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Favorable Changes in Serum Estrogens and Other Biological Factors After Weight Loss in Overweight or Obese Breast Cancer Survivors

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Abstract

Background—Obesity is associated with increased risk for recurrence and all-cause mortality in breast cancer survivors. Excess adiposity is associated with increased estrogen, insulin, and leptin, and decreased sex hormone binding globulin (SHBG) concentrations, which may promote breast cancer progression and recurrence. This study aimed to assess the effects of weight loss on these factors.

Patients and Methods—Overweight or obese breast cancer survivors ($N = 220$) who were enrolled in a weight loss intervention study provided baseline and follow-up blood samples and weight data. Serum estrogens, SHBG, insulin, and leptin were measured at baseline, 6 and 18 months.

Results—Weight loss of 5% of initial weight decreased leptin and insulin compared with those who did not achieve that amount of weight loss ($P < .0001$). Weight loss also increased SHBG at 6 and 18 months ($P < .01$). Postmenopausal women who lost 5% of body weight at 6 months had lower estrone ($P = .02$), estradiol ($P = .002$), and bioavailable estradiol ($P = .001$) concentrations than women who did not lose at least 5% of body weight, and weight loss at 18 months was significantly related to change in serum bioavailable estradiol concentration ($P = 0.02$).

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Conflict of Interest

The authors have stated that they have no conflicts of interest.

Conclusion—Favorable changes in estrogens, SHBG, insulin, and leptin were observed in association with weight loss in these overweight or obese women who had been diagnosed and treated for breast cancer. Weight loss appears to have favorable effects on hormonal and biological factors associated with increased risk for recurrence and poorer prognosis.

Keywords

Hormones; obesity; weight reduction; leptin; insulin

Introduction

Approximately 226,870 new cases of invasive breast cancer are expected to be diagnosed in 2012 in the U.S., and 39,510 will likely die from the disease that year.¹ Although breast cancer is the second most common cause of cancer death in women, death rates have been steadily declining since 1990, and currently, there are more than 2.6 million breast cancer survivors in the United States.¹ Overweight or obesity is a major risk factor linked to recurrence and morbidity in both pre- and postmenopausal women,^{2–7} and it has been observed that most early stage breast cancer patients experience weight gain during treatment.^{8, 9} In a large study of 3,993 women diagnosed with breast cancer, each 5-kg gain was associated with a 12% increase in all-cause mortality, a 13% increase in breast cancer-specific mortality, and a 19% increase in cardiovascular disease mortality.¹⁰ Patterson et al. reviewed lifestyle factors that affect breast cancer outcomes in women with a history of breast cancer, and the most consistent finding among these observational studies was a 30% increased risk of mortality associated with adiposity.¹¹ In a meta-analysis of 43 studies of women diagnosed with breast cancer, Protani et al. found a significant increase in all-cause and breast cancer specific mortality in obese compared to non-obese women.⁵

Several hormonal and other biological factors have been implicated as possible mediators linking obesity to breast cancer recurrence and progression, including estrogens, sex hormone binding globulin (SHBG), insulin, and leptin. One study showed a twofold increase in breast cancer risk among postmenopausal women with higher compared to lower levels of serum estrogens, and several studies have demonstrated that increased insulin and leptin levels are linked to an increased risk of breast cancer and progression.^{12–14}

Excess adipose tissue results in increased production of estrogens, insulin, and leptin, and a decreased production of SHBG.^{15–17} Estrogenic stimulation promotes breast cancer pathogenesis and tumorigenesis, and insulin and leptin exhibit proliferative, mitogenic, and anti-apoptotic activities in mammary cells, thus promoting tumor growth.^{5, 18, 19} While there may be additional biological factors linking obesity to increased breast cancer risk and progression, these particular biological factors appear to be associated with greater likelihood of recurrence and mortality.

This analysis was conducted to examine how weight loss, through diet and exercise, may influence selected biological factors, including serum levels of estrogens, SHBG, insulin, and leptin, in overweight or obese breast cancer survivors. Specifically, we aimed to compare changes in these hormones and biological factors in women who lost at least 5% of their baseline body weight to women who did not lose 5% of their initial weight at the 6 and

18 month follow-up visits. We hypothesized that estrogen, insulin, and leptin concentration would decrease, while SHBG concentration would increase in association with at least 5% weight loss.

