Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer

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Abstract **Androgen deprivation therapy (ADT) for prostate cancer is now used in earlier disease stages and as adjuvant treatment. Recognizing and reducing the toxicity of this therapy, including worsened lipid levels and cardiovascular disease (CVD) risks, has become an important clinical concern. Oral estrogen therapy induces hypogonadism and mitigates many side effects of ADT, but has a high thrombosis risk. Transdermal estrogen therapy (TDE) has a lower thrombosis risk than oral estrogen and may improve CVD risk compared with ADT. This prospective pilot study of 18 men with androgen-independent prostate cancer receiving ADT measured effects of TDE on lipid and inflammatory CVD risk factors before and after 8 weeks of TDE (estradiol 0.6 mg/day). During treatment, estradiol levels rose 17-fold; total cholesterol, LDL cholesterol, and apolipoprotein B levels decreased. HDL_2 cholesterol increased, with no changes in triglyceride or VLDL cholesterol levels. Dense LDL cholesterol decreased and LDL buoyancy increased in association with a decrease in HL activity. Highly sensitive C-reactive protein levels and other inflammatory markers did not worsen. Compared with ADT, short-term TDE therapy of prostate cancer improves lipid levels without deterioration of CVD-associated inflammatory markers and may, on longer-term follow-up, improve CVD and mortality rates.**—Purnell, J. Q., L. B. Bland, M. Garzotto, D. Lemmon, E. M. Wersinger, C. W. Ryan, J. D. Brunzell, and T. M. Beer. **Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer.** ***J. Lipid Res.*** **2006.** 47: **349–355.**

Supplementary key words estradiol • apolipoprotein • inflammation • androgen deprivation therapy

A thorough understanding of the adverse effect profile of androgen deprivation therapy (ADT) for prostate cancer is particularly important now because of the marked increase in the use of ADT, especially at earlier stages of disease, where treatment exposes younger patients to long-term toxicities. Previous practice had largely limited the use of ADT to patients with advanced metastatic prostate cancer (1). Reports of benefit from randomized clinical trials of ADT as adjuvant treatment in patients with clinically localized disease (2–4) have, however, lead to widespread use of ADT in these patient populations. Further, therapeutic enthusiasm among U.S. physicians has also led to a marked increase in the use of ADT as sole therapy for the treatment of localized prostate cancer. These trends in prostate cancer care have recently been documented by CAPSURE investigators (5).

Concerns have arisen, however, regarding the short- and long-term consequences of ADT. Initial side effects to ADT are well known and include loss of libido, erectile dysfunction, hot flashes, anemia, and depression (6). Prolonged androgen deprivation in men is associated with decreased bone density (7, 8) and changes in body composition (8, 9). In addition to these changes in body composition, ADT has been shown to have adverse effects on lipid levels, insulin levels, and arterial stiffness (10). These alterations in cardiac risk factors are consistent with epidemiological data linking hypogonadism with increased risk for coronary artery disease in the general population (11, 12). Recent data in men with prostate cancer have shown that the mortality from prostate cancer has declined such that by 1996, cardiovascular disease (CVD) had become a more likely cause of death than their cancer in these men (13).

In studies lasting longer than three months, medical or surgical castration led to increases in total cholesterol,

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Abbreviations: ADT, androgen deprivation therapy; CVD, cardiovascular disease; DEXA, dual energy X-ray absorptiometry; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; SHBG, sex hormone binding globulin; TDE, transdermal estrogen therapy; TNFα, tumor necrosis factor-α.

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triglyceride levels, and LDL and HDL cholesterol (10, 14, 15). Oral estrogen therapy has been used to suppress testosterone levels and improve some lipid levels in men with prostate cancer (16–18), but in early studies, oral formulations were associated with an unacceptably high risk of thromboembolic disease and CVD (19, 20). Subsequent studies have shown that oral estrogen significantly increases the risk of thromboembolic complications, increases triglyceride levels, and raises levels of inflammatory markers in both women and men. These effects may underlie the neutral or detrimental effects on cardiovascular and cerebrovascular disease previously reported from randomized trials of oral estrogen in men and women (21–24). Parenterally administered estrogens, on the other hand, avoid this first-pass effect on hepatic protein synthesis, and an increased prothrombotic risk has not been reported in men with prostate cancer treated with estrogen using this route of administration (25, 26).

