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Adipocytokines, Obesity, and Insulin Resistance During Combined Androgen Blockade for Prostate Cancer: Evidence for a Distinct Hypogonadal Metabolic Syndrome?

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Abstract

Objectives—Gonadotropin-releasing hormone agonists increase fat mass, decrease insulin sensitivity, and increase serum triglycerides—changes suggestive of the classic metabolic syndrome. These analyses were designed to assess the effects of gonadotropin-releasing hormone agonist treatment on other markers of the metabolic syndrome including adiponectin, resistin, and plasminogen activator inhibitor type 1 (PAI-1) levels and to evaluate relationships between changes in adipocytokines, body composition, and insulin sensitivity.

Methods—In this prospective 12-week study, 25 nondiabetic men with locally advanced or recurrent prostate cancer and no radiographic evidence of metastases were treated with leuprolide depot and bicalutamide. Outcomes included changes from baseline to week 12 in body composition, insulin sensitivity, and levels of adiponectin, resistin, and PAI-1.

Results—Mean ($\pm$ SE) percentage fat body mass increased by $4.3 \pm 1.3\%$ from baseline to week 12 ($P=0.002$). Insulin sensitivity index decreased by $12.9 \pm 7.6\%$ ($P=0.02$). Serum adiponectin levels increased by $37.4 \pm 7.2\%$ from baseline to week 12 ($P<0.001$). In contrast, serum resistin levels did not change significantly. Changes in adiponectin were associated with changes lean mass ($r=0.448$; $P=0.02$) and fat mass ($r=-0.383$; $P=0.06$) but not changes in insulin sensitivity.

Conclusions—Combined androgen blockade with leuprolide and bicalutamide significantly increased serum adiponectin levels but did not alter PAI-1 or resistin levels. This pattern of metabolic changes appears distinct from the classic metabolic syndrome.

Key terms

prostate cancer; GnRH agonist; obesity; insulin resistance; adiponectin; resistin

INTRODUCTION

About one-third of the estimated two million prostate cancer survivors in the United States currently receive treatment with a gonadotropin-releasing hormone (GnRH) agonist.^{1,2} GnRH agonists are the mainstay of treatment for metastatic prostate cancer and a standard part of management for many men with local and local-regional disease.³

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In men with prostate cancer, GnRH agonists are associated with a pattern of metabolic alterations similar to the insulin resistance syndrome. GnRH agonists increase fat mass and decrease lean body mass.⁴⁻⁶ GnRH agonists increase fasting plasma insulin levels^{7, 8} and decrease insulin sensitivity.⁹ GnRH agonists also increase serum triglycerides and low density lipoprotein cholesterol.^{5, 8, 10} Consistent with these adverse metabolic effects, GnRH agonists are associated with greater risk of incident diabetes mellitus and cardiovascular disease in men with prostate cancer.¹¹

Adipocytokines may link changes in body composition and metabolic alterations during GnRH agonist treatment for prostate cancer. In murine models of obesity, circulating levels of adiponectin are decreased and resistin levels are increased.^{12, 13} Low adiponectin levels and elevated resistin levels have been implicated in insulin resistance in obese mice.^{12, 13} In humans, plasma adiponectin levels are lower in obese individuals and most insulin resistant states including type 2 diabetes mellitus.¹⁴ The role of resistin in obesity and insulin resistance in humans is controversial.¹⁵

To better characterize the metabolic phenotype of men receiving GnRH agonist for prostate, we prospectively evaluated changes in adiponectin, resistin, and plasminogen activator inhibitor type 1 (PAI-1) levels during combined androgen blockade in nondiabetic men with prostate cancer. We also evaluated the relationships between treatment-related changes in adipocytokines, body composition, and insulin sensitivity.

MATERIALS AND METHODS

Subjects

Study participants were recruited at Massachusetts General Hospital between March 2003 and May 2005. Subjects had locally advanced or recurrent prostate cancer. Men with bone metastases by radionuclide bone scan were excluded. Men with Karnofsky performance status <90, history of diabetes mellitus or glucose intolerance, treatment with medications known to alter glucose or insulin levels, or serum creatinine concentration > 2.0 mg/dL (177 μ mol/L) were also excluded. Subjects who met the criteria for diabetes mellitus (fasting plasma glucose $\geq$ 126 mg/dl or 2-hour post-load glucose $\geq$ 200 mg/dL during oral glucose tolerance test¹⁶ at baseline visit were excluded.

