Androgen-Deprivation Therapy and Metabolic Syndrome in Men With Prostate Cancer

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Purpose/Objectives: To examine the trajectory of changes in body composition and metabolic profile in men who receive androgen-deprivation therapy (ADT) for prostate cancer.

Design: Prospective longitudinal design with repeated measures.

Setting: Urban medical center in the southwestern United States.

Sample: 55 men starting radiation therapy for prostate cancer.

Methods: Changes in the parameters of metabolic syndrome were estimated with ADT (n = 31) and non-ADT (n = 24) groups by repeated-measures analysis of variance implemented by general linear mixed-effects models. Models included interactions between groups and follow-up time to test differences between the groups.

Main Research Variables: Body composition and metabolic variables.

Findings: The ADT group demonstrated a transient increase in waist circumference at the nine-month time point and significant changes in measures of insulin resistance were noted at the three month point. Values for diastolic and systolic blood pressure, plasma glucose, high-density lipoprotein, and triglycerides were not altered for either group. Differences in metabolic variables or measures of body composition did not differ significantly between the groups.

Conclusions: The findings demonstrate the development of insulin resistance in men receiving ADT as early as three months after starting ADT.

Implications for Nursing: Addressing survivorship concerns can lead to the development of nursing interventions designed to reduce adverse effects associated with ADT.

Key Words: prostate cancer, androgen-deprivation therapy, metabolic syndrome

With the exception of skin cancer, prostate cancer is the most common type of cancer among men in the United States (Higano, 2012). The American Cancer Society (ACS) estimated that more than 238,000 new cases of prostate cancer were diagnosed in the United States in 2013, representing 25% of all new cancer diagnoses among men in that year (Siegel, Naishadham, & Jemal, 2013). In the 1990s, a dramatic increase in the use of androgen-deprivation therapy (ADT) occurred (Shahinian, Kuo, Freeman, Orihuela, & Goodwin, 2005). ADT is thought to avoid the physical and psychological discomforts of orchiectomy (Lepor & Shore, 2012). About half of the two million survivors of prostate cancer are treated with ADT at some point (Higano, 2012), particularly men with intermediate- or high-risk disease undergoing radiation therapy (RT), or men with locally obstructive or metastatic disease (Lepor & Shore, 2012). In addition, some evidence suggests that ADT benefits men post-prostatectomy with lymph node involvement, or can be used as cytoreductive therapy in men with large prostate volume anticipating brachytherapy (Myklak & Wilson, 2011; Quon & Loblaw, 2010).

However, emerging evidence suggests that the adverse effects of ADT on body composition and metabolic parameters may lead to the development of metabolic syndrome, a constellation of risk factors implicated in the development of diabetes and cardiovascular disease (Alberti, Zimmet, & Shaw, 2005; Nobes, Langley, & Laing, 2009). The ADT-induced increase in truncal obesity and decrease in lean body mass are associated with insulin resistance, a central component of the metabolic syndrome (Yannucci, Manola, Garnick, Bhat, & Bubley, 2006). Because of the high use of ADT and extended survival of men with prostate cancer, the potential risk for the development of metabolic syndrome is high. Therefore, the purpose of this prospective study was to examine the trajectory of changes in body composition and metabolic profile in men who receive ADT as treatment for prostate cancer.

In 1941, Charles Huggins documented the dependence of the prostate gland on androgens, providing

a pathway for androgen deprivation in the treatment of prostate cancer (Denis & Griffiths, 2000; Rashid & Chaudhary, 2004). Gonadatropin-releasing hormone agonist (GnHR) is intended to interrupt the supply of testosterone to the prostate cancer cell, interfering with its growth. However, because androgens also are important determinants of body composition, glucose and insulin levels, and insulin resistance (Basaria, Muller, Carducci, Egan, & Dobs, 2006; Smith, 2007), this medically-induced hypogonadal state is accompanied by significant adverse effects with both direct and indirect effects on the development of metabolic syndrome.

Literature Review

The long-term effects of ADT on body composition, glucose, and insulin metabolism, as well as the prevalence of metabolic syndrome, have been documented in three critical studies comparing men with prostate cancer who receive ADT with men who are ADT-naive. Basaria et al. (2002) conducted a cross-sectional study (N = 58) comparing (a) men receiving ADT for at least 12 months, (b) men post-treatment (prostatectomy and/or radiotherapy) for local disease without ADT, and (c) age-matched healthy men. Men receiving ADT demonstrated significantly lower bone mineral density, higher fat mass, reduced upper body strength, poorer sexual function, and lower quality-of-life scores than men who were ADT-naive.

