ORIGINAL RESEARCH

Androgen Deprivation Therapy Reversibly Increases Endothelium-Dependent Vasodilation in Men With Prostate Cancer

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***Background*—**Androgen deprivation therapy (ADT) is a standard treatment for patients with aggressive prostate cancer. Although ADT improves survival, it increases the risk of diabetes. Emerging evidence suggests that ADT increases adverse cardiovascular events as early as 3 months after initiation in patients with cardiovascular disease, but the mechanism is unknown. We hypothesized that ADT may impair endothelium-dependent vasodilation due to increases in lipids and insulin resistance and may provide a link for heightened cardiovascular risk in this population.

***Methods and Results*—**We prospectively evaluated conduit artery endothelium-dependent and -independent vasodilation, lipids, and insulin resistance in 16 consecutively treated men (mean age 66±7 years; 25% with diabetes) with prostate cancer before and after 3 months of ADT. High-resolution B-mode ultrasound was used to assess flow-mediated (endothelium-dependent) and nitroglycerine-mediated (endothelium-independent) brachial artery vasodilation. ADT significantly increased insulin resistance, total cholesterol, HDL, and LDL. Endothelium-dependent vasodilation was greater at 3 months than at baseline (10.8% [interquartile range: 7.7% to 14.6%] versus 8.9% [interquartile range: 4.0% to 12.6%], respectively; P=0.046, allometric P=0.037). Nitroglycerine-mediated vasodilation did not change from baseline (P>0.2). The subset of participants on ADT for 6 months returned for reevaluation at 1 year. In this group, endothelium-dependent vasodilation increased from baseline to 3 months and returned to baseline 6 months after ADT withdrawal (9.4% [interquartile range: 6.9% to 10.9%], 11.6% [interquartile range: 7.9% to 15.2%], and 9.0% [interquartile range: 5.1% to 12.5%], respectively; P=0.05).

***Conclusions*—**In contrast to our expectation, ADT improved endothelium-dependent vasodilation and its cessation returned endothelium-dependent vasodilation to baseline. Determining the mechanism of this change requires further investigation. **(*J Am Heart Assoc*. 2015;4:e001914 doi: 10.1161/JAHA.115.001914)**

Key Words: androgen deprivation therapy • endothelial function • inflammation • insulin resistance • prostate cancer

Androgen deprivation therapy (ADT) has been a mainstay of the treatment of prostate cancer since the observation by Huggins of improved outcomes after orchiectomy.[1] In the past decade, 2 risks of ADT have become apparent: metabolic derangement and cardiovascular events. The first has translated into increased total and LDL cholesterol, increased insulin resistance, and loss of lean body mass. The second has been associated with increased cardiovascular morbidity and mortality.

Keating and colleagues, using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, reported a 44% increased risk of incident diabetes, a 16% increase in coronary heart disease, an 11% increase in myocardial infarction, and a 16% increase in sudden cardiac death in men with prostate cancer treated with a gonadotropin-releasing hormone agonist.[2] The risk of incident coronary heart disease began 3 months after ADT was initiated. Recently, a nationwide Danish population-based cohort study similarly noted a 31% increased risk of myocardial infarction and a 19% increased risk of stroke in men treated with ADT.[3] This and other work prompted a science advisory from the American Heart Association, the American Cancer Society, and the American Urological Association, with endorsement by the American Society for Radiation Oncology,[4] raising fear of the use of an effective treatment in high-risk patients.

A strong candidate link among ADT, the observed metabolic changes, and cardiovascular events is impairment of

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vascular endothelial function. Increases in fat mass, lipids, and insulin resistance have all been demonstrated to cause endothelial dysfunction with reduction in the bioavailability of endothelium-derived nitric oxide. We hypothesized that therapeutic ADT would impair endothelium-dependent vasodilation in men with prostate cancer at 3 months to match the timing of the increase in cardiovascular events.