Study Design

Subjects were evaluated at the General Clinical Research Center at Massachusetts General Hospital at baseline and after 12 weeks of treatment. Subjects received a 75-gram oral glucose tolerance test in the morning after a 12-hour overnight fast. Blood samples were collected on the morning of each visit. Serum testosterone and plasma glucose levels were measured at Massachusetts General Hospital laboratories. Additional plasma samples were stored at -70 degrees Celsius for subsequent batch measurement of insulin, adiponectin, and resistin. A research dietitian performed anthropomorphic measurements. Percentage fat body mass and percentage lean body mass were measured by dual energy x-ray absorptiometry.

After the baseline visit, subjects received leuprolide 3-month depot (Lupron Depot®; TAP Pharmaceuticals; Incorporated; Deerfield, Illinois) (22.5 milligrams intramuscularly every 12 weeks). Subjects also received bicalutamide (Casodex®; AstraZeneca PLC; London, United Kingdom) (50 milligrams by mouth daily) for four weeks to prevent the potential flare associated with the first administration of a GnRH agonist.

Primary study results were reported previously.⁹ The current analyses were designed to assess the effects of GnRH agonist treatment on other markers of the metabolic syndrome including

adiponectin, resistin, and plasminogen activator inhibitor type 1 (PAI-1) levels and to evaluate relationships between changes in adipocytokines, body composition, and insulin sensitivity.

The institutional review board of the Harvard Cancer Center reviewed and approved the study and all subjects gave written informed consent.

Outcome Measures

Body Composition—Fasting subjects were weighed wearing a hospital gown and no shoes. Body weight was measured to the nearest 0.1 kg using a digital platform scale (Blue Bell BioMedical Model 500; SR Instruments, Tonawanda, NY). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Percentage fat body mass and percentage lean body mass were determined by dual energy x-ray absorptiometry with a Hologic QDR 4500A densitometer (Hologic, Inc, Waltham, MA; software version 11.1).¹⁷

Oral glucose tolerance tests (OGTT)—In the morning after a 12-hour overnight fast, subjects received a 75-gram oral glucose tolerance test. Blood samples were collected at 0, 30, 60, 90, and 120 minutes for measurement of plasma glucose and insulin concentrations. The whole-body insulin sensitivity index (ISI) was calculated from fasting plasma insulin and glucose concentrations and mean plasma insulin and glucose concentrations during the OGTT, with $ISI = 10,000 / \text{square root of (fasting plasma glucose} \times \text{fasting plasma insulin)} \times (\text{mean OGTT glucose} \times \text{mean OGTT insulin})$.¹⁸

Biochemical Assays—Plasma adiponectin was measured using a quantitative sandwich enzyme immunoassay with a sensitivity of 0.246 ng/mL and intra-assay and interassay coefficients of variation of 2.5 to 4.7% and 5.8 to 6.9%, respectively (R&D Systems, Inc.; Minneapolis, MN). Resistin was measured using a quantitative sandwich enzyme immunoassay with a sensitivity of 0.026 ng/mL and intra-assay and interassay coefficients of variation of 3.8 to 5.3% and 7.8 to 9.2%, respectively (R&D Systems, Inc.; Minneapolis, MN). PAI-1 was measured using a quantitative sandwich enzyme immunoassay with a sensitivity of 1.0 ng/mL and intra-assay and interassay coefficients of variation of 3.7 to 4.0% and 4.3 to 4.9%, respectively (American Diagnostica, Inc.; Greenwich, CT). Plasma insulin was measured using a radioimmunoassay with a sensitivity of 2 mU/L and intra-assay and interassay coefficients of variation of 2.2 to 4.4% and 2.9 to 6.0%, respectively (Linco Research; St. Charles, MO). Serum testosterone was measured by radioimmunoassay with an intra-assay coefficient of variation of approximately 5 percent for values within the normal range and 18 percent for values in the castrate range, and an interassay coefficient of variation of 7–12 percent (Diagnostic Products, Los Angeles, CA). Serum estradiol was measured by radioimmunoassay with a sensitivity of 3 pg/mL and intra- and interassay coefficients of variation of 10 percent and 14 percent, respectively (Nichols Institute, San Juan Capistrano, CA).

Statistical Analyses

Longitudinal changes between baseline and 12 week values for all outcome measures were examined using two-sided paired t tests. Pearson's correlation analyses were performed to examine the linear relationships between changes in adipocytokines, body composition, and insulin resistance. Statistical analyses were performed using SAS Version 8.1 (SAS Institute Incorporated; Cary, North Carolina). Values are reported as means $\pm$ standard error. All P values are two sided and values <0.05 are considered statistically significant.