A second cross-sectional study (Basaria et al., 2006) with three similar comparison groups (N = 53) was designed to evaluate the long-term effects of ADT on fasting glucose, insulin levels, and insulin resistance. Men in the ADT group demonstrated significantly higher fasting levels of glucose, insulin, leptin, and insulin resistance. A significant negative correlation existed between total and free testosterone and fasting glucose, insulin, leptin, and insulin resistance, which led the authors to conclude that adverse effects appeared secondary to androgen deprivation (Basaria et al., 2006).

The third study (Braga-Basaria et al., 2006) also used three similar comparison groups (N = 58) and was designed to evaluate the prevalence of metabolic syndrome in men receiving ADT for prostate cancer. Men receiving ADT demonstrated significantly higher body mass index, lower total and free testosterone, and a higher prevalence of metabolic syndrome than men who had not received ADT. Fifty-five percent of men receiving ADT met the criteria for metabolic syndrome, compared with 22% of men who were ADT-naive and 20% of age-matched healthy men. Analysis of the components of metabolic syndrome revealed that men in the ADT group had a higher prevalence of hyperglycemia and abdominal obesity when compared to men in the other two groups (Braga-Basaria et al., 2006).

Although those studies provide evidence supporting the adverse metabolic effects of ADT, they do not address the timing or sequence of development of metabolic abnormalities. Understanding the timing of these factors may help to identify those at risk, influence the timing of screening measures, and lay a foundation for the development of timely interventions designed to mitigate this risk. For example, if the increase in fat mass precedes insulin resistance, it may not only serve as a marker for the eventual development of insulin resistance, but ultimately could be the focus of interventions. Therefore, studies that are prospective address the limitations of cross-sectional studies.

Four prospective studies provide preliminary evidence of the change trajectory in body composition and glucose and insulin metabolism secondary to ADT. Smith et al. (2002) used dual X-ray absorptiometry (DEXA), computed tomography (CT), and bioelectrical impedance analyses, and documented increases in weight and fat body mass with decreases in lean body mass after 48 weeks of ADT. These findings were supported by Smith et al. (2008), who used DEXA and CT measurements and found increases in fat mass with accompanying decreases in lean body mass in men receiving ADT. The changes were evident for 80% of the participants after six months. In addition, Smith, Lee, and Nathan (2006) used DEXA and oral glucose tolerance tests and found an increase in fat mass, fasting insulin, and mean glycosylated hemoglobin, as well as worsening insulin sensitivity in men receiving ADT after 12 weeks. Haidar, Yassin, Saad, and Shabsigh (2007) evaluated men with insulin-dependent diabetes who were receiving ADT, and documented deterioration in all biochemical cardiovascular risk markers assessed. However, the aforementioned studies did not include comparison groups of men who were ADT-naive, and included relatively small samples (25–32 men).

The association among ADT, diabetes, and cardiovascular disease cannot be overstated and has been examined in several large studies. In an effort to determine the relationship between ADT and the incidence of diabetes, Lage, Barber, and Markus (2007) examined a medical claims database containing data from 8,481 men. This large cohort study compared men with prostate cancer without a diagnosis of diabetes who received ADT with those who did not receive ADT. Unadjusted data revealed a greater incidence of diabetes in men who received ADT. After controlling for demographic characteristics, general health, comorbidities, and use of statins, men who received ADT had a significantly higher risk of being diagnosed with diabetes. However, Lage et al. (2007) reported no information on the trajectory of changes in the metabolic profile (i.e., insulin resistance, hyperinsulinemia, and hyperglycemia) culminating in the diagnosis of diabetes.

In a large cohort study of 73,196 men, Keating, O'Malley, and Smith (2006) identified the risks of ADT for diabetes and coronary heart disease, myocardial infarction, and sudden cardiac death. Use of GnRH agonist was associated with an increased risk for all disease endpoints. In another large, observational study (N = 19,079), Alibhai et al. (2009) determined that ADT use was associated with an increased risk of diabetes, although not an increased risk of acute myocardial infarction or sudden cardiac death. The extant literature is without consensus on the effects of ADT on cardiovascular risk.

The American Heart Association, the American Cancer Society, and the American Urological Association established the existence of a reasonable, though not confirmed, relationship between ADT and cardiovascular events and death (Levine et al., 2010). Based on a review of the literature, the current study's researchers also acknowledged the possible association between ADT and cardiovascular events.

Although adverse effects of ADT on body composition and measures suggestive of the metabolic syndrome have been observed in cross-sectional and uncontrolled longitudinal studies, some of the adverse changes remain undocumented in controlled, prospective longitudinal studies. Such studies would provide helpful information in the timely initiation of screening measures and development of interventions. The aims of the current study were (a) to determine whether 12 months of ADT treatment worsens components of the metabolic syndrome (fasting insulin and glucose, insulin resistance, fasting triglycerides and high-density lipoprotein [HDL], hypertension, and abdominal obesity), and (b) to describe the trajectory of changes in components of the metabolic syndrome during treatment with ADT to identify the onset of adverse changes in metabolism and body composition.