Methods

Participants

Men with high-risk but not metastatic prostate cancer were recruited prior to initiation of ADT. No patient had received prior ADT, and no patient underwent surgery. ADT was to be applied per the treating attending physician. All participants received combined androgen blockade consisting of 50 mg oral bicalutamide daily plus an injection of 22.5 mg leuprolide acetate every 3 months for a minimum of 6 months. All participants underwent screening medical history, physical examination, and laboratory analysis, including serum electrolytes, glucose, blood urea nitrogen, creatinine, and total and LDL cholesterol. Men with acute coronary syndrome, stroke, and coronary or peripheral artery intervention within 1 year were excluded. The protocol was approved by the human research committees of the Dana-Farber Cancer Institute and the Brigham and Women's Hospital. All participants provided informed consent prior to participation.

Protocol

The effect of ADT on endothelium-dependent and -independent vasodilation of the brachial artery was studied using a single-arm trial of men at baseline and after 3 months of ADT. We chose 3 months because this time point is the earliest an increase in diabetes and coronary heart disease has been reported.[2] All participants were studied in the morning in the postabsorptive state, fasting after the previous midnight. Participants also underwent evaluation of fasting lipids, insulin sensitivity, inflammation, and testosterone and estradiol levels at each time period. In addition, participants who received 6 months of ADT were invited to return at 12 months, 6 months after ADT was discontinued, for reevaluation.

Vascular Reactivity Studies

Brachial (conduit) artery vascular function was assessed according to standard methods and as we have previously performed.[5–8] All participants were studied in the morning in the postabsorptive state, fasting after the previous midnight. Cyclooxygenase inhibitors, alcohol, and caffeine were prohibited for 24 hours before the study. Participants were studied in a quiet, temperature-controlled, dimly lit room after resting supine for a minimum of 5 minutes. High-resolution B-mode ultrasonography of the brachial artery was performed with a 7.5-MHz linear array probe (GE VIVID 7; GE Healthcare). The brachial artery was imaged longitudinally just proximal to the antecubital fossa. The transducer position was adjusted to obtain optimal images of the near and far walls of the intima. The video output and electrocardiographic signal of the ultrasound machine were connected to a computer equipped with a Data Translation Frame-Grabber video card, (Dataviz). The R wave on the electrocardiogram served as a trigger to acquire frames at end diastole. After baseline image acquisition, a sphygmomanometric cuff placed on the upper arm was inflated to suprasystolic pressure (200 mm Hg) for 5 minutes. On cuff release, reactive hyperemia caused flow to increase through the brachial artery subserving the forearm. Flow-induced endothelium-dependent vasodilation of the brachial artery was determined by acquiring images from 60 to 70 seconds after cuff deflation. Flow-mediated vasodilation at this time point is largely endothelium dependent and nitric oxide mediated and can be inhibited by administration of the nitric oxide synthase antagonist NG-monomethyl L-arginine.[5] Ten minutes after cuff release, the brachial artery was imaged again to reestablish basal conditions. Subsequently, to determine endothelium-independent vasodilation, participants received 0.4 mg nitroglycerin sublingually. The brachial artery was imaged 3 minutes later. Brachial artery blood flow velocity was determined via velocity–time integral measurement. Nitroglycerin was not administered if the systolic blood pressure was <100 mm Hg or if the participant refused nitroglycerin, usually to avoid a severe headache during the second visit.

Laboratory Analyses

All chemistry and immunoassay testing with the exception of insulin was performed using the Cobas 6000 analyzer (Roche Diagnostics). Total and HDL cholesterol, triglycerides, and blood glucose were measured by the standard colorimetric assays CHOL2, HDLC3, TRIGL, and GLUC3. LDL cholesterol levels were measured directly, using the LDL-Cholesterol plus second generation (LDL-C) assay. High-sensitivity C-reactive protein concentrations were tested using the immunoturbidimetric CRPHS assay. This method has been standardized against the reference preparation of the Institute for Reference Materials and Measurements BCR470/CRM470. Testosterone and estradiol were measured on the e601 module of Cobas 6000 using immunoassays with electrochemiluminescent detection Estradiol II and Testosterone II. Insulin concentrations were measured on the Centaur XP immunoanalyzer using the Insulin IRI assay (Siemens Healthcare Diagnostics).