RESULTS

These analyses included 25 nondiabetic men with prostate cancer. Mean ($\pm$ SE) age was 68 ± 2 years. All of the men were white. Mean body mass index (BMI) was 29.1 ± 0.8 kg/m². Twenty men (80%) were overweight (BMI 25.0–29.9 kg/m²) or obese (BMI 30 kg/m²).

As previously reported⁹, mean serum testosterone concentrations decreased from 431 ± 37 ng/dL (15 ± 1 nmol/L) at baseline to 24 ± 3 ng/dL (0.8 ± 0.1 nmol/L) at week 12 ($P < 0.001$). Serum estradiol concentrations decreased from 31 ± 2 pg/mL (114 ± 7 pmol/L) to 9 ± 2 pg/mL (33 ± 7 pmol/L) ($P < 0.001$). Percentage fat body mass increased by $4.3 \pm 1.3\%$ ($P = 0.002$) and percentage lean body mass decreased by $1.4 \pm 0.5\%$ ($P = 0.006$) from baseline to week 12 (Table 1). Body-mass index did not change significantly.

Figure 1 shows oral glucose tolerance test results before and after combined androgen blockade. As previously reported⁹, mean fasting plasma insulin levels increased by $25.9 \pm 9.3\%$ ($P = 0.04$) (Table 1). Whole-body insulin sensitivity index decreased by $12.9 \pm 7.6\%$ ($P = 0.02$) (Table 1). Fasting plasma glucose levels did not change significantly.

Serum adiponectin levels increased by $37.4 \pm 7.2\%$ from baseline to week 12 ($P < 0.001$) (Table 1). In contrast, serum resistin levels did not change significantly. PAI-1 levels also did not change significantly.

Pearson's correlation analyses were performed to assess the linear relationships between changes in adipocytokines, body composition, and insulin resistance (Table 2). Changes in adiponectin were positively associated changes in lean body mass ($r = 0.448$; $P = 0.02$). Conversely, changes in adiponectin tended to be negatively associated with changes in fat mass ($r = -0.383$; $P = 0.06$). Changes in fat mass were inversely associated with changes in lean mass (Pearson correlation coefficient -0.884 ; $P < 0.001$). Changes in adiponectin, resistin, and body composition were not significantly associated with changes in insulin sensitivity.

COMMENT

In this prospective study of nondiabetic men with prostate cancer, combined androgen blockade with leuprolide and bicalutamide significantly increased plasma adiponectin levels but did not alter plasma resistin or PAI-1 levels. Combined androgen blockade also significantly increased fat mass and decreased insulin sensitivity. Changes in body composition were associated with changes in plasma adiponectin levels but not with changes in insulin sensitivity.

Our results are consistent with a previous report that short-term treatment with a GnRH agonist significantly increases adiponectin levels in younger men. In a prospective study of 28 healthy men aged 18–35 years, treatment with a GnRH agonist increased serum adiponectin levels by 49% after 21 days.¹⁹ Our results are also consistent with the observations that adiponectin levels decrease following testosterone replacement therapy in hypogonadal men²⁰ and supraphysiologic testosterone administration in eugonadal men.¹⁹

In contrast to the significant increases in mean adiponectin levels and fat mass in this prospective study of men with prostate cancer, cross-sectional studies have reported lower adiponectin in obese individuals and most insulin resistant states including type 2 diabetes mellitus.¹⁴ Changes in adiponectin levels in our subjects, however, tended to be inversely associated with changes in fat mass and directly associated with changes in lean body mass. The unexpected inverse relationship between changes in adiponectin and fat mass in our subjects may help explain the apparent differences between cross-sectional studies and the results of prospective studies of treatments to either raise or lower testosterone levels in men.

In cross-sectional studies, low adiponectin levels are associated with features of the metabolic syndrome including obesity, hypertension, low HDL cholesterol levels, high triglyceride levels, and insulin resistance.²¹ In prospective studies of men with prostate cancer, GnRH agonists increase fat mass and triglycerides and decrease insulin sensitivity—all changes consistent with the metabolic syndrome.^{4–9} In contrast to the metabolic syndrome, however, our results and the results of an earlier prospective study in normal young men show that GnRH agonists increase rather than decrease adiponectin levels. Combined androgen blockade did not significantly change PAI-1 levels in our subjects, in contrast to the characteristic elevation of PAI-1 levels in the metabolic syndrome.²² In addition, GnRH agonists significantly increase HDL cholesterol levels^{5, 9} and preferentially increase subcutaneous rather than visceral fat mass.⁵ We propose the term “hypogonadal metabolic syndrome” to distinguish the phenotype of GnRH agonist treated men from that of the classical defined metabolic syndrome. These distinct metabolic changes (elevated adiponectin and HDL cholesterol levels and preferential accumulation of subcutaneous fat) associated with GnRH agonist treatment suggest that additional research is warranted to better characterize the metabolic effects of GnRH agonist treatment and to assess their relationship to clinical outcomes including diabetes and cardiovascular disease.