Methods

Study Design, Sample, and Setting

A prospective longitudinal design with repeated measures was used to identify the effects of ADT on body composition and components of the metabolic syndrome, including insulin resistance. Men receiving RT, either external beam or brachytherapy, who were prescribed ADT were compared with men also receiving RT but not receiving ADT (control). Measurements occurred every three months for one year.

Metabolic syndrome in men was defined as the presence of any three of the following five components: central obesity (i.e., waist circumference greater than 102 cm), hypertension (i.e., blood pressure greater than 130/85 mm Hg), elevated triglycerides (i.e., greater than 150 mg/dl), low HDL-cholesterol (i.e., lower than 40 mg/dl), and fasting hyperglycemia (i.e., less than 100 mg/dl) (Alberti et al., 2009). Participants receiving medication for hypertension and diabetes were considered positive for the respective component of metabolic syndrome, while those receiving niacin or fibrates (e.g., fibric acid, gemfibrozil) were considered to have elevated triglycerides.

A convenience sample was recruited from the urology and oncology ambulatory care departments of a large, urban VA medical center. Inclusion criteria included a diagnosis of prostate cancer, the ability to read and write English, and RT treatment with or without ADT. Exclusion criterion included oral or injectable steroid use.

Procedure

The study was approved by the Carl T. Hayden Veterans Affairs Medical Center institutional review board. Potential participants were given an informational flyer describing the study during a regularly scheduled clinic appointment. Patients expressing an interest in the study were introduced to a member of the research staff, who explained the study. Patients agreeing to participate signed a consent form. Baseline data were collected after obtaining voluntary informed consent prior to the administration of ADT. Follow-up data were collected at three-month intervals for one year. Data were collected from May 2009 through July 2012.

Data and Measurements

The study measures included demographics, clinical information, physical measurements, and physiologic data. Demographic information was collected via interview and included age, marital and employment status, education, race, and ethnicity. Clinical information was collected from the participant electronic health record and included Gleason score and stage of prostate cancer at diagnosis, current medications, and the presence of comorbidities. Physical measurements included weight and height, waist and hip circumference, and body composition. Physiologic data, including serum glucose, insulin, and lipids, were measured on fasting blood samples using standard techniques at the medical center outpatient laboratory.

Sample Size and Power

A sample size of 33 in both ADT and non-ADT groups originally was proposed, with a plan to oversample by 5%, allowing for a 5% dropout. This sample size was selected to provide 80% power at two-sided alpha (0.05) to allow detection of a 0.7 standard deviation (SD) difference between groups. This effect size was hypothesized based on differences between men receiving and not receiving ADT as reported in cross-sectional studies (Basaria et al., 2002, 2006; Braga-Basaria et al., 2006). The final sample included 31 participants receiving ADT (29 of whom completed the study) and 24

participants not receiving ADT (22 of whom completed the study), which provided 80% power at two-sided alpha (0.05) to detect a 0.81 SD difference between baseline and one-year for ADT and non-ADT groups. Twenty-nine participants receiving ADT completed the study, which gave researchers 80% power at two-sided alpha (0.05) to detect a 0.54 SD difference between baseline and one-year follow-up measurements. The authors evaluated power to characterize and estimate significant adverse changes in metabolic parameters, which were defined as a 0.5 SD change in the adverse direction. With 31 participants receiving ADT, 29 of whom completed the study, researchers had a 74%–77% power to estimate the time at which adverse change in the metabolic parameters were significant. For the 24 participants not receiving ADT, 22 of whom completed the study, the corresponding power to detect adverse changes in metabolic parameters was 60%–65%.

Data Analysis and Interpretation

The distribution of independent and dependent variables was explored, and transformations were applied where needed to approximate normality. Descriptive statistics were computed for demographics, medical information, laboratory, and physical measures at baseline and at the end of the study. Continuous measures were compared by independent samples t tests, either without or, if needed, after appropriate transformation. Categorical measures were compared by chi-square tests or, when appropriate, by Fisher's exact test. The dependent variables for the first aim were the changes in measures of the metabolic syndrome after one year of ADT treatment and differences in one-year changes in components of the metabolic syndrome for patients treated with ADT compared with patients not treated with ADT. Dependent variables were identical for the second aim, and all follow-up times were considered to determine the time at which adverse changes in individual parameters of the metabolic syndrome were first significant.