Homeostatic model assessment insulin resistance was calculated as fasting glucose (mg/dL) times fasting insulin (μIU/mL) divided by 405.[6] Homeostatic model assessment β cell function was calculated as (20×fasting insulin)/(fasting glucose−3.5).

Statistical Methods

Descriptive and anthropomorphic measures are reported as mean±SD. Experimental measures are reported as median (interquartile range [IQR]). Descriptive measures were compared by paired 2-tailed *t* test. Experimental measures were initially tested for normality using Shapiro–Wilks testing and found to be nonnormally distributed. Wilcoxon signed rank tests were used for comparison of experimental measures, including vascular function and laboratory measures. Changes in flow-mediated vasodilation were also assessed using the allometric method of comparison to account for changes in baseline diameter.[9–11] Correlations of anthropomorphic characteristics and the change in flow-mediated vasodilation were tested using Spearman's ρ because of the nonnormal distribution of data. Prior to study initiation, we determined the sample size needed to find a significant decrease in flow-mediated endothelium-dependent vasodilation with ADT. Based on our previous work in diabetes,[6,7] assuming a test value for flow-mediated endothelium-dependent vasodilation of 8% at entry with a decrement to 5.5% at 3 months, SD of the sample of 3%, and an α error level of 5%, 15 participants were needed to achieve power of 89%. Statistical significance was accepted at the 95% confidence level ($P<0.05$). All statistics were run on SPSS Base 22 (IBM).

Results

Baseline characteristics of the recruited participants are shown in Table 1. The participants were 66±7 years, 12 of 16 participants (75%) were white, the majority carried the diagnosis of hyperlipidemia, 4 had type 2 diabetes, and none smoked within 1 year of study entry. Ten participants carried the diagnosis of hypertension, but blood pressure prior to the administration of androgen deprivation was controlled on medication. Five participants took angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, 8 took statins, and 8 took aspirin. No participant had a history of myocardial infarction, stroke, or peripheral artery disease. The median Gleason grade of the enrolled participants was 7 (IQR: 6 to 8). During the course of the study, there were no changes in medications, no participants had a medical procedure or surgery, and there were no hospitalizations.

Table 1. Baseline Demographics

Characteristic	N=16
Age	66±7
BMI	28.8±4.8
SBP	131±19
DBP	75±8
HR	61±12
White	75%
Diabetes	25%

Data are presented as mean±SD. BMI indicates body mass index; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Laboratory Analyses

Anthropomorphic findings are noted in Table 2. The effect of ADT on our participants yielded the expected metabolic changes (Table 3). ADT reduced serum testosterone and estradiol levels significantly. Fasting insulin levels and fasting glucose levels and homeostatic model assessment insulin resistance increased significantly from baseline to 3 months, respectively. Each component of the lipid profile except triglycerides increased significantly with ADT. Finally, there was no change in systemic inflammation as measured by high-sensitivity C-reactive protein.

Androgen and Vascular Function

Baseline brachial artery diameter decreased with androgen deprivation, but ADT did not significantly change the reactive hyperemic stimulus or shear rate (Table 4). At baseline, flow-mediated endothelium-dependent vasodilation was 8.9% (IQR: 4.0% to 12.6%), and it increased to 10.8% (IQR: 7.7% to 14.6%) after 3 months of ADT ($P=0.046$). When flow-mediated endothelium-dependent vasodilation was compared using an allometric method that accommodated for the change in baseline diameter, the change remained statistically significant (allometric $P=0.037$).[9,10] Similarly, there was a significant increase in absolute diameter size with the reactive