Our group has recently reported results from a pilot study of men receiving ADT for prostate cancer who were followed for 8 weeks after changing their therapy to transdermal estrogen therapy (TDE) (27). In that report, TDE was well tolerated and not associated with thromboembolic complications or clinically important changes in several coagulation factors. With the possibility that parenteral estrogen may be an alternative to ADT that alleviates some of the unfavorable changes in lipids seen with hypogonadism in men, we sought to determine the effect of transdermal estrogen on lipid levels, levels of enzyme activities involved in lipoprotein processing, and inflammatory cytokines associated with cardiovascular risk in a subset of this group of men. Measures of body composition and abdominal fat were included to determine whether measured effects were independent of changes in body fat stores. In the present pilot study, our overall goal is to investigate the possibility that transdermal estradiol may prove to be a safer method of ADT and more suitable for use in patients with long life expectancies than conventional ADT.

MATERIALS AND METHODS

Experimental subjects

Androgen-deprived patients with prostate cancer (metastatic or prostate-specific antigen–only, Eastern Cooperative Oncology Group Performance Status ≤2, and serum testosterone ≤50 ng/dl) were recruited through local urology and oncology clinics. Subjects were excluded if they had other significant medical illness or had received prior treatment for prostate cancer with chemotherapy, diethylstilbesterol or another estrogen, or PC-SPES®. Eligible subjects came to the Oregon Health and Science University General Clinical Research Center following an overnight fast and had blood samples collected for baseline labs as well as imaging studies to quantify body composition and abdominal fat. Subjects discontinued their previous medical ADT and began treatment with transdermal estradiol (0.6 mg/day) (Climara; Berlex Laboratories, Montville, NJ). Following 8 weeks of TDE therapy, subjects underwent repeat fasting blood sampling. Of the original 24 subjects previously reported (27), 6 subjects without paired measurements of lipids and body composition from baseline and follow-up were excluded, and the remaining 18 with complete datasets were included in this report (**Table 1**). Prior to enrollment, 16 participants (90%) had been treated with an anti-androgen medication and 1 participant had been treated with hydrocortisone. These medications were stopped at least 6 weeks prior to study enrollment. Subjects previously treated with surgical or medical orchiectomy had similar baseline values and responses to estrogen treatment with regard to lipids, lipase activities, and levels of inflammatory markers. The Institutional Review Boards of the Oregon Health and Science University and the Portland VA Medical Center approved this protocol, and written informed consent was obtained from all patients before enrollment.

Body composition and abdominal fat quantification

Total body and truncal fat, percent fat, and lean mass were measured by dual energy X-ray absorptiometry (DEXA) scan

TABLE 1. Characteristics of the men with prostate cancer treated with transdermal estrogen that were included or excluded from the present study

Characteristic	All	Included in lipid study	Excluded from lipid study[b]
No. of patients	24	18	6
Age (years)[a]	75 (49–91)	74 (50–92)	77 (73–83)
BMI (kg/m^2)[a]	28 (20–41)	29 (24–41)	27 (20–31)
PSA (ng/ml)[a]	22.3 (6.6–560.3)	22.3 (6.6–560.3)	21.9 (11.9–383.5)
	%		
Site of metastases			
Bone only	50	56	33
Lymph only	13	6	33
Bone, lymph nodes	13	11	17
None (PSA only)	25	28	17
Prior therapy			
Orchiectomy[a]	29	22	50
GnRH agonist[b]	75	78	67
Antiandrogen use	79	83	67
Ketoconazole	13	6	33

PSA, prostate-specific antigen.
[a] Results are median (range).
[b] One patient had an orchiectomy after 5 years on GnRH agonist.
[c] Subjects were excluded if they did not have paired measurements of lipids and body composition from baseline and follow-up.

