older population of men receiving treatment for prostate cancer, as similar effects have been observed in young, healthy men who were administered GnRH agonists [38]. The changes in body composition induced by ADT occur rapidly, since even short-term ADT has been demonstrated to cause changes in lean body and fat mass [30, 39, 40]. The

term sarcopenic obesity has been used to describe the body compositional changes occurring in patients undergoing ADT [41].

Lipid Profile Alterations

GnRH agonist therapy alters lipid profiles, as evidenced by prospective studies documenting increases in total cholesterol by up to 10.6%, triglycerides by over 25%, and HDL by 8–20% [36, 39, 42]. Short-term studies have reported no changes in LDL [39, 42], but a prospective study of 40 patients treated for 12 months with GnRH agonist therapy documented increases in LDL levels of 7.3%, along with a 9% increase in total cholesterol, 11.3% increase in HDL, and 26.5% increase in triglycerides [36]. In contrast, androgen receptor antagonist therapy with bicalutamide has not been associated with changes in lipid profiles [43]. As with the changes in body composition, the time course for these changes in lipid profiles is rapid. In one study, for example, increases in total cholesterol and HDL were observed during the first three months of therapy [40].

The significance of increasing triglyceride and LDL levels, while also increasing HDL levels is not known. Prior work has documented a strong relationship between serum cholesterol and cardiovascular mortality [44, 45]. Some studies have reported associations between triglycerides and risk of coronary heart disease [46] and stroke [47]. A recent analysis of data from 68 prospective studies on lipid profiles and vascular outcomes attempted to decipher the contributions of individual changes in lipid profiles to vascular events, including myocardial infarction, angina, and stroke [48]. On multivariate analysis, triglycerides were not associated with an increased hazard ratio for vascular events (AHR 0.99, 95% CI 0.94–1.05). As would be predicted, elevated HDL was protective (AHR 0.78, 9% CI 0.74–0.82) and elevated LDL (as captured by non-HDL) was associated with increased risk (AHR 1.50, 95% CI 1.39–1.61). On the basis of this data, there would appear to be no increase in cardiovascular risk conveyed by increases in triglycerides. Furthermore, the risk conveyed by the increases observed in LDL could be balanced by the protective increases observed in HDL. The significance of the pattern of lipid profile alterations observed during ADT is thus unclear and could be neutral with respect to cardiovascular outcomes.

Insulin Resistance

Approximately one-quarter of the general population is estimated to have insulin resistance [49, 50]. Insulin resistance occurs in prediabetes, diabetes, and obesity, and has been demonstrated to predict coronary heart disease and stroke [50, 51] as well as ischemic heart disease [49]. Prior prospective work by Pitteloud [52] reported a strong correlation between testosterone levels and insulin sensitivity in a study of 60 men. Supporting a causal role for testosterone in mediating insulin resistance, multiple randomized controlled trials have revealed that testosterone replacement restores insulin sensitivity in hypogonadal men [53].

Several small prospective studies have reported evidence for decreased insulin sensitivity following GnRH agonist therapy [30, 39, 40]. In a twelve-week study of 25 non-diabetic men with locally advanced or recurrent prostate cancer, fasting plasma insulin levels increased by 25.9% ($p=0.04$) after 3 months of GnRH agonist therapy, while insulin

sensitivity decreased by 11% by whole-body insulin sensitivity index and 12.8% by homeostatic model assessment ($p=0.02$) [40]. There was also a small but statistically significant increase in hemoglobin A1c levels (5.62 compared to 5.46, $p<0.001$), although there was no statistically significant increase in fasting glucose measurements.

Metabolic Syndrome

Metabolic syndrome refers to a constellation of cardiovascular risk factors. The National Cholesterol Education Program's Adult Treatment Panel (ATP III) criteria for metabolic syndrome include fasting hyperglycemia, hypertriglyceridemia, decreased serum HDL, increases in waist circumference, and hypertension [54]. Cross-sectional studies have established that hypogonadism is associated with an increased risk of metabolic syndrome [55, 56].