Table 2. Effect of Androgen Deprivation Therapy on Anthropomorphic Data

Parameter	Baseline	3 Months	*P* Value
Height, cm	174±9	174±9	>0.2
Weight, kg	86.0±13.1	86.9±11.8	>0.2
BMI	28.6±4.9	28.9±4.5	>0.2
SBP, mm Hg	131±19	129±13	>0.2
DBP, mm Hg	76±8	78±7	>0.2
HR, bpm	61±12	60±11	>0.2

Data are presented as mean±SD. BMI indicates body mass index; bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Table 3. Effect of Androgen Deprivation Therapy on Metabolism

Measure	Baseline	3 Months	*P* Value
Insulin, μIU/mL	5.6 (4.6 to 8.6)	10.0 (6.5 to 14.8)	0.005
Glucose, mg/dL	96 (85 to 99)	100 (95 to 123)	0.037
$HOMA_{IR}$	1.3 (1.1 to 1.7)	2.6 (1.6 to 3.6)	0.005
$HOMA_{B}$	65 (53 to 112)	76 (57 to 127)	>0.2
Total cholesterol, mg/dL	159 (131 to 194)	200 (158 to 219)	0.005
HDL cholesterol, mg/dL	45 (39 to 53)	59 (39 to 53)	0.028
LDL cholesterol, mg/dL	101 (70 to 125)	126 (87 to 149)	0.005
Triglycerides, mg/dL	78 (69 to 104)	95 (71 to 118)	>0.2
hs-CRP	0.4 (0.2 to 1.7)	0.8 (0.5 to 1.6)	>0.2
Estradiol, pg/mL	22.9 (19.3 to 40)	5.0 (5.0 to 12.2)	<0.005
Testosterone, ng/dL	451 (317 to 794)	6 (3 to 14)	<0.005

Data are presented as median (interquartile range). $HOMA_{B}$ indicates homeostatic model assessment β cell function; $HOMA_{IR}$, homeostatic model assessment insulin resistance; hs-CRP, high-sensitivity C-reactive protein.

hyperemic stimulus. In contrast, nitroglycerin-mediated endothelium-independent vasodilation did not change significantly with ADT. There was no correlation between any anthropomorphic characteristic and the change in flow-mediated endothelium-dependent vasodilation (P>0.2 for age, body mass index, and blood pressure).

Results at 1 Year

Of the 16 enrolled participants, 3 were treated with long-term ADT, and 2 decided to end participation after 3 months, but 11 participants returned for assessment at 1 year. In this group, there were no changes in anthropomorphic variables from 3 to 12 months. The discontinuation of ADT resulted in return to baseline for laboratory analyses such that there were no statistical differences between the baseline and 1-year time points (Table 5). In these participants, there was no significant difference in baseline arterial diameter or reactive hyperemic stimulus at any time point (Table 6). In contrast, flow-mediated vasodilation was 9.4% (IQR: 6.9% to 10.9%) at baseline, 11.6% (IQR: 7.9% to 15.2%) at 3 months (P=0.05), and 9.0% (IQR: 5.1% to 12.5%) at 1 year (Figure). Nitroglycerine-mediated vasodilation was similar at all 3 time points.

Discussion

In contrast to our hypothesis, gonadotropin-releasing hormone agonist–mediated ADT increased conduit artery flow-mediated vasodilation in men with prostate cancer between baseline and 3 months and returned to baseline 6 months after ADT cessation. These results suggest that the mechanism of increased cardiovascular events that occurs within weeks to months of ADT initiation is not related to reductions in the bioavailability of endothelium-derived nitric oxide. To our knowledge, this report is the first in intact ambulatory humans demonstrating conduit artery function before, during, and after the application of ADT.