Patients and Methods

Patients

Data and samples collected from the Breast Cancer Survivors Health and Physical Exercise (SHAPE) study, conducted from January 2005 through December 2009, were used to investigate the effects of weight loss on estrogens, SHBG, insulin, and leptin in overweight or obese breast cancer survivors. This study was approved by the University of California, San Diego, and San Diego State University Institutional Review Boards. All participants provided written consent to participate.

Participants in the SHAPE study included 258 overweight or obese breast cancer survivors who had been diagnosed between 1997 and 2006 and were living in San Diego, California. A primary recruitment method was sending letters to breast cancer survivors listed in the California Cancer Registry, a statewide cancer surveillance system.²⁰ Other strategies for recruitment included advertisements in a local newspaper, booths at community events, and clinical referrals from local physicians. The protocol involved clinic visits at enrollment and 6 and 18 months, during which a fasting blood sample was collected, height and weight were measured using standard procedures, and body mass index (BMI, $\text{wt}[\text{kg}]/\text{ht}[\text{m}^2]$) was computed. This analysis includes all women in the cohort who provided follow-up blood samples at 6 and/or 18 months ($N = 220$).

The inclusion criteria for the SHAPE study were: 18 years and older; diagnosed with stage 0-IIIa breast cancer within the previous 10 years; completion of initial treatments (i.e. surgery, adjuvant chemotherapy, radiation therapy); initial BMI $>25.0 \text{ kg/m}^2$; 15 kg over ideal weight (as defined by the Metropolitan Life Insurance tables²¹); willingness and ability to attend group meetings and to maintain contact with the investigators for 18 months; and ability to provide dietary and exercise data by telephone at prescribed intervals. An exclusion criterion was the inability to participate in physical activity due to severe disability (e.g., severe arthritic conditions).

Procedures and Intervention

Following a 2-month run-in period and written consent, participants were randomly assigned to one of two study arms, immediate intervention or wait-list control group, stratified by BMI ($25.0\text{--}29.9$ versus $>30.0 \text{ kg/m}^2$) and age (<50 , $51\text{--}65$, and >65 years). The intervention focused on promoting regular physical activity, a modest reduction in energy intake, and healthy eating attitudes and behaviors in order to facilitate weight loss. The immediate program curriculum consisted of group sessions that met weekly for 6 months and then approximately once per month through 18 months. The group meetings were closed group contingents with an average of 12–15 women, led by trained investigators and research staff. The sessions consisted of discussion and educational sessions, emphasizing planned aerobic exercise, increased daily physical activity, strength training, and dietary guidance to promote

weight loss and maintenance. Additionally, the curriculum incorporated psychological components (e.g., self-acceptance, body image). In addition to the group sessions, participants received individualized telephone-based counseling from the study coordinator with four contacts in the initial two weeks, weekly calls over the following ten weeks, and once a month thereafter. During the immediate intervention period, wait-list participants were followed and received general contact (such as mailed communication, seasonal cards, and monthly check-up calls) and were invited to educational sessions. At the end of the immediate intervention period, they were provided all written intervention material and a facilitated discussion in a seminar format.

Data Collection and Measures

Demographic and clinical characteristics—Initial demographic and clinical data collected included: age, weight, BMI, race/ethnicity, education level, marital status, stage of breast cancer at diagnosis, treatment modalities, menopausal status, medical history (including comorbidities and medications), medications post-diagnosis, and weight history, including highest and lowest adult, non-pregnant weight.

Blood samples and assays—Serum aliquots from the blood samples collected were stored at -80° until analysis (batched by study time period) by the Endocrine Research Laboratory, UCSD Department of Reproductive Medicine. The hormonal and biological factors measured in this study included follicle stimulating hormone (FSH, measured only at baseline), estrogens (estrone, estradiol, and bioavailable estradiol), SHBG, serum insulin, and leptin. Individual controls (2 to 4 commercially available standards) were run in each batch. Blanks (undetectable in assays) were also used for quality control.