Longitudinal trends for data were analyzed with general linear mixed-effects models with random coefficients. One-year changes in parameters of the metabolic syndrome for the ADT and non-ADT groups were assessed in the same mixed model. A grouping variable (ADT versus non-ADT) and interaction between group and time variables were included, which allowed estimating changes in each group individually, as well as estimating and testing differences in one-year changes between ADT and non-ADT groups. The mixed models included a random effect for patient and a random effect for time, reflecting the time of sample measurement since enrollment in this study (baseline sample time = 0). Higher ordered (squared, cubic) time factors were considered, and their contribution to the models was evaluated with reference to the Akaike Information Criteria. Models also included (as fixed effects) age, race (Caucasian versus other), ethnicity (Hispanic versus other), and Gleason score (6 or less, 7, 8 or greater). For the second aim, the time at which adverse changes in individual parameters of the metabolic syndrome were first significant was estimated for each group separately in the same mixed models by fitting appropriate contrasts. In a secondary analysis, the researchers considered whether any change occurred that was distinguishable from the null as statistically significantly.

Results

Baseline data were collected on 55 participants, 24 in the control group and 31 in the ADT group. Demographic and clinical characteristics of the sample are summarized in Table 1. No baseline differences existed between the two groups for either demographic or medical characteristics, with the exception of Gleason score (the ADT group demonstrated a significantly higher Gleason score [$p < 0.001$]). Thirty-two (58%) participants met criteria for metabolic syndrome at the start of the study. Table 2 summarizes the presence of elements of metabolic syndrome at baseline.

Changes in Components of Metabolic Syndrome

To address aim 1, data were analyzed for within-group and between-group changes over time. The ADT group demonstrated a transient increase in waist circumference ($\bar{X} = 2$, standard error [SE] = 0.9 cm, $p < 0.03$) at the nine-month time point, as well as significant changes in measures of insulin resistance over the data collection period. A linear trend for homeostatic model assessment–insulin resistance (HOMA-IR) was noted ($p < 0.02$) for the ADT group. No trend was noted in the non-ADT group. The p value for group-by-visit interaction was 0.24, indicating that a difference in the time trend for HOMA-IR between groups could not be detected. At one year, HOMA-IR had increased 39% (95% confidence interval [CI] [7, 78], $p < 0.05$) for the ADT group. None of the other measures that were assessed changed during the study in the ADT group.

In the non-ADT group, several statistically significant changes were noted during the study: lean body mass had increased at 12 months (SE = 0.18, $p < 0.05$); weight was increased significantly at 6, 9, and 12 months ($p < 0.02$); body fat and hip circumference were transiently increased at nine months ($p < 0.002$) and six months ($p < 0.02$), respectively; and waist-to-hip ratio was transiently decreased at six months ($p < 0.02$).

One-year values for diastolic and systolic blood pressure, plasma glucose, and HDL triglycerides did not alter from baseline for either group. Differences between one-year changes for ADT and non-ADT groups

were not significant for any of the metabolic variables or measures of body composition. However, the increase in HOMA-IR appeared to be larger for the ADT group, and the increase in lean body mass appeared larger for the non-ADT group.

Trajectory of Adverse Changes

To address aim 2, data were analyzed for the first appearance of clinically significant changes in the markers of metabolic syndrome. In the ADT group, HOMA-IR was significantly different (32% increase) from baseline at the three-month follow-up time (95% CI [7, 64], $p < 0.02$). At the nine-month visit, HOMA-IR had increased significantly ($p < 0.003$) compared with baseline and met the predetermined criteria of an increase of 0.5 SD or more. At one year, HOMA-IR remained significantly elevated compared with baseline, but this increase no longer met the predetermined criteria of a 0.5 SD more adverse than baseline. A small, statistically significant increase (2 cm, SE = 0.9, $p < 0.05$) in waist circumference occurred in the ADT group at nine months, but this difference was no longer statistically significant at one year and changes in waist circumference at all time points were far less than the 0.5 SD (7 cm) criteria set for clinically significant increases. For the non-ADT group, no measures were altered adversely by 0.5 SD or more during the study. However, several changes from baseline during the study were statistically significant, as noted previously.

Table 1. Demographic and Clinical Characteristics by Group

Characteristic	ADT and RT (n = 31) $\bar{X}$	ADT and RT (n = 31) SD	RT (n = 24) $\bar{X}$	RT (n = 24) SD	Combined (N = 55) $\bar{X}$	Combined (N = 55) SD	p
Age (years)	65.8	6.5	67	5.3	66.3	6	0.49
BMI (kg/m²)	31.2	5.9	30.7	5.7	31	5.7	0.75
Body fat by BIA	29	10.2	27	10.7	28.2	10.4	0.47
Body fat (%)	29.3	5.5	27.3	5.4	28.4	5.5	0.18
DBP (mm Hg)	85	16	82	9	84	13	0.41
Lean body mass (%)	18.3	1.3	18.6	1.1	18.4	1.2	0.26
SBP (mm Hg)	141	23	134	12	138	19	0.12
Waist circumference (cm)	112	15	110	14	111	15	0.55
Waist-to-hip ratio	1.03	0.06	1.03	0.04	1.03	0.05	0.95
Characteristic	**n**		**n**		**n**		**p**
Race							1[a]
Caucasian	27		21		48		
Ethnicity							0.62[a]
Non-Hispanic	28		23		51		
Education							0.19
High school or less	13		6		19		
Greater than high school	18		18		36		
Marital status							0.87
Partnered	20		16		36		
Gleason score							< 0.001
6 or less	5		19		24		
7	13		4		17		
8–10	13		1		14		
Characteristic	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**p**
Hip circumference (cm)	105	97, 117	105	97, 113	105	97, 114	0.54
Glucose (mg/dl)	100	94, 113	98	90, 108	100	93, 109	0.7
HOMA-IR	3.1	1.6, 4.5	2.7	1.7, 3.9	2.8	1.6, 4.4	0.85
HDL (mg/dl)	42	35, 52	46	40, 54	46	38, 54	0.27
Triglyceride (mg/dl)	127	97, 165	98	83, 172	116	94, 169	–