(Discovery A; Hologic, Inc., Bedford, MA). Intra-abdominal fat (IAF) and subcutaneous abdominal fat (SQF) depots were manually separated and quantified using a single abdominal MRI (1.5 T; GE, Fairfield, CT) image obtained on inspiration at the level of the umbilicus. A single blinded observer quantified the cross-sectional region of interest using SliceOmatic (TomoVision; Montreal, Quebec, Canada).

Lipids and postheparin lipase activities

Cholesterol and triglyceride analysis by enzymatic determination were completed using standardized methods at the Oregon Health and Science University lipid laboratory (28). Ultracentrifugation methodology was used to isolate and quantitate VLDL, with calculated LDL and quantitated HDL (28). HDL_2 and HDL_3 fractions for cholesterol analyses were obtained by a dextran sulfate Mg^{2+} double-precipitation procedure (29, 30). An immunoturbidimetric method was used to quantify lipoprotein [a] (Lp[a]) (Polymedco, Inc.; Cortlandt Manor, NY). Apolipoprotein B (apoB) was determined by radioimmunoassay (RIA) at the Northwest Lipid Laboratory (Seattle, WA) (31). LDL buoyancy [relative floatation rate (Rf)] was determined by nonequilibrium density gradient ultracentrifugation in a Sorvall TV-865B vertical rotor (DuPont; Wilmington, DE) (32). Briefly, 1 ml of plasma was adjusted to a density of 1.08 g/ml (total volume 5 ml) and layered below a 1.006 g/ml NaCl solution. Samples were then centrifuged at 65,000 rpm for 90 min at 10°C and fractionated into 38 fractions (each 0.47 ml), and cholesterol was measured in each fraction by an enzymatic kit (Diagnostic Chemicals; Prince Edward Island, Canada). The between-rotor coefficient of variation (CV) for LDL buoyancy (determined by dividing the fraction number containing the peak level of cholesterol within the LDL range by the total number of fractions, or 38) was 3.5%. This technique was optimized to separate subfractions of apoB-containing particles and not the denser HDL species.

The total lipolytic activity was measured in plasma after heparin bolus, as previously described (33). Glycerol tri(1-14C)oleate (Amersham; Arlington Heights, IL) and lecithin were incubated with postheparin plasma for 60 min at 37°C, and the liberated C14-labeled free fatty acids were then extracted and counted. Lipoprotein lipase activity was calculated as the lipolytic activity removed from the plasma by incubation with a specific monoclonal antibody against LPL, and HL activity was determined as the activity remaining after incubation with the LPL antibody. For each assay, a bovine milk LPL standard was used to correct for inter-assay variation and a human postheparin plasma standard was included to monitor inter-assay variation. The intra-assay coefficients of variation of this assay are 7% for LPL and 6% for HL; the inter-assay coefficients of variation are 8% for LPL and 10% for HL.

Chemistries

The following assays were performed in the General Clinical Research Center Core Laboratory at Oregon Health and Science University. Interleukin-6 (IL-6) was measured in duplicate by an enzyme-linked immunosorbent assay (Quantikine high sensitivity; R and D Systems, Minneapolis, MN; sensitivity: 0.04 pg/ml). The percent difference between duplicates was 4.3%. Tumor necrosis factor-α (TNFα) was measured in duplicate by an enzyme-linked immunosorbent assay (Quantikine high sensitivity; R and D Systems; sensitivity: 0.12 pg/ml). Leptin was measured in duplicate by an immunoradiometric assay (DSL, Webster, TX; sensitivity: 0.10 ng/ml). High-sensitive C-reactive protein (hs-CRP) was measured by a high-sensitivity chemiluminescent immunometric assay using the Immulite system (DPC, Los Angeles, CA; sensitivity: 0.01 mg/dl).