Women who reported that they had menstruated in the previous year or whose measured level of FSH at study entry was lower than 10 mIU/mL were considered premenopausal; those who had been amenorrheic for 12 months, aged over 55 years, or whose FSH exceeded 30 mIU/mL were considered postmenopausal. For those women who were still menstruating, blood collections were scheduled to coincide with menstrual cycle points so that cycle phase did not confound estrogen measures.

Estrone and estradiol were measured using a modified method described by Anderson et al.,²² using radioimmunoassay (RIA) for quantification after chromatographic separation. Bioavailable estradiol measurement was based on the method described by Tremblay and Dube.²³ For SHBG, a time-resolved fluoroimmunoassay (Delphia SHBG, E G & G, Diagnostic Systems Laboratories, Webster, TX) was used. FSH measurement was conducted with a solid-phase immunoradiometric assay (Diagnostic Products Corporation, Los Angeles, CA) that used a highly specific FSH antiserum with low cross reactivity and with structurally related glycoproteins.

Inter-assay coefficients of variation (CV)s reported are specific to our study population, and intra-assay CV's are standard for the laboratory. For estradiol, inter-assay CV is 5.1% and intra-assay CV is 5.87%. Inter-assay CV for bioavailable estradiol is 6.3% and intra-assay CV is <5%. The SHBG inter-assay CV is 6.7% and intra-assay CV is 2.63%. For estrone, inter-assay CV is 7.3% and intra-assay CV is 8.23%. The inter-assay CV is 3.8% and the

intra-assay CV is 2.9% for FSH. The cross-reactivities of antibodies used in the RIAs have been checked against all closely related substances and any cross-reacting substances are separated out in the column chromatography step before the RIA is done.

A double antibody radioimmunoassay, with <0.2% cross-reactivity with human proinsulin, was used for the analysis of insulin (Linco Research, Inc., St. Charles, MO). The intra-assay CV is 3.2%, and the inter-assay CV is 3.9%, over a range of 8 to 54 μ IU/mL, and the assay sensitivity is 2 μ IU/mL. Leptin was measured using a double antibody RIA using 125-iodinated leptin as the tracer (Linco Research, Inc., St. Charles, MO), and the sensitivity of the assay is 0.5 ng/mL. Within % CV ranges from 2.5% at 25.6 ng/mL to 4.5% at 4.9 ng/mL, and between % CV ranges from 3.6% at 25.6 ng/mL to 6.2% at 4.9 ng/mL.

Statistical Analysis

The focus of this analysis was to examine how weight loss affects biological factors that have been suggested to be predictive of prognosis rather than to compare study arms. Data were analyzed for participants who provided blood samples and whose weight was measured at either or both follow-up visits. Dichotomous variables were created to categorize those who achieved the >5% weight loss goal. We selected this cut-point because previous studies found this degree of weight loss, although modest, to be associated with clinically significant improvements in metabolic and other risk factors for chronic disease.^{24–26} Serum measures were compared among women who did and did not lose at least 5% of initial weight at the follow-up visits (6 or 18 months). Estrogen analyses were stratified by menopausal status because menopausal status influences serum levels of estrogens. Variables with skewed distributions were log transformed to improve normality. Independent t-tests were used to evaluate the differences between the two groups for each biological factor.

Changes in estrone, estradiol, bioavailable estradiol, and SHBG were also computed for each participant at each time period by subtracting the individual's baseline value. Regression models for postmenopausal participants, in which weight and biological values were modeled as continuous variables, controlled for baseline levels, were used to examine the association between change in the biological factor and change in weight. An alpha value < .05 was considered statistically significant. Data were analyzed using SPSS for Windows, Version 19.0 (2010) and SAS version 9.2.

Results

Demographic and clinical characteristics for the participants who provided the follow-up data and blood samples are presented in Table 1. The participants ranged from 28 to 81 years of age, with a mean age of 55 years. The majority of the participants were non-Hispanic white (84%), married (69%), well-educated (86% had completed at least 13 years of education), and postmenopausal (86%). Approximately 35% of the cohort (53% of immediate intervention and 16% of wait-list control) achieved a >5% weight loss at 6 months, and 31% of the women (37% of intervention and 25% of control) exhibited that degree of weight loss at 18 months. The immediate intervention arm participants were more likely to achieve >5% weight loss than the control group, although we noted a substantial

“drop in” effect at 18 months in the control group. As Table 2 shows, those who successfully maintained a >5% loss of baseline weight lost a mean of 8.7 kg. Further, one-half of the women were obese at baseline, but only 22% of those who lost at least 5% of initial weight remained obese at follow-up.

