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Insulin Sensitivity during Combined Androgen Blockade for Prostate Cancer

Matthew R. Smith, Hang Lee, and David M. Nathan

Division of Hematology-Oncology (M.R.S.), Mallinckrodt General Clinical Research Center (H.L.), and Diabetes Center (D.M.N.), Massachusetts General Hospital, Boston, Massachusetts 02114

Context: GnRH agonists markedly increase fat mass in men with prostate cancer, but little is known about the effects of treatment on insulin sensitivity.

Objective: The objective of the study was to assess the effects of short-term GnRH agonist treatment on insulin sensitivity.

Design: This was a prospective 12-wk study.

Setting: The study was conducted at a general clinical research center.

Patients or Other Participants: We studied 25 men with locally advanced or recurrent prostate cancer, no radiographic evidence of metastases, no history of diabetes mellitus, and no evidence of diabetes mellitus at baseline visit.

Intervention: Leuprolide depot and bicalutamide were used in the study.

Main Outcome Measures: Oral glucose tolerance tests and body composition assessment by dual-energy x-ray absorptiometry were performed at baseline and wk 12. The primary study outcome was change in insulin sensitivity index.

Results: Mean (± SE) percentage fat body mass increased by 4.3 ± 1.3% from baseline to wk 12 ($P = 0.002$). Insulin sensitivity index decreased by 12.9 ± 7.6% ($P = 0.02$). Insulin sensitivity by homeostatic model assessment decreased by 12.8 ± 5.9% ($P = 0.02$). Fasting plasma insulin levels increased by 25.9 ± 9.3% ($P = 0.04$). Mean glycosylated hemoglobin also increased significantly ($P < 0.001$).

Conclusions: Short-term treatment with leuprolide and bicalutamide significantly increased fat mass and decreased insulin sensitivity in men with prostate cancer. These observations suggest that GnRH agonists may increase the risk of diabetes mellitus and cardiovascular disease in older men. **(*J Clin Endocrinol Metab* 91: 1305–1308, 2006)**

GnRH AGONISTS ARE the cornerstone of treatment for metastatic prostate cancer and a routine part of management for many men with local and local-regional disease (1). GnRH agonists have a variety of adverse effects including marked alterations in body composition (2–6). In two prospective studies of men with locally advanced or recurrent prostate cancer, for example, GnRH agonists decreased lean body mass by 2.4–3.8% and increased fat mass by 9.4–11.0% after 12 months (5, 6). Significant changes in lean mass and fat mass have also been observed after short-term treatment with a GnRH agonist (7, 8).

Obesity is a major correlate of insulin resistance in adults (9, 10). Insulin resistance is a common metabolic abnormality that underlies type 2 diabetes mellitus (11) and is an independent risk factor for cardiovascular disease (12, 13). Insulin resistance is also linked to a variety of abnormalities associated with cardiovascular disease risk including obesity, hypertension, elevated triglyceride levels, decreased high-density lipoprotein cholesterol levels, inflammation, and impaired vascular endothelial function (14–17).

Although treatment with a GnRH agonist markedly increases fat mass, little is known about the effects of GnRH agonists on insulin sensitivity in prostate cancer survivors. We conducted a 12-wk prospective study to characterize the short-term effects of GnRH agonist treatment on insulin sensitivity and other biomarkers of metabolism in men with prostate cancer. The primary study outcome was change in whole-body insulin sensitivity index (ISI) (18).

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Abbreviations: BMI, Body mass index; CIR, corrected insulin response; HDL, high-density lipoprotein; HOMA IR, homeostasis model assessment for insulin resistance; ISI, insulin sensitivity index; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test.

Subjects 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 less than 90, history of diabetes mellitus or glucose intolerance, treatment with medications known to alter glucose or insulin levels, or serum creatinine concentration greater than 2.0 mg/dl (177 μmol/liter) were also excluded.

Study design

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

TABLE 1. Body composition by anthropometry and dual energy x-ray absorptiometry in GnRH agonist-treated men with prostate cancer

	Baseline	wk 12	Change, %	*P* value
Weight (kg)	89.5 ± 2.7	89.9 ± 2.5	0.6 ± 0.7	0.50
BMI (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

Values are means ± SE.

After the baseline visit, subjects received leuprolide 3-month depot (Lupron depot; TAP Pharmaceuticals Inc., Deerfield, IL) (22.5 mg im every 12 wk). Subjects also received bicalutamide (Casodex; AstraZeneca PLC, London, UK) (50 mg by mouth daily) for 4 wk to prevent the potential flare associated with the first administration of a GnRH agonist.

The Institutional Review Board of Dana Farber Partners Cancer Care 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 QDR 4500A densitometer (software version 11.1; Hologic, Inc., Waltham, MA) (5).