Consistent with the metabolic changes reported in prospective clinical trials, a cross-sectional study reported greater prevalence of some features of the metabolic syndrome in men receiving ADT for prostate cancer compared to age-matched controls [57]. Notably, however, the prevalence of hypertension and low HDL levels was not different between groups. In a prospective trial of 26 patients with locally advanced or recurrent prostate cancer treated with 12 months of leuprolide, increases in fat mass and concomitant decreases in lean body mass were observed, along with elevated triglycerides [37]. However, weight-to-hip ratio and blood pressure were not significantly affected, and serum HDL levels actually increased. In contrast to the visceral fat deposition observed in classic metabolic syndrome [58], the fat accumulation was predominantly subcutaneous, accounting for 94% of the increase in fat mass [37]. Finally, adiponectin levels were increased by 36% and C-reactive protein levels unchanged [37], while in classic metabolic syndrome, adiponectin and C-reactive protein levels are generally decreased and increased, respectively [59].

Prior data had associated the presence of metabolic syndrome with increased cardiovascular mortality [60]. However, more recently, others have challenged the notion that metabolic syndrome conveys any more than the additive risk contributed by the individual components of the syndrome [61–63]. Furthermore, the existence of multiple definitions to define metabolic syndrome, lack of prospective data to support the distinctions between definitions, and arbitrary cut-offs raise questions about the usefulness of diagnosing this entity [61]. This is particularly true for the metabolic changes induced by ADT, which appear to precipitate a distinct phenotype from classically described metabolic syndrome (See Table 1).

Diabetes Mellitus

Multiple cross-sectional studies have reported links between hypogonadism and the risk of diabetes mellitus (reviewed in [64]). In the prospectively designed Massachusetts Male Aging Study, low free testosterone levels predicted for the subsequent development of diabetes; for a 4ng/dL decrease in free testosterone level, the odds ratio for developing diabetes was 1.58 [65]. In addition testosterone-replacement therapy was observed to improve hemoglobin A1c and fasting glucose measurements in a randomized double-blind study in diabetic patients [66].

Multiple large, population-based, linked cancer registry studies have consistently reported a significant link between ADT and subsequent diagnosis of diabetes (see Table 2). The first was the Surveillance, Epidemiology, and End Results program and Medicare (SEER-Medicare) study of 73,196 men diagnosed with local or locoregional prostate cancer, approximately $\frac{1}{3}$ of whom received treatment with ADT, with a median follow-up of 4.5 years [21]. On multivariate analysis, incident diabetes mellitus was significantly increased in men receiving ADT (AHR 1.42, $p < 0.001$) and in the 6.9% of men who received surgical castration (AHR 1.34). Another retrospective, claims-based study of 1231 men with prostate cancer treated with ADT also reported an increased risk of incipient diabetes in men receiving ADT [67]. Although men who initiated ADT were significantly older, with poorer overall health status as measured by Charlson comorbidity scores, and an increased incidence of co-morbid hypertension, the increased risk of diabetes persisted after multivariate analysis (HR 1.36, $p = 0.01$). A matched cohort study of 19,079 men aged 66 and older from the Ontario Cancer Registry given continuous ADT for at least six months or treated with bilateral orchiectomy reported an elevated risk of diabetes with the use of ADT of 1.16 (95% CI 1.11–1.21) [68]. The number needed to harm (NNH) for a new case of diabetes was 91. In both the SEER and Ontario studies, there was a trend towards an increased risk of diabetes with increasing duration of ADT. A recent Veterans Healthcare Administration database study evaluated the records of 37,443 men treated for local/regional prostate cancer. After controlling for other factors, GnRH agonist therapy was significantly associated with subsequent diagnosis of diabetes (AHR 1.28, 95% CI 1.19–1.38) [69]. In summary, four large studies have reported an increased risk of diabetes with the use of ADT (see Figure 1 and Table 2). Treatment-related hyperinsulinemia and insulin resistance provide a rational pathophysiologic mechanism for the increased risk of diabetes observed with ADT. Thus, ADT appears to be causally linked to diabetes in men with prostate cancer.

Cardiovascular Outcomes

Cardiovascular disease accounts for the majority of non-cancer related mortality in men with prostate cancer [70, 71]. Furthermore, there is evidence associating hypogonadism unrelated to ADT with cardiovascular disease. Men with positive coronary angiograms had significantly lower bioavailable testosterone than men with negative angiograms ($p = 0.013$) [72]. ADT has been demonstrated to increase arterial stiffness in patients treated with LHRH agonists [30, 39], and arterial stiffness in patients with hypogonadism unrelated to ADT was improved by testosterone replacement [73]. There are conflicting data regarding testosterone levels and all-cause mortality, with two prospective studies in older men demonstrating an association of low testosterone with increased all-cause mortality [74, 75], while no such association has been demonstrated in two prospective studies performed in middle-aged men [76, 77].