There were no significant differences in age or education between participants who were or were not successful at losing >5% of initial weight. Weight and obesity did not differ at baseline between participants who lost >5% body weight and those who did not (shown in Table 2). Baseline BMI was slightly lower in those who successfully lost weight at 6 months ($P = .03$), but this baseline difference was not observed at 18 months.

As Table 3 shows, baseline insulin, leptin, or SHBG did not differ across the two groups ($P > .05$ for all). Independent sample t-tests showed that weight loss of at least 5% resulted in lower leptin and insulin levels at each follow-up time point, compared to those who did not achieve a 5% weight loss. Weight loss also resulted in increased SHBG at 6 and 18 months ($P < 0.01$ for each).

Table 4 shows changes in estrogens associated with weight loss. Notably, in premenopausal women, estrone, estradiol, and bioavailable estradiol did not vary by weight loss category at either follow-up visit. However, postmenopausal women who lost at least 5% of body weight at 6 months had lower estrone ($P = .02$), estradiol ($P = .002$), and bioavailable estradiol ($P = .001$) than women who did not lose at least 5% of body weight at follow up visits. Regression models for changes in the hormonal and biological factors in postmenopausal women (shown in Table 5) revealed that weight loss was associated with a decrease in bioavailable estradiol at 18 months (adjusted $R^2 = .10$, $P = .02$).

Discussion

Results from this study demonstrate that weight loss promotes favorable changes in biological factors that have been linked to increased risk for recurrence and mortality in overweight or obese breast cancer survivors. Specifically, weight loss of at least 5% was associated with an increase in SHBG and a decrease in leptin and insulin concentrations in pre- and postmenopausal women, as well as a decrease in estrone, estradiol, and bioavailable estradiol in postmenopausal participants.

The majority of the observational studies that have examined the association between obesity and risk for recurrence and mortality in breast cancer survivors have found an adverse effect, although not all studies have shown this adverse effect, as evident in large reviews of published epidemiologic evidence.^{5,11} Also, it is possible that obesity does not adversely affect survival for some women who have been diagnosed and treated for breast cancer, depending on the type of cancer and other individual characteristics. Results from a randomized trial that examines the effect of weight loss on cancer outcomes and survival are needed to clarify this relationship, because observational studies have well-known limitations such as confounding.

The biological mechanisms underlying the adverse effects of excess adipose tissue on breast cancer prognosis and recurrence have yet to be elucidated; however, several theories exist

relating to the biological factors under study. In postmenopausal women, aromatase and 17 β -hydroxysteroid dehydrogenase enzymes in adipose tissue promote the conversion of adrenal androgens to estrogens.^{15, 27} Excess endogenously-produced estrogens are believed to play a causal role in the pathogenesis of breast cancer,^{19, 28–30} and endogenous circulating estrogen levels are significantly higher in postmenopausal obese women than in postmenopausal non-obese women.^{15, 31} Decreases in estrogenic stimulation through suppression of ovarian function or use of anti-estrogen medications lowers risk for breast cancer recurrence and progression.²⁸ Obesity also leads to reduced levels of SHBG, resulting in higher levels of bioavailable estrogen in the circulation, which increases risk for breast cancer progression.^{17, 18}

Another possible mechanism for breast cancer progression involves the mitogenic role of insulin, which is associated with increased adipose tissue. Higher levels of insulin are associated with adiposity, due to obesity-related insulin resistance, and have been linked to increased risk and progression of breast cancer.^{16, 32} In fact, an observational study involving breast cancer patients showed a 3-fold increased risk of all-cause mortality in women with high insulin levels compared to women with low insulin levels, measured years after diagnosis.³³ Insulin increases synthesis of insulin-like growth factor (IGF-1) and increases the bioactivity of IGF-1 by altering key binding proteins.^{5, 8} *In vitro* studies have demonstrated increased mammary cell proliferation and inhibition of apoptosis due to insulin and IGF-1.³⁴ Insulin and IGF-1 also increase synthesis of sex steroids and decrease blood levels of SHBG.³⁵

