Obesity and Sex Steroids during Gonadotropin-Releasing Hormone Agonist Treatment for Prostate Cancer

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Abstract

Purpose: To evaluate effects of obesity on sex steroid levels during treatment with a gonadotropin-releasing hormone agonist in men with prostate cancer.

Experimental Design: Forty-nine hormone-naïve men with recurrent or locally advanced prostate cancer were included in the analyses. All subjects were treated with leuprolide 3-month depot for 48 weeks. Serum levels of estradiol, sex hormone – binding globulin, total testosterone, and free testosterone were assessed at baseline, 24 weeks, and 48 weeks. Subjects were categorized by body mass index (BMI) and percent body fat.

Results: Pretreatment serum sex hormone – binding globulin and total testosterone levels were significantly lower in overweight and obese men than in men with normal BMI. In the overall study population, mean serum testosterone concentrations decreased from 372 $\pm$ 18 ng/dL at baseline to 13 $\pm$ 1 ng/dL at week 48 ($P < 0.001$). Free testosterone decreased from 6.75 $\pm$ 0.33 ng/dL at baseline to 0.21 $\pm$ 0.02 ng/dL at week 48 ($P < 0.001$). During treatment with leuprolide, obese men had significantly higher total and free testosterone levels than men with normal BMI. Compared with normal men, total and free testosterone levels during treatment were 1.8-fold and 2.3-fold higher in obese men. Similar results were observed when subjects were categorized by body fat.

Conclusions: Despite lower pretreatment serum testosterone levels, obese men have higher total and free testosterone levels during leuprolide treatment than men with normal BMI. These differences may contribute to the association between obesity and increased prostate cancer mortality.

Obesity is an epidemic in the United States. Between 1980 and 2002, the prevalence of obesity doubled in U.S. adults (1). Currently, >30% of men older than 60 years are classified as obese (2).

Several large prospective cohort studies have observed an association between obesity and greater risk for prostate cancer death (3–5). Several factors have been implicated as potential mechanisms for greater prostate cancer mortality in obese men, including detection bias, variations in energy balance, and alterations in sex steroid metabolism (6, 7). In older men, greater body mass index (BMI) is associated with lower serum levels of testosterone and sex hormone–binding globulin (SHBG) and higher serum levels of estradiol (8, 9). Obesity is also associated with lower serum levels of androstenedione (10, 11) but greater peripheral conversion of androstenedione to estrone and estradiol (12).

Androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist is the mainstay of treatment for advanced prostate cancer. Nearly all men with fatal prostate cancer receive treatment with a GnRH agonist either as primary therapy for metastatic disease or as salvage therapy following surgery or radiation therapy for clinically localized disease (13). Although the effects of body composition on sex steroid metabolism in untreated men are well characterized, little is known about the relationship between obesity and sex steroid levels in men receiving GnRH agonist therapy.

The hypothesis of this study was that sex steroids levels would vary between normal, overweight, and obese men during GnRH agonist treatment for prostate cancer. Prospective 12-month data for men receiving initial treatment with leuprolide depot for nonmetastatic prostate cancer were analyzed to determine the relationships between obesity and sex steroid levels. Baseline and posttreatment sex steroid levels were compared between subjects according to BMI and body composition.

Materials and Methods

Subjects and study design. The analyses included subjects from two previously reported 48-week prospective studies of GnRH agonist treatment in men with locally advanced or recurrent nonmetastatic prostate cancer (14, 15). Men with bone metastases, metabolic bone disease, serum calcium <8.4 or >10.6 mg/dL, or serum creatinine concentration >2.0 mg/dL (177 μmol/L) were excluded from the studies. Subjects with prior exposure to hormone therapy were excluded from the current analyses.