Keating et al first described the association between GnRH agonists and cardiovascular disease in men with prostate cancer. In a SEER/Medicare retrospective study of 73,196 men treated diagnosed with local or locoregional prostate cancer, there was an increased risk of coronary heart disease (AHR 1.16, $P < 0.001$), myocardial infarction (AHR 1.11, $P = 0.03$) and ventricular arrhythmia or sudden cardiac death (AHR 1.34, $P < 0.001$) in patients treated with a GnRH agonist, but not in men who underwent bilateral orchiectomy [21]. The

cardiovascular effects were apparent in men who had only been on ADT for 1–4 months and persisted with continuing treatment. The observed cardiovascular associations were unchanged after using propensity-based scoring methods to address potential confounding attributable to differences between ADT users and non-ADT users. Thus, Keating's work established a causal association between ADT and diabetes and a more modest association with cardiovascular morbidity (see Figure 1).

Most, but not all subsequent studies confirmed the association between ADT and incident cardiovascular disease (Table 3). Another SEER/Medicare study of 22,816 patients with newly diagnosed prostate cancer treated for at least one year with ADT generated similar concern, with 20% higher cardiovascular morbidity at one year in patients treated with ADT (AHR 1.20; 95% CI, 1.15–1.26) [78]. Recently, an observational Veterans Healthcare Administration study reported an increased risk of cardiovascular disease in men treated with ADT, with adjusted hazard ratios of 1.19 (1.10–1.28) for incident coronary artery disease 1.19 (1.10 to 1.28), 1.28 (1.08–1.52) for myocardial infarction, and 1.35 (1.18–1.54) for sudden cardiac death. In contrast to the SEER studies, a large, matched cohort study of men with prostate cancer treated with ADT from the Ontario Cancer Registry described no significant association between ADT and acute myocardial infarction [68]. The lack of cardiovascular morbidity attributable to ADT in the Ontario study may be related to differences in the baseline characteristics of the study populations or methods utilized to capture cardiac events.

Most studies have reported no association between ADT and cardiovascular mortality. A retrospective study of 13,000 patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database revealed no increase in cardiovascular mortality in the overall study population. A subset analysis of a small number of men older than 65 treated with radical prostatectomy and receiving ADT demonstrated greater cardiovascular mortality (a total of 24 cardiac events in this group versus 9 in the non-ADT group) [79]. Given the small number of patients and cardiac events in this subset, as well as the lack of association of greater cardiovascular mortality with prior cardiovascular disease or diabetes, the significance of this subset result is unclear. A pooled analysis of three small randomized controlled trials of men treated with short-term ADT for clinically localized prostate cancer did not describe any increase in cardiovascular mortality in the overall population but reported an earlier onset of fatal myocardial infarction in the subset of men 65 years and older [80]. In contrast to these reports, no change in cardiovascular mortality or fatal cardiac events was observed in post-hoc analyses of five large randomized, controlled trials of ADT in the neoadjuvant or adjuvant setting conducted by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [7, 11, 81–83]. Although cardiovascular mortality was not a primary endpoint in these studies, the large sample size, number of cardiac events in each group, and randomized study design are major strengths of the analyses.

Conclusions

ADT is associated with metabolic alterations, including changes in body composition, altered lipid profiles, and reduced insulin sensitivity. The use of ADT appears to be causally

linked to a significantly increased risk of diabetes and associated with more modest increases in cardiovascular morbidity. Accordingly, recommendations were recently published regarding patients initiating ADT for prostate cancer, which were adapted from existing guidelines for the management of hyperlipidemia, diabetes, and cardiovascular disease [84]. The data associating ADT with diabetes and adverse cardiovascular outcomes merit further study. Gaining further clarity on the issue of cardiovascular mortality in particular will require prospectively-designed trials of patients with prostate cancer treated with ADT.