Leptin and other adipokines are also linked to breast cancer prognosis in *in vitro* and epidemiologic studies.^{36, 37} Adipocytes secrete leptin and other adipokines, and leptin concentration is positively correlated with total adipose tissue.³⁸ Although it can be challenging to separate the effects of leptin from other adipokines, some studies have shown leptin levels to have independent prognostic effects on breast cancer. One study found that leptin levels are positively associated with risk for both pre- and postmenopausal breast cancer. Moreover, the results from that study showed that leptin levels were higher in more advanced tumor stage in postmenopausal estrogen receptor-positive breast cancer.³⁸ Another study showed that leptin and its receptor are strongly co-expressed in breast cancer cells and that high expression of leptin receptor is positively correlated with tumor size. This finding suggests that leptin may be a growth factor for mammary cells.³⁹ Ishikawa et al. also showed that in human breast cancer cells, leptin receptors are overexpressed compared to normal breast tissue leading to tumor growth through increased signaling.⁴⁰ Leptin appears to be mitogenic and anti-apoptotic, inducing cellular transformation and angiogenesis, promoting cellular proliferation, aromatase expression (which results in increased production of estrogen), and expression of many other pathways *in vitro*.^{18, 41, 42}

Premenopausal women, who have functioning ovaries that produce large amounts of estrogen, would be expected to continue to have high levels of estrogen regardless of weight loss. However, in postmenopausal women, estrogen is produced by adipose tissue, and thus, in this subgroup, weight loss could favorably influence disease-free survival via effects on estrogen. Because obese postmenopausal women have significantly higher estrogen levels than non-obese postmenopausal women,^{15, 31} a number of studies in postmenopausal

women without breast cancer have shown success in lowering estrogen levels and increasing SHBG levels with weight loss through diet and exercise. Campbell et al. conducted a study with 399 postmenopausal women and found that weight loss over a 12-month period through a reduced energy diet, with or without exercise, resulted in statistically significant reductions in estrogens (serum estrone, estradiol, and free estradiol) and an increase in SHBG.²⁷ Another study of 61 postmenopausal obese women found a 15.6% weight loss and a 30% reduction in estradiol following a weight loss protocol.⁴³ Finally, a review by Morisset concluded that reduced energy diets, promoting significant weight loss, lead to increased SHBG concentration.¹⁷

A few previous studies have shown decreased leptin and insulin levels with weight loss. The study by Campbell et al. that found favorable effects on estrogens and SHBG also noted a decrease in insulin and leptin with weight loss.²⁷ A study by Thomson et al. on weight loss in overweight breast cancer survivors on hormonal therapy showed a modest, statistically significant reduction in insulin levels with weight loss.⁴⁴ A trial involving obese breast cancer survivors noted that those who lost >10% of baseline body weight had a significant reduction in leptin levels.⁴⁵ In a study by Considine et al., a significant decrease in insulin and leptin with weight loss was observed in obese individuals, including both men and women. Specifically, they found that a reduction of 10% in body weight was associated with a 53% decrease in serum leptin.⁴⁶ The results of the present study are consistent with these previous reports.

This study had several limitations. First, the relatively small number of premenopausal women in the study and their wide variability in measured estrogen levels prevented us from identifying significant associations with weight loss and estrogens in that subgroup. Second, due to the predominance of non-Hispanic white well-educated women in the study, the results may not be generalizable to breast cancer survivors of other racial and ethnic groups or education levels. Finally, method variance or bias is an inherent potential issue in behavioral research and should always be considered when interpreting such findings.

This study is unique in that we explored the relationship between modest weight loss and circulating levels of estrogens, SHBG, insulin, and leptin specifically in breast cancer survivors, in whom the independent effect of obesity on prognosis has been quite consistently observed. The present study is one of the largest studies to date that has investigated the effect of weight loss on these biological factors. The evidence suggests that weight loss may reduce the risk of breast cancer recurrence and mortality in overweight or obese breast cancer survivors by affecting these potentially mediating factors.