The relationship between adiponectin and cardiovascular disease risk is controversial. Low adiponectin levels are associated with prevalent cardiovascular disease.^{23–25} Some but not all prospective studies of healthy individuals have reported that higher adiponectin levels are associated with decreased risk of incident myocardial infarction in men and women.^{26–29} In contrast, a recent prospective study reported that higher adiponectin levels are associated with greater cardiovascular mortality in men.²⁹ Further research is needed to evaluate the relationship between adiponectin levels and cardiovascular outcomes in hypogonadal men.

Consistent with the estimated 74 percent prevalence of overweight and obesity in United States men aged 60 or more years³⁰, eighty percent of subjects were overweight or obese. Treatment-related changes in adipocytokines, however, may differ in men with a normal body-mass index. Additional studies are needed to assess the long-term effects of GnRH agonist treatment on adipocytokines and to assess whether the observed treatment-related changes in metabolism are reversible after discontinuation of treatment. Larger long-term studies are also necessary to evaluate the relationships between the characteristic metabolic changes associated with GnRH agonist therapy and incident diabetes and associated morbidity.

CONCLUSIONS

The classic metabolic syndrome is characterized by visceral obesity, insulin resistance, low HDL cholesterol, high triglycerides, elevated PAI-1, and low adiponectin levels. In men with prostate cancer, GnRH agonists increase fat mass, decrease insulin sensitivity, and increase serum triglycerides. In contrast to the metabolic syndrome, however, GnRH agonists preferentially increase subcutaneous fat, increase HDL cholesterol and adiponectin levels, and do not change PAI-1 levels. Additional research is necessary to better characterize the metabolic effects of GnRH agonist treatment in men with prostate cancer and to understand implications for diabetes and cardiovascular disease risk.

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Figure 1.
Oral glucose tolerance tests results before (circles) and after combined androgen blockade (squares).

TABLE 1

Changes In Body Composition, Insulin Sensitivity, And Adipocytokines In GnRH Agonist-Treated Men With Prostate Cancer

	Baseline	Week 12	% Change	P value
Body-mass index (kg/m ²)	29.1 ± 0.8	29.3 ± 0.8	0.8 ± 0.6	0.39
Dual energy x-ray absorptiometry				
Percentage fat mass	28.7 ± 1.2	29.8 ± 1.1	4.3 ± 1.3	0.002
Percentage lean mass	68.1 ± 1.1	67.1 ± 1.1	-1.4 ± 0.5	0.006
Fasting plasma glucose (mg/dL)	93 ± 2	95 ± 2	+2.0 ± 1.4%	0.20
Fasting plasma insulin (mU/L)	13.5 ± 0.9	17.0 ± 2.0	+25.9 ± 9.3%	0.04
Insulin sensitivity index	3.4 ± 0.4	2.8 ± 0.3	-12.9 ± 7.6%	0.02
Adiponectin (ng/mL)	10.5 ± 1.0	13.6 ± 1.0	37.4 ± 7.2%	<0.001
Resistin (ng/mL)	16.1 ± 0.8	15.2 ± 0.9	-2.3 ± 6.7%	0.74
PAI-1 (ng/mL)	266 ± 43	244 ± 46	-10.2 ± 7.5%	0.17

Plus-minus values are means ± standard error.

PAI-1, plasminogen activator inhibitor, type 1

Pearson Correlation Coefficients For Changes In Adipocytokines, Body Composition, Insulin Sensitivity In GnRH Agonist-Treated Men With Prostate Cancer

	Adiponectin	Resistin	Fat mass	Lean mass	ISI
Adiponectin		-0.300 (P=0.16)	-0.383 (P=0.06)	0.448 (P=0.02)	0.033 (P=0.88)
Resistin			-0.107 (P=0.63)	0.019 (P=0.93)	0.070 (P=0.75)
Fat mass				-0.884 (P<0.001)	-0.026 (P=0.90)
Lean mass					0.002 (P=0.99)
ISI					

ISI, whole body insulin sensitivity index