[a] Fisher's exact test

ADT—androgen-deprivation therapy; BIA—bioelectrical impedance analysis; BMI—body mass index; DBP—diastolic blood pressure; HDL—high-density lipoprotein; HOMA-IR—[fasting insulin (uU/ml) x fasting glucose (mmol/L)]/22.5; IQR—interquartile range; RT—radiation therapy; SBP—systolic blood pressure

Discussion

The findings of this prospective longitudinal study demonstrate the development of insulin resistance as early as three months in men receiving ADT; insulin resistance was not demonstrated in those men not receiving ADT. By nine months, insulin resistance had increased by 43% (0.5 SD), the proposed measure of clinical significance. Although insulin resistance resolved slightly by the end of the study and was no longer elevated at least 0.5, it remained statistically significantly different from baseline. This is clinically important because glucose intolerance may play a significant role in the development of coronary artery disease (Haffner, 2006). Although a transient increase occurred in waist circumference in men receiving ADT at nine months, the increase did not meet the predetermined threshold for clinical increase and was not sustained throughout the 12 months of the study.

Although a significant and persistent increase in waist circumference did not occur throughout the

Table 2. Prevalence of Metabolic Syndrome and Its Components by Group at Baseline

	ADT and RT (n = 31)	RT (n = 24)	Combined (N = 55)	
Variable	n	n	n	p
Glucose levels (greater than 100 mg/dl[a])	13	11	24	0.77
HDL (less than 40 mg/dl)	13	6	19	0.19
Hypertension	29	23	52	0.71
Metabolic syndrome	18	14	32	0.98
Triglycerides (150 mg/dl[a] or greater)	14	10	24	0.8
Waist circumference (greater than 102 cm)	21	17	38	0.81

[a] Or relevant medications as noted in the methods

ADT—androgen-deprivation therapy; HDL—high-density lipoprotein; RT—radiation therapy

study, evidence exists that subcutaneous fat increases with ADT, which may have less of an impact on waist circumference than visceral fat (Smith et al., 2002, 2008). In addition, how well subcutaneous fat is captured with waist circumference is unclear. Magnetic resonance imaging or CT scanning may provide a more accurate assessment of intra-abdominal fat (Shuster, Patlas, Pinthus, & Mourtzakis, 2012).

No evidence exists of a statistically significant increase in glucose levels associated with ADT in the current study, although a significant increase in insulin resistance did occur. This is consistent with the pathogenesis of diabetes, in that hyperinsulinemia precedes the development of hyperglycemia (Basaria et al., 2006). This finding is in agreement with other studies that examined changes in glucose and insulin associated with short-term administration of ADT. Smith et al. (2006) documented significant increases in fat mass and insulin resistance without hyperglycemia after 12 weeks of combined androgen blockade (leuprolide and bicalutamide). Similarly, a study evaluating the short-term effects of ADT (three months of androgen suppression) documented an increase in fasting insulin levels without a corresponding increase in glucose levels (Dockery, Bulpitt, Agarwal, Donaldson, & Rajkumar, 2003). A study conducted by Smith et al. (2001) over a six-month period of ADT showed significant adverse changes in insulin sensitivity without changes in glucose levels. In addition, hyperglycemia was demonstrated in two studies in which ADT was administered over a period of at least 12 months (Basaria et al., 2006; Braga-Basaria et al., 2006). The participants in the current study may have demonstrated hyperglycemia had data collection extended beyond 12 months.