Conclusion

The current study demonstrated that weight loss in overweight or obese breast cancer survivors may have favorable effects on selected biological factors linked to risk for recurrence of breast cancer and morbidity, including estrogens, SHBG, insulin, and leptin. Understanding this relationship has clinical implications due to the potential role these factors may play in breast cancer progression. This study demonstrated that weight loss induced by behavioral changes in diet and exercise can promote favorable effects on

hormonal and other biological factors in breast cancer survivors. Results from this study may help to improve the health and quality of life of breast cancer survivors and possibly decrease their risk of recurrence and improve the likelihood of their survival. These findings may also prove motivating to breast cancer survivors in that even modest levels of weight loss were associated with improvements in prognostic indicators.

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Clinical Practice Points

- Overweight or obesity is a risk factor for breast cancer incidence in postmenopausal women and is linked to poor prognosis following the diagnosis and treatment of breast cancer in both pre- and postmenopausal women.
- Excess adipose tissue is associated with increased estrogens, insulin, and leptin concentrations and decreased SHBG production.
- The results of this study show that moderate weight loss may decrease serum levels of estrogens, insulin, and leptin, and increase SHBG concentration, which may decrease the risk of recurrence and mortality in breast cancer survivors.

Table 1

Demographic and Cancer Characteristics of Study Participants

	Total Cohort (N=220)	5% weight loss at either follow-up (N=102)	<5% weight loss at follow-up (N=118)	P-value
Age, years (mean [SD])	55 (10)	55 (10)	55 (10)	0.85
Postmenopausal (%)	85.9	84.9	87.2	0.62
Education (%)				0.31
12 years	14.1	9.8	16.2	
13–16 years	58.2	55.9	60.7	
17 years	27.7	32.4	23.1	
Race/ethnicity (%)				0.15
Non-Hispanic white	83.6	81.4	87.2	
Hispanic	5.9	9.8	2.6	
African-American	3.2	1.0	4.3	
Asian-American	1.8	2.0	1.7	
Other	5.5	5.9	4.2	
Marital status(%)				0.44
Married	69.1	69.6	69.2	
Divorced	15.9	11.8	18.8	
Single	7.7	8.8	6.8	
Widowed/Separated	7.3	9.8	5.2	
Cancer stage (%)				0.33
0	6.8	5.9	7.7	
I	44.1	50.0	39.3	
II	23.2	19.6	26.5	
IIIA	21.8	23.5	20.5	
Unknown	4.1	1.0	6.0	
Treatment (%)				0.22
Chemotherapy	61.5	56.9	64.1	
Radiation	76.8	83.3	72.7	
Hormone Therapy (Baseline %)				0.10
None	49.8	52.0	47.9	
Selective Estrogen-Receptor Modulators	13.2	8.8	17.9	
Aromatase Inhibitors	36.5	39.2	34.2	
GnRH* Agonist	0.5	0	0.9	

* Gonadotropin-releasing hormone

Table 2

Weight and Body Mass Index by Follow-up Weight Loss Category*

	6-Month Follow-up			18-Month Follow-up		
	5% Weight Loss (n = 74)	<5% Weight Loss (n = 139)	P Value	5% Weight Loss (n = 63)	<5% Weight Loss (n = 140)	P Value
Weight, kg						
Baseline	82.4 (12.5)	85.7 (15.3)	.10	83.2 (16.6)	83.9 (13.6)	.78
Follow-up	74.9 (11.5)	86.0 (15.9)	<.0001	74.5 (15.2)	83.8 (13.7)	<.0001
Weight change	-7.5 (3.3)	0.3 (2.9)	<.0001	-8.7 (4.4)	-0.0 (3.3)	<.0001
BMI, kg/m ²						
Baseline	30.4 (4.1)	31.8 (5.0)	.03	30.9 (5.4)	31.1 (4.5)	.76
Follow-up	27.6 (3.9)	31.9 (5.2)	<.0001	27.7 (5.0)	31.1 (4.5)	<.0001
% Obese [†]						
Baseline	52.7	51.1	.82	49.2	48.6	.93
Follow-up	21.6	50.4	<.0001	20.6	52.9	<.0001

* Values shown are mean (SD) or percentages. P values represent results of t-tests between weight loss categories.

