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Sex steroid levels and response to weight loss interventions among postmenopausal women in the Diabetes Prevention Program

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Abstract

Objectives—To examine whether estrogen use potentiates weight loss interventions via sex steroid levels and whether endogenous sex steroid levels predict response to weight loss interventions among women not using estrogen.

Design and Methods—The Diabetes Prevention Program randomized overweight or obese dysglycemic participants to lifestyle change with the goals of weight reduction of >7% of initial weight and 150 minutes per week of exercise; metformin; or placebo. In this secondary analysis, we examined sex steroid levels and reductions in weight and waist circumference (WC) among postmenopausal women using (n=324) and not using (n=382) oral estrogen.

Results—Estrogen users and non-users randomized to lifestyle change and metformin both lost significant amounts of weight compared to placebo. Reductions in weight and WC over 1 year

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Conflicts of Interest Statement

The authors have no competing interests.

associated with randomization arm were not associated with baseline sex steroid levels among estrogen users or non-users.

Conclusions—Among estrogen users, baseline sex steroids were not associated with reductions in weight or WC, suggesting that exogenous estrogen does not potentiate weight loss by altering sex steroids. Among non-estrogen users, baseline sex steroids were not associated with reductions in weight or WC.

Keywords

sex steroids; waist circumference; weight loss

Introduction

Randomized trials of estrogen therapy suggest that it has neutral(1) or favorable effects(2) on weight loss in overweight or obese postmenopausal women. Reports on whether estrogen therapy can potentiate or interfere with weight loss interventions are few, and contradictory. In one study, postmenopausal women randomized to both an exercise intervention and estrogen use had the greatest reductions in fat mass, followed by women who were randomized to exercise alone; to estrogen alone; and finally no-intervention controls.(3) Such reductions in fat were assumed to occur through changes in sex steroid levels, specifically increases in estradiol (E2) and decreases in androgen levels, although these were not measured in this study. In contrast, two small trials of estrogen therapy reported that women randomized to oral estrogen had increases in fat mass and reductions in lean body mass compared to women randomized to transdermal estrogen, suggesting that altered serum E2 levels were not a key mechanism of weight loss among estrogen users.(4, 5) Another trial of estrogen therapy reported that women randomized to oral estrogen had reductions in lean body mass but no changes in fat mass compared to controls.(6) Finally, another study that randomized women to lifestyle change (7) found that reductions in weight and waist circumference (WC) was similar in interventions vs. controls regardless of estrogen use, suggesting that neither estrogen use nor E2 levels modified response to weight loss interventions. Of note, sex steroid levels were not reported in these studies.

The Diabetes Prevention Program (DPP) randomized non-diabetic, overweight or obese, glucose-intolerant participants to a program of intensive lifestyle modification (ILS), metformin, or placebo.(8) Participants randomized to ILS and metformin had maximal weight loss and reductions in glucose at 1 year after randomization.(8) We have previously reported that postmenopausal women who were overweight and glucose-intolerant had significant reductions in weight and WC when randomized to intensive lifestyle change or metformin compared to placebo.(9) Changes were observed among women who used oral estrogen at baseline and 1-year follow-up as well as among women who did not use any exogenous estrogen at either time.(10)

The DPP data provide the opportunity to examine the pattern of weight loss and WC in estrogen users and non-estrogen users, and whether baseline serum sex steroid levels were associated with the degree of weight loss and reductions in WC among women randomized to interventions. We hypothesized that greater E2 levels and decreased testosterone and

dehydroepiandrosterone (DHEA) levels at baseline would be associated with greater reductions in weight and WC among women randomized to ILS or metformin compared to placebo.

Methods and Procedures

Characteristics of DPP participants have been reported.(8) Briefly, the DPP inclusion criteria included age > 25 years, fasting plasma glucose (FPG) of 95-125 mg/dl and 2-hour plasma glucose of 140-200 mg/dl following a 75-gram glucose load, and body mass index (BMI) 24 kg/m^2 (22 kg/m^2 for Asian Americans). Written informed consent was obtained from all participants before screening, consistent with the guidelines of each participating center's institutional review board.