ADT and Endothelial Function

The relevance of androgens to vascular function stems from the association of heightened mortality in states of androgen

Table 4. Effect of Androgen Deprivation Therapy on Vascular Function

Parameter	Baseline	3 Months	*P* Value
Baseline arterial diameter, mm	3.93 (3.39 to 4.36)	3.79 (3.45 to 4.12)	0.031
Reactive hyperemic stimulus, fold increase (VTI)	4.3 (2.6 to 6.8)	6.0 (3.8 to 7.1)	0.18
Diameter increase, mm	0.34 (0.14 to 0.48)	0.36 (0.29 to 0.55)	0.047
Flow-mediated vasodilation, %	8.9 (4.0 to 12.6)	10.8 (7.7 to 14.6)	0.046
Nitroglycerin-mediated vasodilation, %	16.7 (12.8 to 25.9)	19.2 (13.9 to 25.7)	>0.2
Diameter increase, mm	0.70 (0.56 to 0.82)	0.67 (0.59 to 0.88)	>0.2

Data are presented as median (interquartile range), N=16. VTI indicates velocity–time integral.

Table 5. Effect of Androgen Deprivation Therapy in a Subset on Laboratory Analysis

Measure	Baseline	3 Months	1 Year
Insulin, μIU/mL	8.5 (3.5 to 11.3)	14.4* (8.4 to 19.7)	7.2.0 to 12.3)
Glucose, mg/dL	96 (79 to 118)	101* (99 to 133)	96 (81 to 102)
$HOMA_{IR}$	1.4 (0.7 to 1.7)	3.5* (2.0 to 3.9)	1.7 (1.2 to 2.4)
Total cholesterol, mg/dL	148 (113 to 201)	215* (135 to 220)	163 (110 to 191)
HDL cholesterol, mg/dL	41 (32 to 58)	51 (43 to 64)	41 (38 to 59)
LDL cholesterol, mg/dL	95 (54 to 127)	138* (69 to 152)	110 (57 to 123)
Triglycerides, mg/dL	75 (72 to 144)	103 (85 to 124)	93 (71 to 115)
hs-CRP, mg/dL	0.3 (0.2 to 1.3)	1.1† (0.4 to 1.8)	0.6 (0.4 to 2.2)
Estradiol, pg/mL	23.1 (16.7 to 31.3)	5.0* (5.0 to 14.9)	27.8 (17.2 to 31.1)
Testosterone, ng/dL	346 (158 to 738)	13* (4 to 23)	462 (353 to 565)

Data are presented as median (interquartile range). $HOMA_{IR}$ indicates homeostatic model assessment insulin resistance; hs-CRP, high-sensitivity C-reactive protein.
*P<0.05, compared with baseline.
†P=0.068, compared with baseline.

Table 6. Effect of Androgen Deprivation Therapy in a Subset on Vascular Function

Parameter	Baseline	3 Months	1 Year
Baseline arterial diameter, mm	3.92 (3.35 to 4.07)	3.77 (3.39 to 3.92)	3.79 (3.41 to 4.01)
Reactive hyperemic stimulus, fold increase (VTI)	5.7 (3.3 to 8.0)	6.2 (4.0 to 9.5)	6.4 (4.5 to 7.9)
Flow-mediated vasodilation, %	9.4 (6.9 to 10.9)	11.6* (7.9 to 15.2)	9.0 (5.1 to 12.5)
Nitroglycerin-mediated vasodilation, %	17.4 (15.0 to 26.7)	17.7 (14.0 to 24.9)	17.5 (11.4 to 22.5)

Data are presented as median (interquartile range), n=11. VTI indicates velocity–time integral.
*P=0.05 compared with baseline.

deficiency.[12,13] In the InCHIANTI study, decline of testosterone levels was an independent predictor of mortality over 6 years of follow-up.[14] Similarly a nested case–control study with 6- to 10-year follow-up showed an association with testosterone decline and increased mortality.[15] Longer follow-up, studied in the Massachusetts Male Aging Study, attenuates the relationship.[16] Possible mechanisms for increased mortality stem from the association of diminished androgens and increased levels of inflammation and fat mass.[16,17] Pertinent to this work, androgen deficiency has been associated with impaired conduit artery endothelium-dependent vasodilation;[18] however, the relationship is not straightforward. Testosterone replacement has been shown to improve vascular stiffness[19] but also has been shown to worsen endothelium-dependent vasodilation in hypogonadal men.[20] It is likely that the etiology of decreased androgens plays an important role beyond the change in hormone levels per se in determining vascular health. Testosterone may be a biomarker of illness in this setting as well as a contributor to vascular function.