[†] Body mass index ≥ 30 kg/m².

Table 3

Biological Factors by Follow-up Weight Loss Category*

	6-Month Follow-up			18-Month Follow-up		
	5% Weight Loss (n = 74)	<5% Weight Loss (n = 139)	P Value	5% Weight Loss (n = 63)	<5% Weight Loss (n = 140)	P Value
Insulin, μ U/mL						
Baseline	16.9 (9.0)	16.3 (8.1)	.64	16.9 (7.1)	17.1 (8.3)	.08
Follow-up	13.2 (6.1)	19.8 (17.4)	<.0001	15.8 (7.3)	23.0 (13.0)	<.0001
Leptin, ng/mL						
Base	36.4 (18.6)	39.5 (22.4)	.32	34.5 (20.3)	40.3 (22.1)	.08
Follow-up	20.3 (11.4)	34.5 (18.2)	<.0001	20.1 (15.7)	29.8 (14.9)	.0001
Sex hormone binding globulin, nmol/L						
Baseline	58.9 (35.2)	58.4 (32.6)	.92	64.9 (37.9)	55.5 (31.0)	.06
Follow-up	71.7 (37.6)	56.3 (33.2)	.004	63.9 (29.6)	45.1 (26.6)	<.0001

* Values shown are mean (SD). P values represent results of t-tests between weight loss groups.

Table 4

Estrogens and Weight Loss Category by Menopausal Status*

	6-Month Follow-up					
	Premenopausal			Postmenopausal		
	5% Weight Loss (n = 11)	<5% Weight Loss (n = 18)	P Value	5% Weight Loss (n = 63)	<5% Weight Loss (n = 121)	P Value
Estrone, pmol/L						
Baseline	284 (285)	327 (397)	.69	59(69)	87 (76)	.01
6 Months	252 (211)	198(133)	.27	61 (82)	106 (173)	.02
Estradiol, pmol/L						
Baseline	409 (592)	462 (619)	.97	34(71)	34 (30)	.16
6 Months	309 (421)	223 (231)	.75	33 (119)	61 (221)	.002
Bioavailable estradiol, pmol/L						
Baseline	124 (101)	171 (185)	.88	14 (18)	17 (14)	.13
6 Months	113 (161)	106 (130)	.94	13 (27)	25 (64)	.001
	18-Month Follow-up					
	Premenopausal			Postmenopausal		
	5% Weight Loss (n = 10)	<5% Weight Loss (n = 14)	P Value	5% Weight Loss (n = 53)	<5% Weight Loss (n = 126)	P Value
Estrone, pmol/L						
Baseline	203 (122)	388 (464)	.77	87 (97)	70 (63)	.92
18 months	238 (196)	259 (238)	.88	77 (74)	71 (78)	.24
Estradiol, pmol/L						
Baseline	297 (242)	588(775)	.33	44(77)	29 (27)	.21
18 months	273 (373)	273 (270)	.63	26 (32)	28 (82)	.77
Bioavailable estradiol, pmol/L						
Baseline	109 (85)	197 (193)	.26	17 (20)	15 (14)	.55
18 months	103 (148)	116 (103)	.58	11 (13)	15 (36)	.34

* Values shown are mean (SD). *P* values represent t-tests for log-transformed laboratory measurements.

Table 5
Multivariate Models for Changes in Serum Estrogens with Weight Change in Postmenopausal Women *

Variable	6-Month Follow-up			18-Month Follow-up		
	Weight Change *	P	R ²	Weight Change *	P	R ²
Estrone, pmol/L	2.578	.24	.009	0.650	.48	.16
Estradiol, pmol/L	4.170	.19	.05	1.874	.06	.18
Bioavailable estradiol, pmol/L	1.699	.06	.05	0.909	.02	.10
Sex hormone binding globulin, nmol/L	-1.782	<.0001	.20	-1.319	<.0001	.43

* Values shown are regression coefficients modeling change in follow-up estrogen values (compared with baseline) as a function of weight change. Models include age, baseline weight, and baseline concentration.