Five subjects had their hormonal values [estradiol, testosterone, and sex hormone binding globulin (SHBG)] measured at the Portland VA lab, and the other 13 had their values measured using a different assay at the Oregon Health and Science University, which uses the regional Kaiser Reference Lab. This was done as a convenience to the patients at the time of screening in their respective oncology clinics to minimize blood drawing on subsequent visits. Specifically, total testosterone was measured by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN; normal range, 9.9–27.8 nmol/l; intra-assay CV, 1.3–4.6%) or competitive RIA (Kaiser Regional Labs, Portland, OR; normal range, 8.4–33 nmol/l; intra-assay CV, 2.3–6.2%; inter-assay CV, 1.4–4.4%). Estradiol was measured by ADVIA Centaur automated competitive chemiluminescence immunoassay (Bayer HealthCare; normal range, 0–191 pmol/l; intra-assay CV, 4.0–12%; inter-assay CV, 4.5–8.1%) or competitive RIA (Kaiser Regional Labs; normal range, 0–151 pmol/l; intra-assay CV, 5.3–11.3%; inter-assay CV, 4.6–6.7%). SHBG was measured by competitive electrochemiluminescence immunoassay (Roche Diagnostics; normal range, 14.5–48.4 nmol/l; intra-assay CV, 1.1–2.7%) or by immunoradiometric assay (Kaiser Regional Labs; normal range, 20–60 nmol/l; intra-assay CV, 2.3–4.7%; inter-assay CV, 5.9–8.3%). Free testosterone was calculated following the method of Vermeulen, Verdonck, and Kaufman (34), using testosterone, albumin, and SHBG concentrations. Baseline and follow-up studies were performed using the same assay method. Because of the different assays used at baseline, however, cross-sectional analysis using these values was not performed, and only the paired-data results are presented here.

Statistical analysis

Mean on-treatment values were compared with pretreatment using the paired *t*-test if the data were normally distributed or, if not, median on-treatment values were compared with pretreatment using the Wilcoxon signed-rank test. Correlations between changes in variables were tested using the Pearson Product Moment Correlation analysis. P values <0.05 were considered significant.

RESULTS

Subjects

Eighteen prostate cancer patients on ADT were evaluated for lipids, hormones, and body composition by DEXA at baseline and after 8 weeks of TDE. MRI data were available for 13 of these men. Five subjects had previously been on lipid-lowering therapy for at least 3 months (four with a statin, one with a fibric acid derivative), and this treatment was continued without change in dose throughout this study period. Subjects with and without metastases had similar responses in lipid and inflammatory levels to estrogen therapy (data not shown).

Changes in sex steroids

Estradiol levels increased 17-fold on TDE (mean ± SD; 67 ± 23 pmol/l vs. 1,170 ± 760 pmol/l, baseline vs. 8-week follow-up, respectively; $P < 0.001$) (**Table 2**). Total testosterone levels did not change and remained in the anorchid range. Levels of free testosterone fell significantly (7.4 ± 4.7 pmol/l vs. 4.2 ± 2.4 pmol/l, $P < 0.001$), however, due to a rise in SHBG levels.

TABLE 2. Sex steroids in 18 men before and after treatment with transdermal estradiol

	Baseline	8 Weeks	% Change	*P*
Estradiol (pmol/l)	67 ± 23	1,170 ± 760	1,650	<0.001
SHBG (nmol/l)	36.3 ± 22.0	67.0 ± 21.9	86	<0.001
Total testosterone (nmol/l)	0.41 ± 0.22	0.38 ± 0.21	−7	0.58
Free testosterone (pmol/l)	7.4 ± 4.7	4.2 ± 2.4	−43	<0.001

Results are mean ± SD. SHBG, sex hormone binding globulin.

Body composition

During the 8-week study period, the change in percent body fat ranged from a low of −3% to a high of +1.7% on TDE (not significant) (**Table 3**). Correlational relationships between this change and any lipid or inflammatory parameter were not significant. Likewise, no significant changes in other body composition measures, including fat mass, lean mass, truncal fat, IAF, and SQF were found.