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Table 1. Baseline characteristics in normal, overweight, and obese subjects

	Normal (BMI, <25 kg/m^2)	Overweight (BMI, 25-29.9 kg/m^2)	Obese (BMI, >30 kg/m^2)
Subjects, *n*	16	25	9
Age, y	67 ± 3	66 ± 2	62 ± 3
Weight, kg	72.9 ± 2.3	83.2 ± 1.0*	95.3 ± 1.9*†
BMI, kg/m^2	23.4 ± 0.4	27.2 ± 0.3*	31.7 ± 0.5*†
% Body fat	21.5 ± 1.0	25.7 ± 0.8*	31.1 ± 1.3*†

NOTE: Data are given as means ± SE.
*P < 0.05, compared with normal subjects.
†P < 0.05, compared with overweight subjects.

Subjects were evaluated at the General Clinical Research Center at Massachusetts General Hospital at baseline, week 24, and week 48. At each study visit, a serum sample was collected for measurement of testosterone, estradiol, and SHBG. A research dietitian measured subject height and weight. Body composition was measured by dual energy X-ray absorptiometry.

After the baseline visit, subjects received leuprolide 3-month depot (Lupron Depot, TAP Pharmaceuticals, Inc., Deerfield, IL; 22.5 mg intramuscularly every 12 weeks) for 48 weeks. Subjects also received bicalutamide (Casodex, AstraZeneca PLC, London, United Kingdom; 50 mg orally daily) for 4 weeks to prevent the potential flare associated with the first administration of a GnRH agonist. Subjects who discontinued leuprolide depot before week 48 were excluded from the analyses.

The institutional review board of Dana-Farber Partners Cancer Care reviewed and approved the study. All subjects gave written informed consent.

Study end points. 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. The mean of three height measurements was recorded. Body composition was determined by dual energy X-ray absorptiometry using a Hologic QDR 4500 A densitometer (Hologic, Inc., Waltham, MA) with software version 11.2 as previously described (16).

Serum testosterone was measured by RIA with a lower limit of detection of 6 ng/dL (0.2 nmol/L), an intraassay coefficient of variation of ~5% for values within the reference range, and 18% for values in the castrate range, and an interassay coefficient of variation of 7% to 12% (Diagnostic Products, Los Angeles, CA). Serum estradiol was measured by RIA with a lower limit of detection of 3 pg/mL (11 pmol/L) and intraassay and interassay coefficients of variation of 10% and 14%, respectively (Nichols Institute, San Juan Capistrano, CA). SHBG was measured by solid-phase chemiluminescent enzyme immunoassay with a sensitivity of 1 nmol/L and intraassay and interassay coefficients of variation of <7% and <8%, respectively (Diagnostic Products Corporation, Los Angeles, CA). Free testosterone was calculated from total testosterone and SHBG values using the method described by Vermeulen (17).

Statistical analyses. Values are reported as means ± SE. Changes from baseline were tested for significance using one-sample t tests. Results were compared between the groups using t tests. All P values are two sided and P < 0.05 is considered statistically significant.

Results

Baseline characteristics of the subjects. Forty-nine subjects were included in the analyses. Mean (±SE) age was 66 ± 1 years. Forty-four men were white, four were black, and one was Asian. Mean body weight was 82.3 ± 1.5 kg (range, 62.5-104.6 kg). Mean BMI was 26.9 ± 0.5 kg/m^2 (range, 21.0-34.7 kg/m^2). Fifteen subjects (31%) were classified as normal (BMI, <25.0 kg/m^2), 25 (51%) were overweight (BMI, 25.0-29.9 kg/m^2), and 9 (18%) were obese (BMI, ≥30 kg/m^2). Mean fat mass was 25.5 ± 0.7% (range, 14.0-36.1%).