Eligible participants were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily, or ILS. The goals of ILS were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet, plus moderate physical activity for at least 150 minutes per week. (8) Weight and WC were measured semiannually, and participants had an annual oral glucose tolerance test and semiannual FPG test. At the time of randomization, all women completed a questionnaire about their menses, gynecological history including surgeries, and about estrogen use (contraceptive and postmenopausal therapy). Medication use was reassessed every 6 months.

Women were classified as postmenopausal if they met any of the following criteria: bilateral oophorectomy, lack of menses for at least one year while retaining uterus and at least one ovary, cessation of menses prior to hysterectomy, cessation of menses within the past year and age > 55 years, and cessation of menses with hysterectomy and age > 55 years. For this report, we included women who consented for participation in ancillary studies, were postmenopausal at randomization, had an available stored serum sample for sex steroid measurement, and could be categorized as oral estrogen users both at randomization as well as at 1 year follow-up (n=324), or as non-users both at randomization and 1 year follow-up (n=382). Women who used injection, implant, transdermal, or transvaginal estrogen were excluded, as were women who used any estrogen at baseline but not at follow-up and vice-versa. We have previously reported the characteristics of estrogen users(10); of the 324 women who reported using oral estrogen at baseline and at follow-up, 266 women were estrogen-only users at baseline and 58 women used estrogen-progestin; at year 1 follow-up, 258 women were estrogen-only users and 66 women used estrogen-progestin, and the most common estrogen used was conjugated equine estrogen.

For diabetes diagnosis, an oral glucose tolerance test was performed between 7 a.m. and 11 a.m. after an overnight fast. Venous blood was sampled before and 2 hours after a 75 gram oral glucose load (Trutol 75; Custom Laboratories, Baltimore, MD). Plasma glucose was measured fasting and at 2 hours; plasma insulin was measured fasting. Insulin sensitivity was assessed using inverse fasting insulin levels ($1/\text{fasting insulin}$). All analytical measurements were performed at a central Biochemistry Laboratory (University of Washington, Seattle, WA). Plasma glucose was measured on a chemistry autoanalyzer by

the glucokinase method. Insulin measurements were performed by a radioimmunoassay method using an anti–guinea pig antibody that measures total immunoreactive insulin. The insulin assay is a 48-h polyethylene glycol–accelerated method with coefficients of variation (CVs) of 4.5% for high-concentration quality control samples and 6.9% for low-concentration quality control samples. The CV for masked split duplicates in this assay was <8.5%.

We have previously reported sex hormone measurement procedures.(9) Briefly, SHBG, follicle stimulating hormone (FSH), total E2, total T, and DHEA were measured on heparinized plasma collected at baseline and year 1. SHBG was measured at Endoceutics (Quebec City, Canada) using ELISA (Bioline) with interassay coefficients of variation of 7.8 and 5.0 at 18.2 and 63.1 nmol/l, respectively. FSH was measured at Endoceutics using ELISA (Bioline) with interassay coefficients of variation of 3.6 and 4.4 at 27.1 and 72.9 mIU/ml, respectively. E2, T, and DHEA were analyzed using gas chromatography/mass spectrometry at Endoceutics. The limits of detection were 3.0 pg/ml for total E2; 8.0 ng/dl for total T, and 0.30 ng/ml for DHEA. Interassay coefficients of variation for E2 were 17.5% at 4.7 pg/ml, for T were 13.0% at 14 ng/dl, and for DHEA were 24.0% at 0.77 ng/ml. The ratio of T:E2 was also examined as a potential indicator of aromatase activity, and bioavailable T and E2 were calculated according to the method described by Sodergard and colleagues (courtesy of Frank Stanczyk, University of Southern California) taking the concentrations of total T, total E2, and SHBG into account and assuming a fixed albumin concentration of 4.0 g/dl.(11)