Changes in lipids and postheparin lipase activity

After 8 weeks of TDE, levels of total cholesterol (4.94 ± 0.96 mmol/l vs. 4.42 ± 0.91 mmol/l, $P < 0.001$) and apoB (1.04 ± 0.19 g/l vs. 0.91 ± 0.23 g/l, $P < 0.001$) decreased, compared with baseline, but triglyceride and Lp[a] levels did not change (Table 3). HDL cholesterol increased (1.06 ± 0.25 mmol/l vs. 1.16 ± 0.28 mmol/l, $P = 0.01$) on therapy primarily as a result of a significant increase in cholesterol in HDL_2 levels (0.17 ± 0.04 mmol/l vs. 0.23 ± 0.09 mmol/l, $P = 0.002$). Using density gradient, nonequilibrium ultracentrifugation (**Fig. 1**), the reduction in total and LDL cholesterol was found to be predominantly due to reductions of cholesterol in dense LDL subfractions, resulting in an average increase in the peak LDL fraction buoyancy (an increase in Rf, 0.22 ± 0.03 vs. 0.23 ± 0.03, $P = 0.02$). In addition, total VLDL cholesterol did not increase (Table 3), although small increases in dense VLDL and buoyant intermediate density lipoprotein (IDL) particles were detected (Fig. 1). Activities of enzymes involved in lipoprotein particle processing were also measured. Lipoprotein lipase activity did not change with estrogen therapy, but HL activity decreased significantly by 32% (405 ± 185 nmol/ml/min vs. 276 ± 71 nmol/ml/min, $P < 0.001$). This change in HL activity did not correlate with changes in peak LDL particle buoyancy (Rf) or with changes in the cholesterol levels in the HDL subspecies. Subjects treated with lipid-lowering therapy had changes in lipid levels and lipase activities in response to TDE similar to those of the nontreated group (data not shown).

Changes in levels of inflammation and leptin

Despite the large increase in serum estradiol levels, levels of hs-CRP, TNFα, IL-6, and leptin did not change significantly (**Table 4**). No significant correlations were detected between changes in estrogen or free testosterone levels and changes in the levels of any of the lipids, lipase activities, or inflammatory markers (data not shown).

DISCUSSION

The present study was undertaken to determine the effect of transdermal estrogen on levels of lipids, activi-

TABLE 3. Body composition, fat distribution, lipid and apolipoprotein levels at baseline and after transdermal estrogen therapy

	Baseline	8 Weeks	% Change	*P*
Percent fat	31 ± 5.3	31 ± 5.6	0	0.49
Fat mass (kg)	29.2 ± 9.06	29.3 ± 9.32	0.3	0.66
Lean mass (kg)	60.2 ± 8.66	61.1 ± 8.59	1.5	0.12
Truncal fat (kg)	15.9 ± 4.92	15.9 ± 5.26	0	0.88
IAF (cm^2)	159 ± 38	151 ± 41	−5	0.42
SQF (cm^2)	276 ± 63	278 ± 69	0.7	0.77
Total cholesterol (mmol/l)	4.94 ± 0.96	4.42 ± 0.91	−11	<0.001
Triglycerides (mmol/l)	1.80 ± 0.66	1.67 ± 0.49	−7	0.28
VLDL cholesterol (mmol/l)	0.85 ± 0.36	0.78 ± 0.22	−8	0.20
LDL (mmol/l)	3.00 ± 0.80	2.48 ± 0.78	−17	<0.001
HDL (mmol/l)	1.06 ± 0.25	1.16 ± 0.28	9	0.01
HDL_2 (mmol/l)	0.17 ± 0.04	0.23 ± 0.09	35	0.002
HDL_3 (mmol/l)	0.91 ± 0.21	0.93 ± 0.23	2	0.41
ApoB (g/l)	1.04 ± 0.19	0.91 ± 0.23	−13	<0.001
Lp[a] (mg/dl)	12.8 ± 13.4	13.1 ± 13.1	2	0.61
LDLRf	0.22 ± 0.03	0.23 ± 0.03	5	0.02
LpL (nmol/ml/min)	241 ± 61	252 ± 71	5	0.40
HL (nmol/ml/min)	405 ± 185	276 ± 132	32	<0.001

Results are mean ± SD. ApoB, apolipoprotein B; HL, hepatic lipase; IAF, intra-abdominal fat; Lp[a], lipoprotein [a]; LDLRf, peak LDL particle density; LpL, lipoprotein lipase; SQF, subcutaneous abdominal fat. N = 18, except for IAF and SQF, where n = 13.