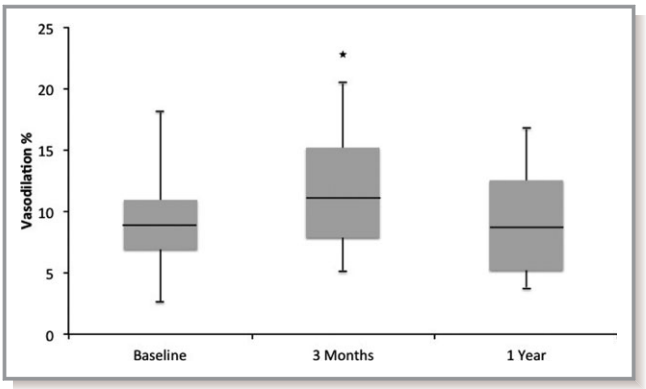

Figure. Flow-mediated vasodilation of the brachial artery. Flow-mediated vasodilation at baseline, after 3 months of androgen deprivation therapy (ADT), and 6 months after ADT cessation (n=11). Androgen deprivation increased flow-mediated vasodilation (*P=0.05 compared with baseline) at 3 months and returned to baseline after cessation.

In contrast to illness or aging states, therapeutic androgen deprivation is applied to men without underlying cause for androgen deficiency. The effect of androgen deprivation has been evaluated by 2 groups with conflicting results. Herman and colleagues compared endothelium-dependent vasodilation in men with prostate cancer treated with orchiectomy or androgen blockade for >6 months, in healthy controls, and in men in remission from nonprostate cancers.[21] The men with prostate cancer had testosterone concentrations of 23 ng/dL

compared with 548 ng/dL for healthy controls and 461 ng/dL for men in remission from nonprostate cancers. Brachial artery endothelium-dependent vasodilation was significantly higher in the men with ADT (6.2%) compared with healthy controls (2.7%) or men in remission from nonprostate cancers (2.0%). In contrast, Gilbert and colleagues studied men with prostate cancer treated with ADT and controls matched for sex, age, and body mass index.[22] Similarly, the ADT-treated men had significantly lower testosterone levels compared with controls (12 versus 533 ng/dL). In this study, however, brachial artery endothelium-dependent vasodilation was lower in men with prostate cancer treated with ADT (3.9%) compared with matched controls (5.9%).

Our investigation in a similarly aged population with a similar reduction in testosterone showed an increase in endothelium-dependent vasodilation in men treated with ADT compared with baseline. These results remained consistent when controlling for the change in baseline arterial diameter. Several possibilities may explain the variance among the studies. The most obvious difference is the duration of ADT. In our participants who received 3 evaluations, ADT was measured at 3 months. Herman and colleagues studied men with a mean ADT duration of 18 months. In contrast, Gilbert and colleagues studied men with a mean treatment duration of 37 months. The application of long-term ADT suggests a sicker population and metabolic and vascular changes that may not have been manifest at the time we studied the participants. One advantage to our study is its pre–post design that permits the evaluation of the changes in androgen production, lipids, and insulin resistance, which are not captured in a cross-sectional analysis. The decrease in size in baseline arterial diameter is suggestive of an adaptation to the change in the vascular environment, similar to that found in severely obese patients who lose significant amounts of weight.[23] The change in baseline arterial diameter did not affect our determination because we used an allometric model. As noted by Atkinson and colleagues, "An allometric model involving the flow-mediated response (on a log scale) as the outcome and Dbase (log-transformed) as a covariate can completely eradicate the problem of Dbase dependency."[10] Chung and colleagues showed that as the atherosclerotic risk factor profile worsens, resting brachial artery diameter increases.[24] The return to baseline for laboratory and vascular assessments demonstrates the impact of ADT and its potential for reversibility when applied for 6 months. Further human and basic biological study is needed to determine the mechanism underlying these changes.

