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Karen Choong & Shehzad Basaria

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REVIEW

Emerging cardiometabolic complications of androgen deprivation therapy

KAREN CHOONG & SHEHZAD BASARIA

Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts, USA

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Abstract
Prostate cancer (PCa) is the most common malignancy in men. Androgen deprivation therapy (ADT) is used in the treatment of locally advanced and metastatic PCa. Although its use has improved survival in a subset of patients, it also has negative consequences. Osteoporosis, sexual dysfunction, hot flashes and adverse changes in body composition are well-known and well-studied complications of ADT. Recent studies have also found metabolic complications in these men such as insulin resistance, diabetes and metabolic syndrome. In addition, these men might also experience higher cardiovascular mortality. Studies are needed to determine the mechanism behind these complications and to employ strategies to prevent them.

Keywords: *Androgen deprivation, metabolic syndrome, coronary disease*

Introduction

Prostate cancer (PCa) is the most common malignancy in men and is second only to lung cancer as the cause of cancer-related mortality [1]. It is estimated that approximately 192,280 cases of PCa will be diagnosed in the United States in 2009 with roughly 27,360 men dying of it. Androgen deprivation therapy (ADT) is used in patients with PCa based on the well-recognised role of androgens in stimulating prostate tissue [2]. Androgen deprivation can be achieved surgically (orchiectomy) or via medical means (GnRH agonist/antagonist). ADT appears to be effective in improving disease-free and overall survival in a subset of patients. It is used as an adjuvant treatment along with radiation therapy for locally advanced disease, where it has shown survival benefit [3,4]. It is also used in men with metastatic PCa where it improves quality of life. Although use of ADT has merit in these subset of patients, it is increasingly being used even for early stage PCa and in men with biochemical recurrence, even though no survival benefit has been shown [5]. The use of ADT has increased from 3.7% in 1991 to 30.9% in 1999 for the treatment of localised PCa, and it is estimated that more than half a million Americans are on it [6].

On the basis of the current guidelines for ADT, the goal is to achieve serum testosterone levels < 50 ng/dl. This level is six-times lower than the lower limit of normal in young men (normal range: 300–1000 ng/dl). Low testosterone levels have been associated with complications such as osteoporosis, sarcopenia, increased fat mass, adverse lipid profile, insulin resistance and diabetes [7,8]. Longitudinal studies in men without PCa also show that testosterone insufficiency is independently associated with CV and overall mortality [9]. This review will focus on metabolic and cardiovascular effects of ADT.

Complications of androgen deprivation therapy

ADT and body composition

We will review body composition changes first as they are associated with metabolic perturbations and cardiovascular risks. It is well known that serum testosterone levels correlate positively with lean body mass (LBM) and negatively with fat mass (FM). Testosterone dose dependently increases skeletal muscle mass. [10]. Testosterone therapy in sarcopenic hypogonadal men with HIV and chronic obstructive lung disease results in greater gains in

Correspondence: Shehzad Basaria, Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston Medical Center, 670 Albany Street, 2nd Floor, Boston, MA 02118, USA. Tel: +617-638-8182. Fax: +617-638-8217. E-mail: shehzad.basaria@bmc.org

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LBM and muscle strength compared to placebo [11,12]. This effect of testosterone on body composition is seen in both young and older men [13–15]. Similarly, suppression of serum testosterone in healthy young men with a GnRH analogue result in a decrease in LBM and an increase in FM [16], decreased fractional muscle protein synthesis and an associated decline in muscle strength [16].

Several studies have documented unfavourable perturbations in body composition as a result of ADT (Table I). In a prospective study of 79 men undergoing ADT for 12 months, percentage FM significantly increased by 11% whereas LBM decreased by 3.8% [17]. In another study, 32 men with nonmetastatic PCa on GnRH agonist experienced a 2.7% reduction in LBM and an increase of 9.4% in FM [18]. Most of the increase in FM was due to accumulation of subcutaneous abdominal fat. Similarly, a cross-sectional study confirmed these findings [19]. In this study, three groups of men were studied: (1) men on ADT for at least 12 months, (2) men with PCa not on ADT and (3) healthy age-matched controls. The authors noted higher FM in the extremities and the trunk in men on ADT. This study also reported reduced upper body muscle strength in the ADT group.