Statistical Analysis

In the first stage of analysis, women who did not use any estrogen at baseline or follow-up and women who used oral estrogen at both baseline and follow-up were examined separately. For each population, baseline characteristics were described using percentages for categorical variables and means (SD) for quantitative variables. For variables where the distribution was skewed, log-transformed values and median values were used; Table 1 shows medians and interquartile ranges for baseline sex steroid measures and SHBG. In order to assess the association between baseline sex steroid and SHBG level and change in weight, we first used t-tests or Wilcoxon rank-sum tests to compare levels of change in weight between randomization arms. Change in weight was calculated as year 1 weight – baseline weight. Next, we examined the association between baseline sex steroid level and these weight changes. Models which used natural scale and log-transformed sex hormones were similar, and therefore for ease of interpretation and to enable comparisons across sex steroids, β -coefficients were standardized using the standard deviation of each natural scale sex hormone. Due to differences in baseline FSH by randomization arm, as well as previously reported effects of menopausal stage upon sex steroid-adipose tissue relationships,(12) baseline FSH levels were also examined as a covariate.

A series of linear regression models additionally adjusted for baseline weight, as well as age, race/ethnicity, and baseline levels of FSH. In order to determine whether the association between sex steroid and SHBG levels and weight changes varied by randomization arm, an interaction term between sex steroid level and randomization arm was also evaluated.

Additional models stratified by randomization arm. Similar models were created for evaluation of changes in WC. In sensitivity analyses, we also evaluated models that adjusted for fasting insulin, but this did not change the significance of any associations, so only the models adjusting for baseline weight or WC, age, race/ethnicity, and FSH are shown. Next, we compared the baseline characteristics of estrogen users and non-users using similar procedures as those described above. We created multivariable models that introduced an interaction term between exogenous estrogen use and baseline sex steroid and SHBG level, in order to determine whether use of estrogen modified the association between baseline sex hormone measures and changes in anthropometric measures; comparisons were made stratified by randomization arm. The SAS analysis system was used for all analyses (SAS Institute, Cary, NC).

Results

Baseline characteristics of postmenopausal women by estrogen use are shown in Table 1. Similar proportions of women were randomized to ILS, metformin, or placebo among estrogen users and non-users. Reflecting DPP recruitment criteria, all women were overweight or obese at baseline and had elevated glucose levels. Women who did not use estrogen were slightly older and more often non-white than estrogen users. Among non-users, the most common cause of menopause was natural or non-surgical cessation of menses, whereas among estrogen users, the most common cause of menopause was oophorectomy. Non-users weighed more and had greater WCs and higher BMIs than estrogen users. Non-users had higher levels of fasting insulin, FPG, and FSH but lower levels of SHBG and E2 than estrogen users. No differences in T and DHEA between estrogen users and non-users were observed. Among non-users, women had similar characteristics by study arm, with the exception that women randomized to metformin had slightly lower FSH levels than women randomized to placebo (51.5 IU/l vs. 59.3 IU/l, $p<0.05$). Among estrogen users, women had similar characteristics by study arm, with the exception that there were slightly more African-American women in the metformin arm than the placebo arm (9% vs. 5%, $p<0.05$).

Among women not using estrogen at baseline or follow-up, women randomized to ILS, metformin, and placebo lost 6.5 kg, 3.2 kg, and 0.95 kg of weight, respectively, and reduced WC by 6.5 cm, 3.0 cm, and 1.3 cm, respectively ($p<0.05$ for comparisons of each intervention vs. placebo). Among estrogen users, women randomized to ILS, metformin, and placebo lost 7.0 kg, 2.8 kg, and 0.28 kg of weight, respectively, and 6.0, 2.1 cm, and 0.4 cm of WC, respectively ($p<0.05$ for comparisons between interventions vs. placebo).

Table 2 shows the association of baseline sex steroid levels with changes in weight and WC among women who did not use estrogen at baseline or 1-year follow-up. Baseline levels of SHBG and sex steroids (E2, T, DHEA) were not significantly associated with reductions in weight or WC. Interactions between randomization arm and baseline sex hormone levels were not significant, indicating that the strength of associations did not vary by randomization arm. Table 2 also shows the association between baseline sex steroid levels with changes in weight and WC among women who used oral estrogen at baseline and at follow-up. In unadjusted models, baseline levels of E2 were associated with greater

reductions in weight and WC at 1 year after adjustment for baseline anthropometry, specifically among women randomized to metformin (results not shown). However, these associations did not persist after further adjustment for other covariates (Table 2). In particular, adjustment for race/ethnicity reduced the significance of associations between E2 and weight changes and adjustment for FSH reduced significance between E2 and WC changes. Models examining bioavailable E2 yielded similar results (not shown).