Cardiovascular Risk With ADT

Daskavich and colleagues recently reported long-term follow-up of the Prostate Cancer Outcomes Study showing that older men (aged ≥60 years) with multiple comorbid conditions are far more likely to die from causes other than prostate cancer.[25] This observation gains in importance when put in the perspective of the increased risk of cardiovascular events resulting specifically from prostate cancer treatment. Several investigators have noted increased rates of cardiovascular events within the first year of ADT.[2,3,26,27] In examining the populations more closely, it appears that baseline risk significantly affects the observed cardiovascular risk. We showed, for example, that men with a history of congestive heart failure or myocardial infarction,[28] regardless of prior coronary revascularization, had a significantly increased risk of mortality.[29] We also showed that patients with a low-risk profile do not suffer increased cardiovascular events when treated with ADT.[30] It is unclear whether the effect is advancing atherogenesis or activating the vulnerable patient and plaque.

The mechanism by which cardiovascular risk is increased can only be surmised at this time. ADT induces a dysmetabolic state by increasing inflammation, LDL levels, triglycerides, and insulin resistance. Offsetting this risk would be the increase in HDL levels. Interestingly, the change in HDL may be enough to mitigate the rest of the changes in toto.[31,32] Consequently, standard risk profile components including age, smoking, lipids, blood pressure, and inflammation do not appear to explain the observed significant increase in cardiovascular risk during ADT.

In our population, we noted an increase of ≈100% in homeostatic model assessment insulin resistance. Although both pre and post levels are below the threshold considered diagnostic for insulin resistance,[33–35] the change was significant and may be enough to push at-risk individuals to a new risk state of either frank insulin resistance or diabetes. Increasing insulin resistance is directly associated with increasing cardiovascular risk in participants with and without type 2 diabetes, although it should be noted that the mechanism of androgen deficiency–mediated insulin resistance remains unknown.[36–38]

Direct effects of androgens on the vascular wall also may be important. In preclinical models, testosterone has been shown to promote vasodilation through a vascular smooth muscle–mediated mechanism.[39] Interestingly, the vasodilatory effect of testosterone is not dependent on activation of androgen receptors.[40] In human subcutaneous resistance arteries obtained from men with androgen deficiency studied ex vivo, testosterone was a concentration-dependent endothelium-independent vasodilator at the nonphysiological concentration of ≥1 μmol/L.[41] In addition, testosterone therapy attenuated the vasodilatory effect of sodium nitroprusside (a vascular smooth muscle vasodilator) and enhanced the contractile response to norepinephrine (an α agonist).[41] ADT has been associated with increased large artery stiffness and

may participate in adverse cardiovascular outcomes through this mechanism.[42,43] Others have postulated a role for a testosterone-mediated change in oxidative stress as a mechanism for the vascular pathophysiology; however, in humans, higher levels of testosterone have been shown to increase and decrease oxidative stress.[44–46] Elucidation of the mechanism underlying androgen deprivation and heightened cardiovascular risk in high-risk men will require further preclinical and patient-oriented research.

This study did not address all possible atherogenic mechanisms. ADT has been associated with prothrombotic changes including increases in fibrinogen, plasminogen activator inhibitor 1, and tissue plasminogen activator antigen[47,48] that may also explain a reported increase in venous thromboembolism.[49] Platelet counts are unaffected by ADT,[50] but platelet activation has yet to be characterized. In addition, this study did not include a placebo group because withholding ADT from men with prostate cancer and giving it to men without prostate cancer to enable a placebo group are both unethical because of the risks of morbidity and mortality.

Conclusion

ADT increased insulin resistance, altered the lipid profile, and increased conduit artery flow-mediated vasodilation in men studied before and after 3 months of therapy. The effect of ADT on laboratory and vascular parameters resolved 6 months after ADT discontinuation. These results suggest that the biology of androgen deficiency, both endogenous and induced, remains unclear and requires further study to elucidate the mechanism of interaction between sex hormones and the vasculature.

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Disclosures

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