The loss of LBM and development of sarcopenia has serious implications in this population. Diminished muscle strength may lead to compromised physical function. This limits the ability of the elderly to participate in activities of daily living and affects activities such as stair-climbing, load-carrying, rising from a chair and walking. Muscle loss also leads to impairments in gait and balance that increases the risk of falls.

There are currently no guidelines to prevent ADT-related changes in body composition. In healthy older men, resistance exercise training has been shown to improve LBM while reducing FM [20–22]. However, there is paucity of data in men on ADT. One recent study randomised 155 men into resistance exercise three times/week versus control group upon initiation of ADT [23]. After 3 months, body composition did not differ between the two groups; however, the resistance training group experienced less fatigue, better quality of life and higher levels of muscular fitness. Taking these data, we conclude that long-term resistance training in men undergoing ADT is feasible and may result in improved fitness and better quality of life. Long-term studies are needed to confirm these findings.

Metabolic effects of ADT

Insulin resistance. Insulin resistance is a precursor to diabetes and an independent risk factor for cardiovascular disease [24]. As serum testosterone levels are negatively related to insulin sensitivity, hypoandrogenism is an independent risk factor of diabetes and metabolic syndrome in middle age men [25,26]. In a study of 87 men, Haffner et al. [27] demonstrated improved glucose disposal with higher total and free testosterone levels. Improvements in insulin sensitivity were also documented in interventional studies where testosterone was administered to hypogonadal men [28,29]. A double-blinded, placebo-controlled study consisting of 24 hypogonadal men with type 2 diabetes noted improvements in insulin sensitivity as measured by $HOMA^{IR}$ (-1.73 ± 0.67 , $p = 0.02$) with testosterone therapy [29]. Furthermore, HbA1c ($-0.37\% \pm 0.15\%$, $p = 0.03$) and fasting blood glucose (-1.58 ± 0.68 mmol/l, $p = 0.03$) were both reduced in the testosterone treated group as compared to placebo. There was also a reduction in visceral adiposity and waist circumference in the treatment group [29].

The use of GnRH agonists in the management of PCa is associated with insulin resistance (Table II). In fact, development of hyperinsulinemia is seen as early as 3 months into ADT. In a 12-week prospective study, whole body Insulin Sensitivity Index (ISI) decreased by $12.9\% \pm 7.6\%$ ($p = 0.02$), while fasting insulin levels increased by $25.9\% \pm 9.3\%$ ($p = 0.04$) in men on ADT [30]. Fasting glucose levels remained unchanged. In another study, median serum fasting insulin levels were 11.8 mU/l, 15.1 mU/l ($p = 0.02$) and 19.3 mU/l ($p = 0.02$) at baseline, 1 month and 3 months into ADT, respectively. In addition, the authors also noted a direct association between fasting insulin levels with the change in FM ($r = 0.56$, $p = 0.013$), suggesting that hyperinsulinemia and insulin resistance is closely linked to obesity [31].

Although several short-term prospective studies noted the development of hyperinsulinemia as early as 3 months into ADT, Basaria et al. conducted a cross-sectional study investigating the long-term effects of ADT on metabolic parameters in three groups of men: (1) men with PCa on ADT for at least 12 months, (2) men with PCa not on ADT and (3) healthy, age-matched men [32]. After adjusting for age and BMI, men on ADT had higher fasting insulin levels (45.0 ± 7.25 μ U/ml) compared with non-ADT (24.0 ± 7.24 μ U/ml, $p = 0.05$) and healthy age-matched controls (19.0 ± 7.39 μ U/ml, $p = 0.02$). Insulin resistance, as measured by $HOMA^{IR}$, was also higher in ADT (17 ± 2.78), compared to non-ADT (6.0 ± 2.77, $p < 0.01$) and controls (5.0 ± 2.83, $p = 0.01$). The novel finding of the study was that fasting glucose levels were also elevated in men on ADT (131 ± 7.43 mg/dl) compared to non-ADT (100 ± 7.42 mg/dl) and healthy controls (99 ± 7.58mg/dl) (Figure 1). Furthermore, duration of ADT was directly related to the severity of metabolic abnormalities (Figure 2). This study suggested that long-term use of ADT is not only associated with insulin resistance but also diabetes. Soon after this report, Keating et al. [33] in an observational study confirmed these findings and

Table I. Studies documenting changes in body composition with androgen-deprivation therapy.