The absence of significant and sustained adverse changes in body composition is somewhat surprising as suggested by prior studies (Basaria et al., 2002; Braga-Basaria et al., 2006; Smith et al., 2002, 2006, 2008). However, much of the evidence for adverse changes in body composition associated with ADT is derived from cross-sectional studies. Cross-sectional comparisons of men receiving long-term ADT compared with untreated men demonstrated increases in fat mass and decreases in lean body mass (Basaria et al., 2002; Cleffi et al., 2011). ADT-induced changes in body composition may provoke a reduction in insulin sensitivity, contributing to the increased cardiovascular risk profile (Shahani, Braga-Basaria, & Basaria, 2008). The reduction in muscle mass decreases glucose uptake by the muscle (Shahani et al., 2008) and interferes with glycogen synthesis (Braga-Basaria et al., 2006). In addition, the increase in fat mass is a known risk factor for the development of insulin resistance (Braga-Basaria et al., 2006; Choong & Basaria, 2010; Shahani et al., 2008). However, the findings from the current study do not provide evidence to support that hypothesis because insulin resistance developed without accompanying changes in body composition. In addition, no between-group differences in measures of adiposity or lean body mass were noted throughout the course of the current study.

The men in the current sample all were receiving RT at some point during the course of the study, which may have modified changes in weight and body composition. The researchers are not aware of other studies in which the effects of ADT were evaluated in a population of men receiving ongoing RT. This association should be evaluated more in prospective studies. If RT is shown to have an effect on changes in body composition, the implementation of screening protocols and interventions would be greatly affected.

Evidence from several short-term prospective studies failed to demonstrate consistent adverse effects on lipids. Smith et al. (2006) noted increased cholesterol, HDL, and triglycerides in 25 men with locally advanced or recurrent prostate cancer receiving ADT in a 12-week prospective study. In another prospective study of men receiving ADT, Smith et al. (2001) documented elevations in HDL and low-density lipoprotein without change in triglycerides. At three months, the 22 men who received ADT demonstrated increases in fat mass and levels of fasting insulin without accompanying adverse changes in lipids or glucose (Smith et al., 2001).

Similarly, Dockery et al. (2003) reported no significant adverse changes in serum glucose, low-density

lipoprotein, or triglyceride levels among 15 men receiving ADT when evaluated at three months. Yannucci et al. (2006) compared fasting serum lipid, glucose levels, and glycosylated hemoglobin at baseline and days 85 and 169 in men receiving abarelix (a GnRH antagonist), leuprolide acetate (a GnRH agonist), or leuprolide plus the anti-androgen bicalutamide. Significant adverse changes in total cholesterol, triglyceride, and HDL were documented in men receiving either abarelix or leuprolide without the addition of an anti-androgen; adverse changes in lipid metabolism were absent in those receiving total androgen blockade. That study suggests the addition of an anti-androgen may provide a protective effect on adverse changes in lipids. In the current study, the majority of participants were receiving total androgen blockade and were without adverse changes in lipids. Future long-term prospective studies comparing the effects of GnRH administration with and without concomitant anti-androgen would further elucidate this effect.

An emerging body of literature highlights differences between the classic metabolic syndrome and the ADT-induced metabolic syndrome, perhaps explicating the lack of clear association between ADT reception and cardiovascular risk. In contrast to the classic metabolic syndrome, ADT-induced metabolic syndrome increases subcutaneous, rather than visceral, fat and increases, rather than decreases, HDL (Saylor & Smith, 2009; Smith et al., 2008). In addition, the metabolic syndrome is associated with low levels of adiponectin and an increased C-reactive protein (Saylor & Smith, 2009); however, men receiving ADT demonstrated increased levels of adiponectin and unchanged C-reactive protein (Choong & Basaria, 2010; Saylor & Smith, 2009; Smith, et al., 2008).

Adiponectin, a protein derived from adipose tissue, improves insulin sensitivity and is more negatively associated with visceral fat than subcutaneous fat (Trujillo & Scherer, 2005). Perhaps the increase in subcutaneous fat seen in men receiving ADT may not confer the same increased cardiovascular risk associated with an increase in visceral fat. In addition, inflammation, measured by high-sensitivity C-reactive protein, may be an important risk factor in the development of diabetes and cardiovascular disease (Haffner, 2006). Research designed to elucidate the metabolic differences between classic metabolic syndrome and ADT-induced changes in metabolic parameters will be important in the understanding of ADT and cardiovascular risk.

Based on the criteria established by Alberti et al. (2009), most of the participants in the study were considered to have metabolic syndrome at baseline; therefore, the researchers were, in a sense, evaluating a worsening of the syndrome. A future study in a large population of men with prostate cancer receiving ADT who did not satisfy the criteria for metabolic syndrome may have different outcomes. This would be important information to know because the timing and content of interventions might be quite different. In addition, future studies designed to test the differential impact of subcutaneous and visceral fat on the development of metabolic syndrome would be valuable.