Changes in serum sex steroid levels during leuprolide treatment. In the overall study population, mean serum testosterone concentrations decreased from 372 ± 18 ng/dL at baseline to 13 ± 1 ng/dL at week 48 (P < 0.001). Total serum testosterone

Table 2. Serum sex steroid levels in normal, overweight, and obese men

	Group			*P*	
	Normal	Overweight	Obese	Overweight vs normal	Obese vs normal
Estradiol (pg/mL)					
Baseline	24 ± 2	22 ± 1	27 ± 3	0.43	0.45
Wk 24	4 ± 1	6 ± 1	8 ± 1	0.03	0.02
Wk 48	4 ± 1	5 ± 1	8 ± 2	0.61	0.10
SHBG (nmol/L)					
Baseline	48 ± 2	38 ± 2	35 ± 5	0.008	0.04
Wk 24	50 ± 3	39 ± 3	37 ± 6	0.01	0.06
Wk 48	55 ± 4	41 ± 3	35 ± 6	0.02	0.01
Total testosterone (ng/dL)					
Baseline	440 ± 34	343 ± 25	338 ± 31	0.03	0.03
Wk 24	11 ± 1	11 ± 1	20 ± 3	0.76	0.009
Wk 48	10 ± 1	12 ± 1	18 ± 2	0.34	0.01
Free testosterone (ng/dL)					
Baseline	7.3 ± 0.7	6.5 ± 0.5	6.6 ± 0.6	0.32	0.48
Wk 24	0.15 ± 0.02	0.19 ± 0.02	0.40 ± 0.08	0.22	0.01
Wk 48	0.15 ± 0.03	0.21 ± 0.03	0.35 ± 0.06	0.10	0.009

NOTE: Data are given as means ± SE. To convert estradiol from picograms per milliliter to picomoles per liter, multiply by 3.671. To convert testosterone and free testosterone from nanograms per deciliter to nanomoles per liter, multiply by 0.0347.

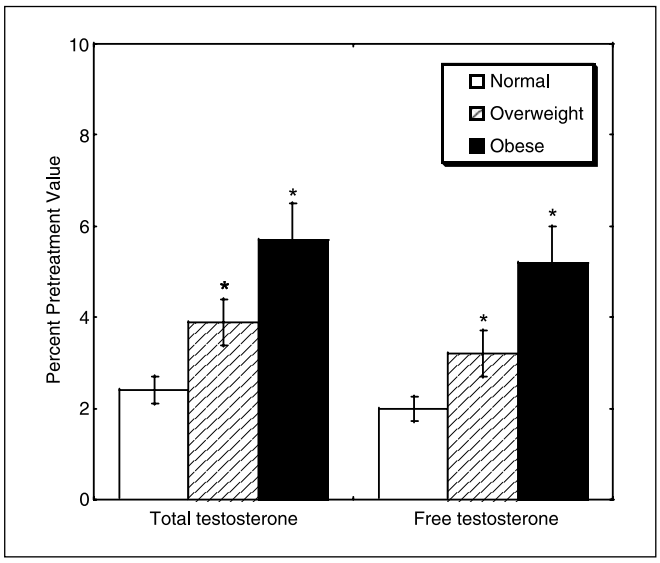

Fig. 1. Mean (±SE) percent pretreatment value for total and free testosterone in normal, overweight, and obese men after 48 wk of leuprolide treatment. *, $P < 0.01$, compared with men with normal BMI.

decreased to <50 ng/dL in all subjects. Serum estradiol concentrations decreased from 24 ± 1 to 5 ± 0.5 pg/mL ($P < 0.001$). SHBG increased from 41 ± 2 to 44 ± 3 nmol/L ($P = 0.02$). Free testosterone decreased from 6.75 ± 0.33 ng/dL at baseline to 0.21 ± 0.02 ng/dL at week 48 ($P < 0.001$).

Obesity and sex steroid levels. Table 1 summarizes the baseline characteristics for normal, overweight, and obese men. Age did not differ significantly between the groups. Compared with men with normal BMI, percentage body fat was significantly higher in overweight and obese men. Serum SHBG and total testosterone levels were significantly lower in overweight and obese men than in men with normal BMI (Table 2). Baseline levels of estradiol and free testosterone did not differ significantly between the groups (Table 2).