Study	Aim(s)	Patient population	Study design	Length of study	Conclusions/comments
Galvão et al. [52]	To assess the effects of ADT on whole-body and regional muscle, fat and bone mass in men with PCa without metastatic bone disease	72 patients with PCa (aged 44–88 yrs) receiving intermittent ADT	Prospective	36 weeks	Overall lean body mass decreased by 2.4% ($p < 0.001$); upper limb by 5.6% ($p < 0.001$) and lower limb by 3.7% ($p < 0.001$). Overall fat mass increased by 13.8% ($p < 0.001$) with accumulation mostly localised to the extremities (upper limb 20.7%, $p < 0.001$ and lower limb 18.7%, $p < 0.001$). Truncal fat increased by 12% ($p < 0.001$)
Smith et al. [18]	To evaluate the treatment effects of GnRH agonist on body composition in asymptomatic men with non-metastatic PCa.	32 subjects with locally advanced, lymph-node positive or recurrent PCa.	Prospective	48 weeks	Compared to baseline, after 48 weeks of leuprolide treatment, weight increased by 2.4% $\pm$ 0.8% ($p = 0.005$), fat mass increased by 9.4% $\pm$ 1.7% ($p < 0.001$) and lean mass decreased by 2.7% $\pm$ 0.5% ($p < 0.001$). Subcutaneous abdominal fat increased by 11% $\pm$ 3.4% ($p = 0.003$) while intraabdominal fat did not change significantly ($p = 0.94$).
Smith [17]	To study the effects of androgen deprivation therapy on body composition in men with non metastatic PCa.	79 men with Stage M0 PCa.	Prospective	12 months	Weight increased by 1.8% $\pm$ 0.5% ($p < 0.001$), fat mass increased by 11% $\pm$ 1.7% ($p < 0.001$) and lean mass decreased by 3.8% $\pm$ 0.6% ($p < 0.001$).
Basaria et al. [19]	To determine the effect of ADT on body composition and muscle strength.	Three groups: (1) 20 men with PCa undergoing ADT for at least 12 months (ADT group) 2) 18 age-matched men with non metastatic PCa not on ADT (non-ADT group) 3) 20 age-matched healthy men (control group)	Cross-sectional	Cross-sectional	Cross-sectional analysis revealed that ADT group had higher overall % fat mass compared to the non-ADT and control group (32.2% $\pm$ 5.4% vs. 26.2% $\pm$ 6.0% and 22.4% $\pm$ 4.1%, respectively, $p \leq 0.0001$). Truncal and extremity fat mass also highest in the ADT group. Upper body muscle strength was lowest in the ADT group compared to non-ADT and control group (47.6 $\pm$ 15.6 kg vs. 79.6 $\pm$ 35.3 and 61.1 $\pm$ 21.4, respectively, $p = 0.001$). Quality of life (QOL) was lowest in men in the ADT group. Men in the ADT group had significant physical limitation ($p = 0.006$), role limitation ($p = 0.02$) and decreased health perception ($p = 0.004$).

Table II. Studies documenting metabolic and cardiovascular perturbations with ADT.