Oral glucose tolerance test (OGTT). In the morning after a 12-h overnight fast, subjects received a 75-g OGTT. Blood samples were collected at 0, 30, 60, 90, and 120 min for measurement of plasma glucose and insulin concentrations. The whole-body ISI was calculated from fasting plasma insulin and glucose concentrations and mean plasma insulin and glucose concentrations during the OGTT, with ISI = 10,000/square root of (fasting plasma glucose × fasting plasma insulin) × (mean OGTT glucose × mean OGTT insulin) (18). The homeostasis model assessment (HOMA IR) was also used to calculate insulin resistance from fasting plasma insulin and glucose concentrations, with HOMA IR = [fasting plasma insulin (milliunits per liter) × plasma glucose (millimoles per liter)/22.5] (19). Insulin secretion was estimated by the corrected insulin response (CIR), based on the plasma insulin and glucose concentrations at 30 min during the OGTT, with CIR = 100 × 30 min OGTT insulin/[30 min OGTT glucose × (30 min OGTT glucose minus 70 mg/dl)] (20).

Biochemical assays. Plasma insulin was measured using a RIA with a sensitivity of 2 mU/liter and intraassay and interassay coefficients of variation of 2.2–4.4 and 2.9–6.0%, respectively (Linco Research, St. Charles, MO). Glycosylated hemoglobin was measured by ion exchange HPLC with intra- and interassay coefficients of variation of 0.65–1.46 and 1.00–1.84%, respectively (Variant II; Bio-Rad, Hercules, CA). Serum testosterone was measured by RIA with an intraassay coefficient of variation of approximately 5% for values within the normal range and 18% for values in the castrate range and an interassay coefficient of variation of 7–12% (Diagnostic Products, Los Angeles, CA). Serum estradiol was measured by RIA with a sensitivity of 3 pg/ml and intra-and interassay coefficients of variation of 10 and 14%, respectively (Nichols Institute, San Juan Capistrano, CA). Serum cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured by colorimetric enzymatic assays on an automated clinical chemistry analyzer with intra- and interassay coefficients of variation of 0.8–1.5 and 1.7–2.6%, respectively (Roche Diagnostics/Roche Molecular Biochemicals, Indianapolis, IN).

Statistical analyses

The primary study end point was the percent change in the whole-body ISI from baseline to 12 wk. Subjects who met the criteria for diabetes mellitus [fasting plasma glucose ≥ 126 mg/dl or 2-h postload glucose ≥ 200 mg/dl during OGTT (11)] at baseline visit were excluded from the analyses. Longitudinal changes between baseline and 12-wk values for all outcome measures were examined using two-sided paired *t* tests. Statistical analyses were performed using SAS (version 8.1; SAS Institute Inc., Cary, NC). Values are reported as means ± SE. All *P* values are two sided, and $P < 0.05$ is considered statistically significant.

Results

Thirty men completed baseline evaluation before initiating treatment; five met criteria for diabetes mellitus and were excluded from the analyses. All of the remaining 25 men were treated with leuprolide and bicalutamide and completed the 12-wk study. Mean (± SE) age was 68 ± 2 yr. All of the men were white. Mean body mass index (BMI) was 29.1 ± 0.8 kg/m^2. Nine men (36%) were overweight (BMI 25.0–29.9 kg/m^2) and 11 men (44%) were obese (BMI ≥ 30 kg/m^2).

Mean serum testosterone concentrations decreased from 431 ± 37 ng/dl (15 ± 1 nmol/liter) at baseline to 24 ± 3 ng/dl (0.8 ± 0.1 nmol/liter) at wk 12 ($P < 0.001$). Serum estradiol concentrations decreased from 31 ± 2 pg/ml (114 ± 7 pmol/liter) to 9 ± 2 pg/ml (33 ± 7 pmol/liter) ($P < 0.001$). Percentage fat body mass increased by 4.3 ± 1.3% ($P = 0.002$), and percentage lean body mass decreased by 1.4 ± 0.5% ($P = 0.006$) from baseline to wk 12 (Table 1). Weight and BMI did not change significantly.

Mean glycosylated hemoglobin levels increased slightly, albeit significantly, from 5.46 ± 0.09% at baseline to 5.62 ± 0.09% at wk 12 ($P < 0.001$) (Table 2). Mean fasting plasma glucose levels and plasma glucose levels 2 h after oral glucose load did not change significantly. One of the 25 subjects met

TABLE 2. Indices of insulin sensitivity, insulin secretion, and glycemia in GnRH agonist-treated men with prostate cancer

	wk 0	wk 12	Change, %	*P* value
Glycoslyated hemoglobin (%)	5.46 ± 0.09	5.62 ± 0.09	+2.9 ± 0.8	<0.001
Fasting plasma glucose (mg/dl)	93 ± 2	95 ± 2	+2.0 ± 1.4	0.20
2-h plasma glucose (mg/dl)	128 ± 7	126 ± 9	+4.4 ± 7.5	0.84
Fasting plasma insulin (mU/liter)	13.5 ± 0.9	17.0 ± 2.0	+25.9 ± 9.3	0.04
Whole-body ISI (18)	3.4 ± 0.4	2.8 ± 0.3	-12.9 ± 7.6	0.02
HOMA IR (19)	7.1 ± 0.9	5.9 ± 0.6	-12.8 ± 5.9	0.02
CIR (20)	0.67 ± 0.8	0.78 ± 0.8	+30.8 ± 13.5	0.12

Values are means ± SE.