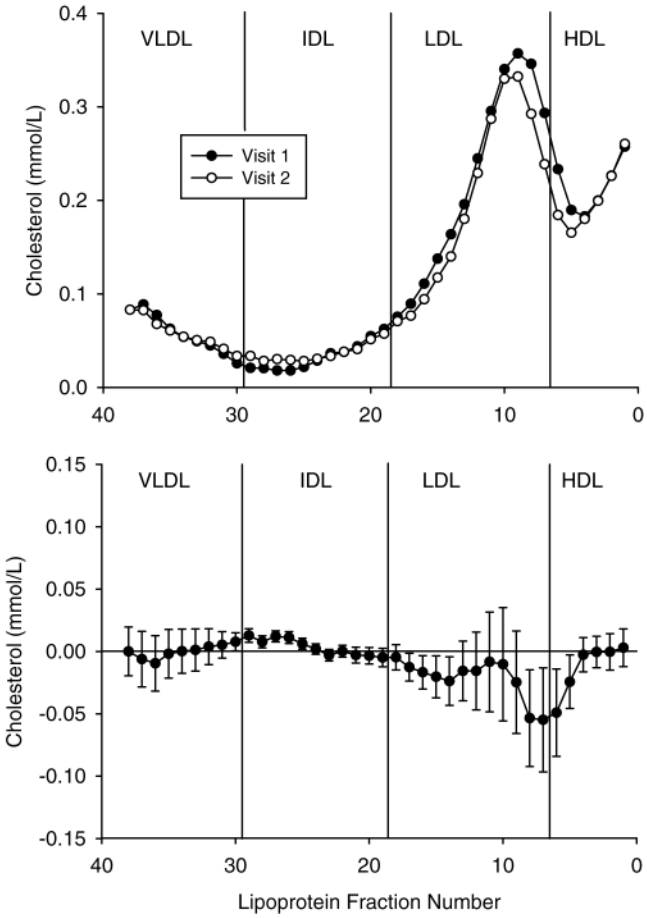

Fig. 1. Top: Distribution of lipoprotein cholesterol across subfractions [from very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), to high density lipoprotein (HDL)] using nonequilibrium density gradient ultracentrifugation in men while on standard androgen deprivation therapy (ADT) (visit 1, baseline, ADT) and while receiving parenteral estrogen (visit 2, 8 weeks on ADT). Bottom: Difference plot shows subtracted mean cholesterol levels of subfractions comparing visit 2 to visit 1 with 95% confidence intervals for this mean difference for each fraction. Mean peak LDL particle buoyancy [relative floatation rate (Rf)] was higher after estrogen treatment (visit 2) compared with ADT (visit 1): 0.23 versus 0.22, visit 1 versus visit 2, respectively, $P = 0.02$. To convert cholesterol values to SI units (mmol/l), multiply values by 0.02586.

ties of enzymes involved in lipoprotein processing, and markers of inflammation in men with prostate cancer. There was no change in mean free or total testosterone levels (due to preexisting ADT); nor was there a change in mean body composition during the brief 8-week period of the study. In contrast, there was a 17-fold increase in estradiol levels. Thus, the effect of parenteral estrogen on the study outcomes could be determined independently of changes in testosterone levels, body fat, or fat distribution.

Long-term consequences of hypogonadism include increased fat mass, loss of lean mass, increased visceral adiposity, and dyslipidemia (35). These adverse consequences may potentially explain evidence linking lower testosterone levels and increased CVD risk in men (11). Although restoration of normal testosterone levels improves body composition and lipid levels (35), this option is not available to men with prostate cancer receiving ADT.

Recent studies have shown that the benefits of testosterone for men's health include effects resulting from its conversion to estrogen by aromatization. This is particularly true for maintaining bone mass (36) and increasing HDL cholesterol levels (37). Through feedback inhibition of pituitary hormones, estrogen therapy can also be used to maintain anorchid testosterone levels and might thus be an alternative therapy to ADT that alleviates many of the side effects of hypogonadism in men. Oral estrogen therapy, however, has neutral to detrimental effects on cardiovascular and cerebrovascular disease in women (22–24) and increases the risk of CVD in men (20, 21, 38). This excess vascular risk may be due to increased hepatic synthesis of procoagulant proteins and thrombotic events. Recent studies have also shown that oral estrogen increases levels of inflammatory cytokines that are independently associated with an increased risk for heart disease, including hs-CRP and IL-6 (39, 40).