Study	Aim(s)	Patient population	Study design	Length of study	Conclusions/Comments
Dockery et al. [61]	To assess metabolic and vascular effects of ADT in men with PCa.	16 men with PCa were given ADT-while a control group of 15 age-matched healthy men were followed for a period of 3 months.	Prospective	3 months	In the ADT group, fasting insulin levels were increased after 3 months from 6.89 ± 4.84 to 11.34 ± 8.16 ($p = 0.02$). No changes were observed in fasting glucose. Decreased arterial compliance was noted in the ADT group compared to the control group ($p = 0.03$).
Smith et al. [30]	To characterize the short-term effects of GnRH agonist on insulin sensitivity.	25 men with PCa followed for 3 months.	Prospective	3 months	Whole body insulin sensitivity index decreased by 12.9% ± 7.6% ($p = 0.02$) after 3 months of ADT. Fasting plasma insulin levels increased by 25.9% ± 9.3% ($p = 0.04$) Fat mass increased by 4.3% ± 1.3% ($p = 0.002$) and lean mass decreased by 1.4% ± 0.5% ($p = 0.006$).
Smith et al. [31]	To determine the effects of ADT on body composition, metabolic parameters and arterial stiffness.	22 men (mean age 67 ± 8 year) with newly diagnosed PCa who were started on ADT and observed for a period of 3 months.	Prospective	6 months	No changes in lipid profiles or serum glucose levels. Median serum fasting insulin rose from 11.8 mU/l to 19.3 mU/l in 3 months ($p = 0.02$). ADT also resulted in increased central arterial pressure and higher pulse wave velocity.
Basaria et al. [32]	To evaluate the long-term effects of ADT on glucose and insulin metabolism	Three study groups: (1) 18 men with PCa on ADT for at least 12 months (ADT group) (2) 17 age-matched men with non metastatic PCa and not on ADT (non-ADT group) (3) 18 age-matched healthy men (control group)	Cross-sectional	Cross-sectional	Men in the ADT group had higher fasting insulin levels compared with the non-ADT and control group. (45.0 ± 7.25 μU/ml vs. 24.0 ± 7.24 μU/ml, $p = 0.05$ & 19.0 ± 7.39 μU/ml, $p = 0.02$ respectively). HOMA IR index was highest in ADT treated men (17 ± 2.78), compared to non-ADT (6.0 ± 2.77, $p < 0.01$) and control group (5.0 ± 2.83, $p = 0.01$). Fasting glucose levels were 131 ± 7.43 mg/dl, 103 ± 7.42 mg/dl, ($p = 0.01$) and 99 ± 7.58 mg/dl ($p < 0.01$) in the ADT, non-ADT and control groups, respectively.
Braga-Basaria et al. [40,51]	To evaluate the prevalence of metabolic syndrome in men undergoing ADT.	Three study groups: (1) 20 men with PCa undergoing ADT for at least 12 months (ADT group) (2) 18 age-matched men with PCa not on ADT (non-ADT group) (3) 20 age-matched healthy controls (Control group)	Cross-sectional	Cross-sectional	55% of men in the ADT group met criteria for metabolic syndrome, compared with 22% and 20% of men in the non-ADT and control groups, respectively (Overall $p = 0.03$).

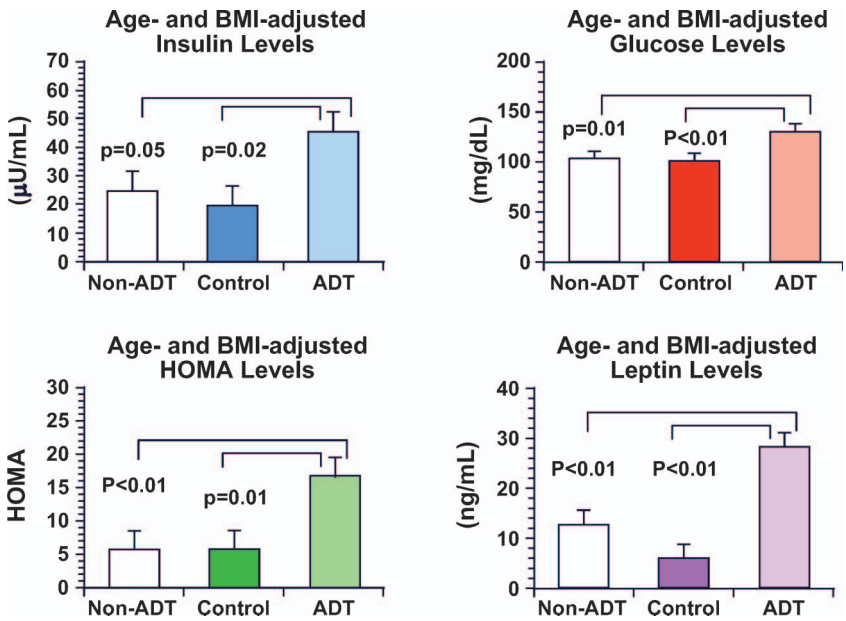

Figure 1. Metabolic parameters in men undergoing long-term ADT compared with non-ADT and healthy controls (adapted from Ref. [32]).