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Figure 1.
Increased Incidence of Diabetes Mellitus and Myocardial Infarction with Androgen Deprivation Therapy [21]

Table 1

Distinctions between the Classic Metabolic Syndrome and Metabolic Features of Androgen Deprivation Therapy

	Classic Metabolic Syndrome	Metabolic Features of ADT
Body Fat	↑ (Primarily visceral)	↑ (Primarily subcutaneous)
Waist circumference	↑	↑
Waist-hip ratio	↑	Unchanged
Blood pressure	↑	Unchanged
Triglycerides	↑	↑
HDL	↓	↑
LDL	Not defined	↑ or Unchanged
Adiponectin	↓	↑
C-reactive protein	↑	Unchanged

Table 2**Androgen Deprivation Therapy and Subsequent Diagnosis of Diabetes Mellitus**

Study	Stage	ADT	Total/Exposed/Unexposed	Median Follow-Up	AHR Diabetes (95% CI)
Medicare/SEER [21]	Locoregional prostate cancer	GnRH agonist Bilateral orchiectomy	73,196/26570/41575	4.6 yrs	GnRH Orchiectomy 1.44 (1.34–1.55) 1.34 (1.20–1.50)
National Claims Database [67]	Any stage	GnRH agonist GnRH antagonist AA alone/combination	8481/1231/7250	NR	Overall risk 12 mo 18 mo 1.36 (1.08–1.71) 1.49 (1.12–1.99)
Ontario Cancer Registry [68]	Any stage	GnRH agonist Bilateral orchiectomy AA alone/combination	38,158/19,079/19,079	6.5 yrs	Overall risk 1.16 (1.11–1.21)
Veterans Administration [69]	Locoregional prostate cancer	GnRH agonist Bilateral orchiectomy GnRH agonist + AA AA alone	37,443/14,603/22,840	2.6 yrs	GnRH Orchiectomy CAB AA Alone 1.28 (1.19–1.38) 1.16 (0.87–1.54) 1.17 (0.96–1.42) 1.02 (0.72–1.45)

Table 3

Androgen Deprivation Therapy and Incident Cardiovascular Morbidity

Study	Study Type/Size	Indication	ADT	Median Follow-Up	AHR Cardiovascular Morbidity
Medicare/SEER [21]	Retrospective/73,196	•Locoregional	GnRH agonist Bilateral orchiectomy	4.6 yrs	GnRH - Coronary artery disease: AHR 1.16 (1.10–1.21) - Myocardial infarction: AHR 1.11 (1.01–1.21) - Sudden Cardiac Death: AHR 1.16 (1.05–1.27) Orchiectomy - Coronary artery disease: AHR 0.99 (0.91–1.07) - Myocardial infarction: AHR 0.94 (0.82–1.09) - Sudden Cardiac Death: AHR 1.01 (0.87–1.18)
Medicare/SEER [78]	Retrospective/22,816	•Any stage	ADT (not including orchiectomy)	NR	Any ADT other than orchiectomy Cardiovascular morbidity: AHR 1.20 (1.15–1.26)
Ontario Cancer Registry [68]	Retrospective/19,079	•Any stage	GnRH agonist Bilateral orchiectomy AA alone/combination	6.5 yrs	All ADT combined: - Myocardial infarction: AHR=0.91 (0.84–1.00) - Sudden Cardiac Death: AHR=0.96 (0.83–1.10)
Veterans Administration [69]	Retrospective/37,443	•Locoregional	GnRH agonist Bilateral orchiectomy GnRH agonist + AA AA alone	2.6 yrs	GnRH - Coronary artery disease: AHR 1.19 (1.10–1.28) - Myocardial infarction: AHR 1.28 (1.08–1.52) - Sudden Cardiac Death: AHR 1.35 (1.18–1.54) Orchiectomy

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Study	Study Type/Size	Indication	ADT	Median Follow-Up	AHR Cardiovascular Morbidity
					• <u>Coronary artery disease</u> : AHR 1.40 (1.04–1.87)
					• <u>Myocardial infarction</u> : AHR 2.11 (1.27–3.50)
					• <u>Sudden Cardiac Death</u> : AHR 1.29 (0.76–2.18)
					Complete Androgen Blockade
					• <u>Coronary artery disease</u> : AHR 1.27 (1.05–1.53)
					• <u>Myocardial infarction</u> : AHR 1.03 (0.62–1.71)
					• <u>Sudden Cardiac Death</u> : AHR 1.22 (0.85–1.76)
					Anti-Androgen Alone
					• <u>Coronary artery disease</u> : AHR 1.10 (0.80–1.53)
					• <u>Myocardial infarction</u> : AHR 1.05 (0.47–2.35)
					• <u>Sudden Cardiac Death</u> : AHR 1.06 (0.57–1.99)