In contrast, studies in women have shown that transdermal estrogen improves cholesterol levels yet does not increase levels of triglyceride, procoagulant proteins, or inflammatory cytokines (41–43). In the present study in men, we show that transdermal estrogen lowers both total and LDL cholesterol by 10% and 17%, respectively, and apoB levels by 13%. Despite the high dose of estrogen used, we found that total triglyceride levels and VLDL cholesterol levels did not increase as is typically reported with oral estrogen therapies. This absence of an increase in triglyceride levels by transdermal estrogen in this study may be of prognostic relevance. Elevated triglyceride levels were a consistent finding in previous treatment studies of men with prostate cancer receiving oral estrogen (19, 44–46), and in one study, mortality rates were worse in those who experienced a rise in triglyceride levels with therapy (19).

TABLE 4. Levels of inflammatory markers and leptin in men treated with transdermal estradiol

	Baseline	8 Weeks	% Change	*P*
hs-CRP (mg/dl)	0.30 (0.01–2.2)	0.31 (0.02–5.1)	3	0.11
IL-6 (pg/ml)	2.4 (1.4–11)	2.8 (1.4–11)	17	0.43
TNFα (pg/ml)	1.0 (0.55–1.8)	0.80 (0.44–2.1)	20	0.50
Leptin (ng/ml)	31 (13–111)	39 (10–114)	26	0.10

Results are median (range). hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; TNFα, tumor necrosis factor-α.

Small increases in the most dense VLDL and buoyant IDL fractions were detected and may represent an accumulation of remnant particles when pharmacological estrogen dosing results in enhanced VLDL secretion (47) without a concomitant increase in lipoprotein lipase activity. Although cholesterol accumulation in these fractions is thought to be predictive of CVD, much larger decreases in cholesterol were found in dense LDL particles, which in addition to reductions in total and LDL cholesterol levels, would predict protection from vascular disease. The mechanism for improvement in the composition of LDL and HDL particles, including increased levels of HDL_2 cholesterol, most likely includes the large decrease in HL activity (48) seen in this study.

We found no effect of parenteral estrogen on levels of the lipid particle Lp[a] or on levels of inflammatory cytokines known to be induced by oral estrogen, including hs-CRP and IL-6. These and the neutral effects on TNFα levels are consistent with studies of transdermal estrogen in women (42, 43, 49–51). Interestingly, we were also unable to detect significant effects of parenteral estrogen on leptin levels in these men. Women are known to have higher levels of leptin than men, and it is thought that this difference remains even after accounting for a higher percent body fat in women than men (52). In addition, transgender females (men → women) increase their leptin levels as a result of androgen deprivation and estrogen therapy (53). Our study is different from previous reports in that the men reported here had previously undergone a prolonged period of androgen deprivation and at baseline were hypogonadal, presumably with the detrimental effects on body composition (increased percent body fat as a result of increased fat mass and loss of lean mass) already present. These data support the hypothesis that estrogen is unlikely to directly affect leptin secretion and are in agreement with previous studies in women demonstrating that hormonal replacement therapy is not significantly related to leptin levels (54, 55).

In summary, data from this pilot study indicate that parenteral estrogen improves both lipid levels and lipoprotein particle composition in androgen-deprived prostate cancer patients. These beneficial effects on lipids, lack of increase in triglyceride or VLDL cholesterol levels, and neutral effects on inflammatory cytokines are in contrast to studies of oral estrogen in both men and women. If the lack of prothrombotic protein induction by parenteral estrogen in men, as shown by our group in the larger cohort from which the subjects in the present study were taken (27) and by others (25), results in a lower thrombotic risk than oral estrogen therapies (38), then these observed changes may have the potential to reduce cardiovascular risk in these men. Randomized, long-term studies of treatment-naïve men with prostrate cancer are necessary to determine the effects of TDE, compared with ADT therapy, on CVD, body composition, fat distribution, and total mortality in these patients. In light of the expansion of the use of ADT to include a large number of patients with earlier stages of disease and therefore long life expectancy, studies that seek to reduce the long-term morbidity of ADT should be pursued.

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