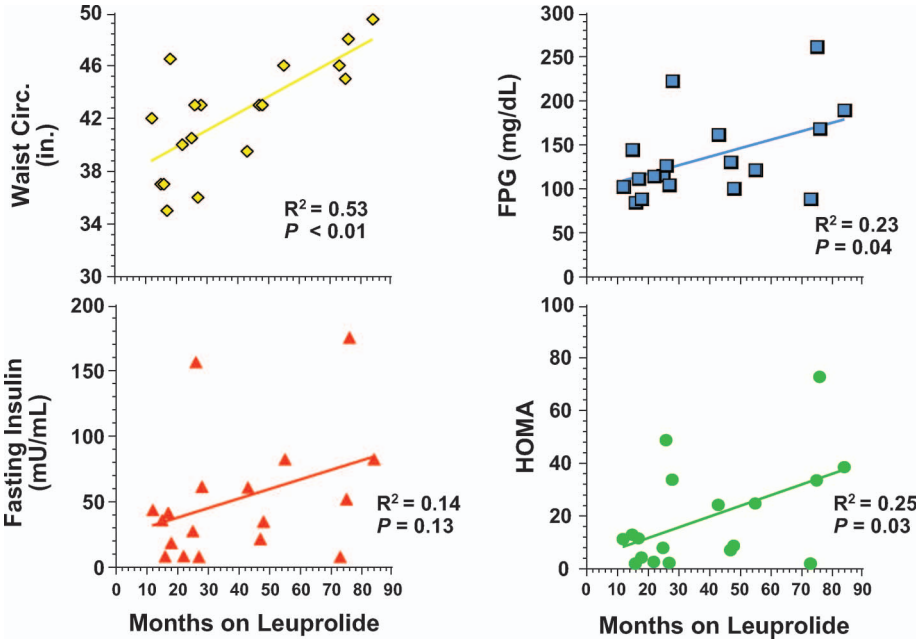

Figure 2. Association between duration of ADT and severity of metabolic abnormalities (adapted from Ref. [32]).

showed that men on ADT have an increased risk of incident diabetes.

Such changes in insulin metabolism are not unanticipated. Testosterone induces muscle hypertrophy by increasing both type I and type II muscle fibres in a dose-dependent manner [34]. Hence, an increase in muscle mass may result in improved glucose disposal. A growing body of evidence shows that androgens stimulate mesenchymal pluripotent stem cells to enter myogenic lineage while inhibiting preadipocytes from developing into mature adipocytes [35,36], thereby enhancing myogenesis and preventing adipogenesis. In a castrated state, such as in ADT, the loss of muscle mass may result in reduced glucose utilisation while an increase in FM may be responsible for insulin resistance. These changes place patients on ADT at a higher risk of developing metabolic syndrome, frank diabetes and accelerated coronary artery disease. Hence, screening for diabetes in patients who are already undergoing or planning to undergo ADT is essential to halt the progression of worsening metabolic profile. Diet, nutrition and lifestyle counselling should be offered to all patients undergoing ADT. If impaired fasting glucose is detected, an oral glucose tolerance test should be performed to detect occult diabetes and referral for an endocrine consultation should be considered.

Dyslipidemia. Studies have shown correlation between lipoprotein levels and serum sex hormones. In men, higher testosterone levels are inversely associated with low-density lipoprotein (LDL) cholesterol, total cholesterol and triglycerides. As far as high-density lipoprotein (HDL) cholesterol is concerned, higher testosterone levels are associated with lower HDL levels [37]. Testosterone administration in hypogonadal men has been shown to improve lipid profile [38,39]. Among men undergoing ADT, dyslipidemia is a well-recognised phenomenon and an unfavourable treatment consequence. In both prospective and cross-sectional studies, ADT has been shown to increase total and HDL cholesterol [18,30,40,59]. In one prospective study, total cholesterol increased by 9.4% ($p \leq 0.001$) and HDL by 9.9% ($p = 0.01$) after 12-weeks of treatment [30]. In another prospective 48-month long study, total, HDL and LDL cholesterol increased by 9, 11.3 and 7.3%, respectively [18]. Several prospective studies have observed an increasing trend in serum triglycerides with ADT. In one study, triglyceride levels increased by 23% [30], while another study showed increments of 26.5% [18]. Attention to hypertriglyceridemia as a CAD risk factor represents an important step in assessing global risk for CAD development because it is an independent risk factor for CAD [41,42].

The significance of increase in HDL during ADT remains unclear. It remains to be seen if it offers any protection towards cardiovascular disease in patients undergoing ADT. In contrast to prospective studies, a recent cross-sectional study showed no difference in HDL levels between men undergoing ADT versus controls [40]. Further, long-term longitudinal studies should be performed to assess the mechanism and impact of elevated HDL on CAD risk in this patient population [43].