TABLE 3. Serum lipoproteins in GnRH agonist-treated men with prostate cancer

	wk 0	wk 12	Change, %	*P* value
Total cholesterol (mg/dl)[a]	172 ± 6	187 ± 7	+9.4 ± 2.4	<0.001
HDL cholesterol (mg/dl)[b]	52 ± 3	57 ± 3	+9.9 ± 2.9	0.01
LDL cholesterol (mg/dl)[c]	100 ± 6	107 ± 7	+8.7 ± 4.7	0.09
Triglycerides (mg/dl)[d]	98 ± 9	115 ± 9	+23.0 ± 8.0	0.04

Values are means ± SE.
[a] To convert cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259.
[b] To convert HDL cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259.
[c] To convert LDL cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259.
[d] To convert triglycerides from milligrams per deciliter to millimoles per liter, multiply by 0.0113.

criteria for diabetes mellitus at the wk 12 OGTT. Whole-body ISI decreased by 12.9 ± 7.6% ($P = 0.02$). Insulin sensitivity by homeostatic model assessment decreased by 12.8 ± 5.9% ($P = 0.02$). Fasting plasma insulin levels increased by 25.9 ± 9.3% ($P = 0.04$). The corrected insulin response increased by 30.8 ± 13.5% ($P = 0.12$).

Serum total cholesterol, HDL cholesterol, and LDL cholesterol concentrations increased by 9.4 ± 2.4% ($P < 0.001$), 9.9 ± 2.9% ($P = 0.01$), and 8.7 ± 4.7% ($P = 0.09$), respectively (Table 3). Serum triglycerides increased by 23.0 ± 8.0% ($P = 0.04$).

Discussion

In this prospective study of nondiabetic men with prostate cancer, short-term treatment with leuprolide and bicalutamide significantly increased fat mass and decreased insulin sensitivity. Treatment also significantly increased glycosylated hemoglobin levels. Among the 25 subjects selected to exclude prevalent diabetes mellitus or glucose intolerance, one developed diabetes during the 12-wk study. The observed increases in fasting plasma insulin levels and corrected insulin response are consistent with a compensatory increase in insulin secretion.

Our results are consistent with previous reports that GnRH agonists increase fasting plasma insulin levels in men with prostate cancer (7, 8). In contrast to the other reports, however, our study excluded subjects with prevalent diabetes and evaluated whole-body insulin sensitivity index after a glucose load, a more reliable method for assessment of insulin sensitivity than fasting plasma insulin levels.(18)

In a short-term physiologic study, gonadal steroid concentrations in the low normal to supraphysiologic range (serum testosterone 8.8–82.2 nM/liter) were not associated with variations in insulin sensitivity (21). Our observation that GnRH agonist treatment significantly decreases insulin sensitivity suggests that the dose-response relationship between gonadal steroids and insulin sensitivity is nonlinear in the severely hypogonadal range (serum testosterone < 1 nM/liter). Alternatively, but less likely, treatment-related deceases in insulin sensitivity may be a direct effect of exposure to leuprolide and/or bicalutamide rather than secondary to hypogonadism.

Consistent with earlier reports (5, 8, 22), we observed that GnRH agonist treatment significantly increased serum triglycerides levels and HDL cholesterol. The observed increase in HDL cholesterol levels contrasts to the low levels of HDL cholesterol associated with the classic metabolic syndrome (14, 15). Additional studies are necessary to evaluate the importance of this difference and characterize the effects of GnRH agonist treatment on other components of the metabolic syndrome including biomarkers of inflammation and fibrinolysis.

Our study has some limitations. Eighty percent of subjects were overweight or obese, similar to estimated 74% prevalence of overweight and obesity in United States men aged 60 yr or older (23). Treatment-related changes in insulin sensitivity, however, may differ in men with a normal BMI. The expected interpatient variation in insulin secretion is greater than the expected variation in insulin sensitivity, and the current study may have been too small to adequately assess the effects of GnRH agonist treatment on corrected insulin response. Additional studies are needed to assess the long-term effects of GnRH agonist treatment on insulin sensitivity and other biomarkers of metabolism and assess whether treatment-related changes in metabolism are reversible after discontinuation of treatment. Larger, long-term studies are also necessary to determine the incidence of treatment-related diabetes and associated morbidity.

In summary, short-term treatment with leuprolide and bicalutamide increases fat mass and decreases insulin sensitivity in men with prostate cancer. These observations raise the possibility that GnRH agonist treatment may increase the risk of diabetes mellitus and cardiovascular disease.

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Address all correspondence and requests for reprints to: Matthew R. Smith, M.D., Ph.D., Massachusetts General Hospital, Cox 640, 100 Blossom Street, Boston, Massachusetts 02114. E-mail: smith.matthew@mgh.harvard.edu.

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