Limitations

Limitations of the study include the potential for measurement errors, particularly in measures of waist and hip circumference. Reliability and validity of the measures may have been a limitation. Waist circumference has been widely used as a surrogate marker for insulin resistance (Ness-Abramof & Apovian, 2008) and, in fact, is one of the five criteria for metabolic syndrome. However, it cannot differentiate between visceral and subcutaneous fat. Similarly, body composition as measured by bioelectric impedance also is unable to differentiate between visceral and subcutaneous fat. The absence of significant adverse changes in the measures of waist circumference and fat and lean body mass, in spite of changes in insulin sensitivity, may be a reflection of the inability to differentiate between subcutaneous and visceral fat. Visceral fat may have a greater contribution toward waist circumference and body fat composition. In addition, although participants were instructed to obtain the indicated laboratory tests while fasting, this directive may not have been met with 100% compliance. In addition, although the sample size was larger than obtained in previous studies, the criteria as determined in the power analysis was not fulfilled (33 in each group). Strengths of the study were the prospective design and the inclusion of a control group.

Knowledge Translation

Clinically significant changes in insulin resistance were noted as early as three months after starting treatment with androgen-deprivation therapy (ADT).

Men not receiving ADT did not develop insulin resistance.

No evidence existed for the development of hyperglycemia in men receiving ADT.

Conclusion and Implications for Nursing

Through education and the development of interventions and research, nurses are in a pivotal position to positively impact the care and quality of life in this large population of prostate cancer survivors. Armed with knowledge of the side effects of therapy, men may

be empowered to adopt lifestyle changes in nutrition and physical activity. Nurses are in an ideal position to participate in the development of evidence-based interventions designed to mitigate the adverse effects of treatment. Strategies may include encouragement for lifestyle modifications, as well as assessment and treatment of cardiovascular risk factors (Saylor & Smith, 2009, 2012). Treatment may include the prescribing and monitoring of medications intended to impact hypertension, hyperlipidemia, and insulin resistance (Levine et al., 2010). Addressing survivorship concerns in this population is of paramount importance, given the large numbers of men affected, their long-term survival, and significant adverse effects of therapy.

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References

Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., . . . Smith, S.C. (2009). Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation, 120,* 1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644

Alberti, K.G., Zimmet, P., & Shaw, J. (2005). The metabolic syndrome—A new worldwide definition. *Lancet, 366,* 1059–1061.

Alibhai, S.M., Duong-Hua, M., Sutradhar, R., Fleshner, N.E., Warde, P., Cheung, A.M., & Paszat, L.F. (2009). Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *Journal of Clinical Oncology, 27,* 3452–3458. doi:10.1200/JCO.2008.20.0923

Basaria, S., Lieb, J., Tang, A.M., DeWeese, T., Carducci, M., Eisenberger, M., & Dobs, A.S. (2002). Long-term effects of androgen deprivation therapy in prostate cancer. *Clinical Endocrinology, 56,* 779–786.

Basaria, S., Muller, D.C., Carducci, M.A., Egan, J., & Dobs, A.S. (2006). Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer, 106,* 581–587.

Braga-Basaria, M., Dobs, A.S., Muller, D.D., Carducci, M.A., John, M., Egan, J., & Basaria, S. (2006). Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *Journal of Clinical Oncology, 24,* 3979–3983.

Choong, K., & Basaria, S. (2010). Emerging cardiometabolic complications of androgen deprivation therapy. *Aging Male, 13,* 1–9.

Cleffi, S., Neto, A.S., Reis, L.O., Maia, P., Fonseca, F., Wroclawski, M.L., . . . Tobias-Machado, M. (2011). Androgen deprivation therapy and morbid obesity: Do they share cardiovascular risk through metabolic syndrome? *Actas Urologicas Espanolas, 35,* 259–265.

Denis, L.J., & Griffiths, K. (2000). Endocrine treatment in prostate cancer. *Seminars in Surgical Oncology, 18,* 52–74.

Dockery, F., Bulpitt, C.J., Agarwal, S., Donaldson, M., & Rajkumar, C. (2003). Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. *Clinical Science, 104,* 195–201.

Haffner, S.M. (2006). The metabolic syndrome: Inflammation, diabetes mellitus, and cardiovascular disease. *American Journal of Cardiology, 97,* 3A–11A. doi:10.1016/j.amjcard.2005.11.010

Haidar, A., Yassin, A., Saad, F., & Shabsigh, R. (2007). Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male, 10,* 189–196.

Higano, C. (2012). Sexuality and intimacy after definitive treatment and subsequent androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology, 30,* 3720–3725. doi:10.1200/JCO.2012.418509

Keating, N.L., O'Malley, A.J., & Smith, M.R. (2006). Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology, 24,* 4448–4456. doi:10.1200/JCO.2006.06.2497

Lage, M.J., Barber, B.L., & Markus, R.A. (2007). Association between androgen-deprivation therapy and incidence of diabetes among males with prostate cancer. *Urology, 70,* 1104–1108. doi:10.1016/jurology.2007.08.012

Lepor, H., & Shore, N.D. (2012). LHRH agonists for the treatment of prostate cancer: 2012. *Reviews in Urology, 14,* 1–12.