Men on ADT deserve regular screening for hyperlipidemia. Management of dyslipidemia in men on ADT should begin with non-pharmacologic therapy such as lifestyle modifications such as diet, exercise and weight control. Pharmacological options should be considered if lifestyle modifications prove unsuccessful or if the patient already has a history of hyperlipidemia or presence of preexisting cardiac disease.

Metabolic syndrome. Metabolic syndrome (MetS) constitutes a cluster of metabolic abnormalities that predisposes subjects to an increased risk of cardiovascular disease and mortality [44–47]. MetS affects one in five people with some studies estimating the prevalence in the United States to be up to 25% of the population [45]. The definition of MetS is somewhat arbitrary, with various health organisations stating different definitions. Currently, the criteria put forth by the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) are the most frequently used in epidemiological studies. For the diagnosis of MetS in men, ATP-III criteria require at least three of the following: fasting plasma glucose level > 110 mg/dl, serum triglyceride ≥ 150 mg/dl, serum HDL cholesterol < 40 mg/dl, waist circumference ≥ 102 cm or 40 inches and blood pressure $\geq 130/85$ mmHg [48].

Serum levels of testosterone have been inversely associated with the presence of metabolic syndrome. Data from the Massachusetts Male Aging Study revealed that low levels of testosterone and SHBG were predictive of metabolic syndrome [49]. In Baltimore Longitudinal Study of Aging, the prevalence of MetS increased with age and was inversely related to total testosterone and SHBG levels [50].

Data regarding the association of ADT with MetS have begun to emerge. A cross-sectional study established that men undergoing ADT for at least a year had higher prevalence of MetS (Figure 3). More than 50% of men in the ADT group met criteria for MetS compared to 22% in non-ADT and 20% in control group. Hyperglycemia and abdominal obesity were major determinants of MetS [51]. The higher prevalence of MetS in the ADT group compared to non-ADT (55% vs. 22%) strongly indicates that ADT itself predisposes to MetS, rather than any direct influence of PCa.

It has been proposed that the MetS seen with ADT is different than the conventional MetS. For instance, to be diagnosed with conventional MetS, the levels of HDL should be < 40 mg/dl. To the contrary, ADT is associated with an increase in HDL cholesterol [18,40,52,53]. Furthermore, adiponectin (adipokine associated with improved insulin resistance) levels have been shown to be inversely related with features of MetS. In contrast, studies in ADT-treated men have shown an elevation in adiponectin levels [53,54]. It appears that additional research is needed to further define and characterise these metabolic effects and their relationship to cardiovascular disease.

Cardiovascular risks and ADT

Epidemiological studies have shown that low serum testosterone is an independent risk factor for aortic atherosclerosis in elderly men [55]. Sex hormones, particularly testosterone, play a pivotal role in determining cardiovascular health [56]. Androgen receptors are not only present in the vasculature but also in the left ventricular wall [57,58]. Animal studies have shown that testosterone relaxes coronary arteries [59]. Human studies have also shown that testosterone administration to hypogonadal men with coronary artery disease improves angina and time to ST-segment depression [60].

The use of ADT is associated with harmful effects on vascular compliance and atherosclerosis. In a study by Smith et al. [31], men treated with a GnRH agonist for 3 months were noted to develop increased central arterial pressure as well as higher pulse wave