During treatment with leuprolide, obese men had significantly higher total and free testosterone levels than men with normal BMI (Table 2). At week 48, for example, obese men had total and free testosterone levels 1.8-fold and 2.3-fold greater than normal men. The relative decrease in serum and total and free testosterone levels from baseline to week 48 was significantly less in overweight and obese men than in normal men (Fig. 1). Total and free testosterone levels, expressed as percentage of pretreatment values, were 2.4-fold and 2.6-fold greater in obese men than in men with normal BMI. Residual testosterone levels correlated significantly with BMI but not age (data not shown).

Obese men had higher estradiol levels and lower SHBG levels than men with normal BMI during leuprolide treatment, although these differences were not statistically significant at both 24 and 48 weeks. Overweight men tended to have sex steroid levels that were intermediate between normal and obese men (Table 2).

Subjects with similar differences in sex steroid levels were categorized by body weight (data not shown).

Fat mass and sex steroid levels. The relationship between body composition and sex steroid metabolism was further evaluated by comparing subjects with high (median value of >25%) and low (<25%) fat body masses (Table 3). Pretreatment levels of estradiol, SHBG, total testosterone, and free testosterone did not differ significantly between the groups. In contrast, subjects with high fat mass had significantly higher levels of estradiol, total testosterone, and free testosterone than subjects with low fat mass during leuprolide treatment. Subjects with high fat mass also had significantly lower SHBG levels than subjects with low fat mass during leuprolide treatment.

Discussion

These analyses show that despite lower baseline serum testosterone levels, obese men had significantly higher serum levels of total and free testosterone during treatment with leuprolide depot than men with normal BMI. Obese men had total and free testosterone levels 1.8-fold and 2.3-fold greater than normal men after 48 weeks of treatment. Similarly, men with body fat mass >25% had significantly higher total and free testosterone levels during treatment with leuprolide depot than men with lower percentage body fat.

Other investigators have reported failure to maintain castrate testosterone levels during GnRH agonist therapy (18, 19). In a prospective study of 37 men receiving leuprolide 3-month depot for prostate cancer, for example, 4 (11%) men failed to achieve testosterone levels <20 ng/dL (18). Notably, all four of these subjects were obese. The manufacturers of leuprolide and other GnRH agonists recommend monitoring of response by measurement of serum testosterone levels (20, 21). The observed significant association between obesity and higher testosterone levels during GnRH agonist treatment in this study suggests that close monitoring of serum testosterone levels is warranted during treatment of obese men.

Sixty-seven percent of subjects in the study were overweight or obese, similar to the estimated 74% prevalence of overweight and obesity in U.S. men ages ≥60 years (22). Notably, all of the obese subjects in the study had class I obesity (BMI, 30-34.9 kg/m^2). Men with class II (BMI, 35-39.9 kg/m^2) or class III (BMI, >40 kg/m^2) obesity may have more marked elevation of sex

Table 3. Serum sex steroid levels by baseline percentage body fat

	Body fat <25% (*N* = 24)	Body fat ≥ 25% (*N* = 25)	*P*
Estradiol (pg/mL)			
Baseline	22 ± 1	26 ± 2	0.09
Wk 24	5 ± 1	7 ± 1	0.04
Wk 48	4 ± 1	6 ± 1	0.03
SHBG (nmol/L)			
Baseline	44 ± 2	37 ± 3	0.09
Wk 24	46 ± 3	37 ± 3	0.04
Wk 48	50 ± 3	39 ± 4	0.03
Total testosterone (ng/dL)			
Baseline	391 ± 22	352 ± 28	0.29
Wk 24	10 ± 1	15 ± 2	0.01
Wk 48	10 ± 1	15 ± 2	0.02
Free testosterone (ng/dL)			
Baseline	6.80 ± 0.45	6.69 ± 0.45	0.87
Wk 24	0.16 ± 0.02	0.28 ± 0.04	0.008
Wk 48	0.16 ± 0.02	0.27 ± 0.03	0.006

NOTE: Data are given as means ± SE.

steroid levels during GnRH agonist treatment than was observed in this study of men with less severe obesity.