Levine, G.N., D'Amico, A.V., Berger, P., Clark, P.E., Eckel, R.H., Keating, N.L., . . . Zakai, N. (2010). Androgen-deprivation therapy in prostate cancer and cardiovascular risk: A science advisory from the American Heart Association, and American Urological Association: Endorsed by the American Society for Radiation Oncology. *CA: A Cancer Journal for Clinicians, 60,* 194–201. doi:10.3322/caac.20061

Myklak, K., & Wilson, S. (2011). An update on the changing indications for androgen deprivation therapy for prostate cancer. *Prostate Cancer, 2011,* 1–8. doi:10.1155/2011/419174

Ness-Abramof, R., & Apovian, C.M. (2008). Waist circumference measurement in clinical practice. *Nutrition in Clinical Practice, 23,* 397–404. doi:10.1177/0884533608321700

Nobes, J.P., Langley, S.E., & Laing, R.W. (2009). Metabolic syndrome and prostate cancer: A review. *Clinical Oncology, 21,* 1–9. doi:10.1016/j.clon.2008.11.013

Quon, H., & Loblaw, D.A. (2010). Androgen deprivation therapy for prostate cancer—Review of indications in 2010. *Current Oncology, 17*(Suppl. 2), S38–S44.

Rashid, M.H., & Chaudhary, U.B. (2004). Intermittent androgen deprivation therapy for prostate cancer. *Oncologist, 9,* 295–301.

Saylor, P.J., & Smith, M.R. (2009). Metabolic complications of androgen deprivation therapy for prostate cancer. *Journal of Urology, 181,* 1998–2008. doi:10.1016.j.juro.2009.01.047

Saylor, P.J., & Smith, M.R. (2012). Adverse effects of androgen deprivation therapy: Defining the problem and promoting health among men with prostate cancer. *Journal of the National Comprehensive Cancer Network, 8,* 211–222.

Shahani, S., Braga-Basaria, M., & Basaria, S. (2008). Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *Journal of Clinical Endocrinology and Metabolism, 93,* 2042–2049.

Shahinian, V.B., Kuo, Y.F., Freeman, J.L., Orihuela, E., & Goodwin, J.S. (2005). Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate cancer. *Cancer, 103,* 1615–1624.

Shuster, A., Patlas, M., Pinthus, J.H., & Mourtzakis, M. (2012). The clinical importance of visceral adiposity: A critical review of methods for visceral adipose tissue analysis. *British Journal of Radiology, 85*(1009), 1–10. doi:10.1259/bjr/38447238

Siegel, R., Naishadham, D., & Jemal, A. (2013). Cancer statistics, 2013. *CA: A Cancer Journal for Clinicians, 63,* 11–30. doi:10.3322/caac.21166

Smith, J.C., Bennett, S., Evans, L.M., Kynaston, H.G., Parmar, M., Mason, M.D., . . . Davies, J.S. (2001). The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *Journal of Endocrinology and Metabolism, 86,* 4261–4267.

Smith, M.R. (2007). Androgen deprivation therapy for prostate cancer: New concepts and concerns. *Current Opinion in Endocrinology, Diabetes, and Obesity, 14,* 247–254.

Smith, M.R., Finkelstein, J.S., McGovern, F.J., Zietman, A.L., Fallon, M.A., Schoenfeld, D.A., & Kantoff, P.W. (2002). Changes in body composition during androgen deprivation therapy for prostate cancer. *Journal of Clinical Endocrinology and Metabolism, 87,* 599–603.

Smith, M.R., Lee, H., McGovern, F., Fallon, M.A., Goode, M., Zietman, A.L., & Finkelstein, J.S. (2008). Metabolic changes during gonadatropin-releasing hormone agonist therapy for prostate cancer. *Cancer, 112,* 2188–2194. doi:10.1002/cncr.23440

Smith, M.R., Lee, H., & Nathan, D.M. (2006). Insulin sensitivity during combined androgen blockade for prostate cancer. *Journal of Clinical Endocrinology and Metabolism, 91,* 1305–1308.

Trujillo, M.E., & Scherer, P.E. (2005). Adiponectin—Journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *Journal of Internal Medicine, 257,* 167–175. doi:10.1111/j.1365-2796.2004.01426.x

Yannucci, J., Manola, J., Garnick, M.B., Bhat, G., & Bubley, G.J. (2006). The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. *Journal of Urology, 176,* 520–525.

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1. This study used data collected over 12 months for each man. Was this sufficient to measure the development of insulin resistance and how would you have improved the design of the study?
2. No difference existed at baseline between the men on androgen-deprivation therapy and the control group in adiposity or lean body mass in this study. How might this have influenced the findings and conclusions of the study?
3. The authors suggest that with the knowledge of side effects of treatment, men may be motivated to make lifestyle changes. How would you address this with patients?

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