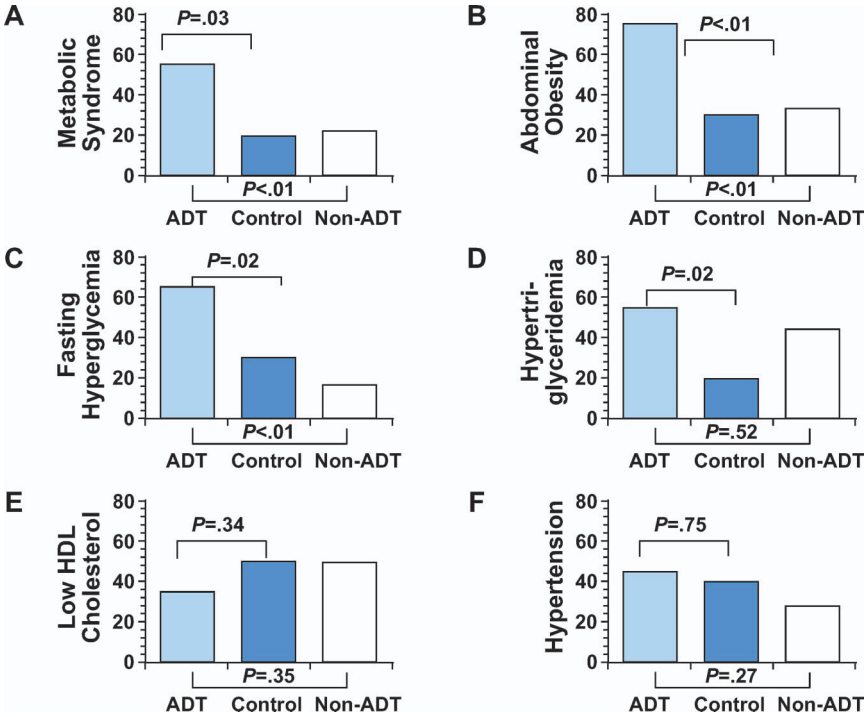

Figure 3. Prevalence of metabolic syndrome in ADT group compared with non-ADT and control groups (adapted from Ref. [51]).

velocity. Taken together, these two indices represent a decrease in vascular compliance. After 3 months, ADT was discontinued in a subgroup of patients while the remainder study cohort continued ADT for 3 additional months. Improvement in hemodynamic indices after cessation of treatment was observed. Another study supported this observation [61]. In this study, 16 men with PCa were treated with ADT and followed for a total of 3 months. Systemic arterial compliance (SAC) was used as a measure of arterial stiffness. Men in the ADT group had decreased SAC measurements (indicating increased arterial stiffness) compared to men in the control group at 3 months. In a large retrospective database analysis of men aged 65 and older with loco-regional PCa, Keating et al. [33] showed that GnRH agonist is associated with incident coronary heart disease, myocardial infarction and sudden cardiac death. Even after adjustment for age, tumor characteristics and co-morbidities, this relationship remained significant [33].

The results from the Cancer of the Prostate Strategic Urologic Research Endeavour (CapSURE) also support an association between ADT use and cardiovascular disease [62]. After adjusting for age, prevalent heart disease and diabetes, use of ADT was associated with a shorter time to death from cardiovascular causes. The 5-year cumulative estimates of cardiovascular mortality in men over 65 years of age were 5.5% in the ADT group compared to 2.0% in the non-ADT group. Likewise, a large population study of $\sim$20,000 men with newly diagnosed PCa who received ADT for at least a year found that patients were 20% more inclined to have serious cardiovascular morbidity than men with PCa not receiving ADT [63]. One recent study did not show increased incidence of cardiovascular disease in men on ADT. In the RTOG 92-02 trial, $\sim$1500 men with locally advanced cancer were randomised to 4 months (short-term) or 28 months (long-term) of ADT [64]. The results showed that longer-term adjuvant ADT was not associated with increased cardiovascular mortality compared to short-term ADT. The 5-year cardiovascular mortality rate was 5.9% in the long-term compared to 4.8% in the short-term ADT group ($p = 0.58$).

Summary

Although these studies suggest that ADT is associated with cardiovascular disease, further confirmation is needed to delineate if there is a direct causal relationship between ADT and cardiovascular disease or if the increase in cardiovascular disease seen with ADT use is a consequence of hypogonadism and the treatment-related metabolic abnormalities. Regardless of the cause-effect consequences, cardiovascular disease mortality remains a growing concern in these men. The rate of death from cardiovascular disease has become the most common cause of non-prostate cancer-related death in these men [65]. Given the data, initiation of early screening for insulin resistance, diabetes, hypertension and hyperlipidemia in patients undergoing ADT is essential for the detection and prevention of cardiac disease. Patients with an underlying history of cardiac disease should have close monitoring for signs and symptoms such as new-onset angina or congestive heart failure. Referral to a cardiologist may be justified in selected cases.

Conclusion

Although ADT can improve overall survival in certain cohorts of patients, it is undeniable that the effects induced by this treatment have serious consequences. The side effects of ADT should be considered and discussed between physicians and patients when making treatment decisions. If the decision is to initiate ADT, proper monitoring and management of weight, insulin resistance, diabetes and hyperlipidemia should be practiced.

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