In men with metastatic prostate cancer, low pretreatment serum testosterone levels (typical with obesity and advanced age) are associated with shorter overall survival (23). The results of the current analyses raise the possibility that higher sex steroid levels during GnRH agonist therapy may also contribute to greater prostate cancer mortality in obese men. The association between obesity and both lower pretreatment testosterone levels and higher posttreatment testosterone levels translates into a substantially smaller relative decline in testosterone levels after GnRH agonist treatment. In the current analyses, residual testosterone levels (expressed as percentage of pretreatment values) were 2.5-fold higher in obese subjects than in men with normal BMI.

In a randomized controlled trial of leuprolide reported in 1984, testosterone suppression was similar for men treated with leuprolide and men treated with diethylstilbestrol (24). In another randomized controlled trials reported in 1991, testosterone suppression was similar for men treated with goserelin and men who underwent bilateral orchiectomies (25). Notably, both studies used less sensitive testosterone assays than currently available and may have overlooked small differences in testosterone suppression between the groups. In addition, the rates of obesity have approximately doubled in the last two decades and these studies may overestimate the efficacy of GnRH agonists in a contemporary more obese population.

What is the optimal level of testosterone suppression during GnRH agonist treatment? Most studies have defined the "castrate range" for serum total testosterone as <50 ng/dL (24, 25), although some authors have described the expected nadir after bilateral orchiectomies as <10 ng/dL (26). The concept that "lower is better" underlies the use of ketoconazole and other agents as secondary hormone therapy for men with disease progression during treatment with a GnRH agonist (27). Additional studies are necessary to assess the relationship between sex steroid levels and survival during treatment with a GnRH agonist and to determine whether interventions to further decrease sex steroids levels improve clinical outcomes.

There are several examples of dose selection of leuprolide based on body size. In Japanese men, typically of smaller stature than American men, the recommended monthly dose of leuprolide depot for prostate cancer is 3.75 mg, which is half the dose approved to treat men with prostate cancer in the United States (28). Similarly, the recommended dose for treatment of uterine leiomyomata in Japanese women is one half that recommended in U.S. women (29). In children with precocious puberty, the recommended dose of leuprolide is based on body weight (30). There are currently no recommendations for dose modification of leuprolide or other GnRH agonists in obese men. Additional studies of obese men are necessary to determine whether higher doses of leuprolide achieve lower serum testosterone concentrations and whether higher leuprolide doses improve clinical efficacy.

Greater BMI is associated with higher serum levels of estradiol in men (8, 9) due to peripheral conversion of androgens to estrogen in adipose tissue (12). In this study, obese men tended to have higher estradiol levels than men with normal BMI before and during treatment with a GnRH agonist. The relative differences between normal and obese men seemed to increase after GnRH agonist treatment, possibly due to treatment-related increases in fat mass.

These analyses have several key strengths. Subjects included in the analyses were participants in prospective clinical trials. Subjects with prior exposure to hormone therapy were excluded. All subjects in the analyses received the same GnRH agonist formulation and dose. Subjects were evaluated at baseline and subsequent time points corresponding to the end of a treatment cycle (immediately before next scheduled treatment). Sex steroid levels were analyzed using sensitive assays [lower limits of detection for testosterone and estradiol were of 6 ng/dL (0.2 nmol/L) and 3 pg/mL (11 pmol/L), respectively]. Only studies with similar strengths may be adequate to confirm or disprove the observed association between obesity and elevated serum testosterone levels during GnRH agonist treatment.

These analyses also have some limitations. All subjects were treated with leuprolide 3-month depot and the results cannot be generalized to other leuprolide formulations or to other GnRH agonists. Sex steroid levels were assessed at the end of the treatment cycle; different results may be observed at earlier time points. Ninety percent of the subjects were Caucasian and additional studies are necessary to evaluate the relationship between obesity and sex steroids during GnRH agonist treatment in non-White men.

In summary, despite lower pretreatment serum testosterone levels, obese men have higher total and free testosterone levels during treatment with leuprolide than men with normal BMI. These results raise the possibility that higher sex steroids levels during GnRH agonist treatment contribute to greater prostate cancer mortality in obese men.

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