Among oral estrogen users, greater baseline levels of T were associated with greater reductions in weight and WC (Table 2). The interactions between baseline levels of T and randomization to placebo vs. interventions were significant. In the placebo arm, the association between baseline T and weight changes ($p=0.02$) and waist circumference changes ($p<0.01$) was significant, but the associations between baseline T and anthropometric changes were not significant among women randomized ILS or metformin. Measures incorporating T, i.e. the ratio of T: E2 showed a similar pattern of associations, as did measures of bioavailable T (results not shown). In unadjusted models, lower baseline levels of DHEA were associated with greater reductions in weight, specifically among women randomized to lifestyle change. However, these associations did not persist after further adjustment for other covariates (Table 2). In particular, adjustment for race/ethnicity reduced the significance of associations between DHEA and anthropometric changes. Baseline levels of SHBG were not associated with changes in weight or WC.

When we examined whether the strength of the associations between baseline sex hormones varied by exogenous estrogen use, we found that interactions between exogenous estrogen and baseline sex hormone levels were not significant, suggesting that the relationship between sex hormones and anthropometric changes was not significant regardless of exogenous estrogen use. The exception was the interaction between estrogen use and sex hormone level was significant for women randomized to placebo, that is, baseline T was significantly associated with anthropometric changes among hormone users only in this arm, as was bioavailable T (results not shown).

Discussion

In a secondary analysis of a randomized trial of weight loss interventions in overweight postmenopausal women, we found that elective estrogen users and non-users had similar patterns of weight loss with lifestyle intervention and metformin compared to placebo. Among estrogen users and non-users, baseline serum sex steroid levels did not predict the magnitude of weight loss or reductions in waist circumference in response to ILS or metformin. This suggests that any effects of exogenous estrogen were not enacted through actual alteration of serum sex steroid levels. While baseline androgen levels did not predict response to ILS or metformin, estrogen users randomized to placebo with lower baseline T and DHEA had greater increases in weight and WC, suggesting that androgen levels could predict women most likely to gain weight or WC in the absence of intervention.

Reports on whether estrogen therapy can potentiate weight loss interventions are contradictory. Kuller et al(7) found that among approximately 500 postmenopausal women with a mean age of 57 years, reductions in weight and WC in response to lifestyle change

was similar regardless of estrogen use. Our findings were similar. DPP women who used and did not use estrogen had similar changes in weight and WC in response to lifestyle change, and the use of estrogen was not assigned by the DPP trial. It is possible that randomization to estrogen therapy leads to favorable changes in weight and waist circumference, but that additional beneficial effects of estrogen on weight loss interventions are minimal. In contrast, Evans et al(3) found that women randomized both to estrogen use and lifestyle changes had the greatest reductions in fat mass, suggesting that the effects of estrogen therapy and lifestyle change could be additive. Our results may differ because we examined elective estrogen therapy in markedly overweight dysglycemic women. We also did not find evidence that actual serum sex steroid levels among estrogen users potentiated weight loss responses. This finding is consistent with small studies of oral and transdermal estrogens, (4-6) which have reported that changes in fat mass differed depending upon the route of estrogen administration; although serum E2 levels were not reported, these might be assumed to be similar regardless of the route of estrogen therapy. While these studies differ as to how estrogen therapy may actually affect weight, these studies and our findings support the hypothesis that exogenous oral estrogen enacts its effects on weight through mechanisms other than sex steroid changes.

Although we did not find associations between baseline sex steroid levels and weight loss among women randomized to interventions, we did find associations among women randomized to placebo. Among estrogen users, greater androgen levels (T and DHEA) at baseline were associated with greater declines in weight and WC. These results contrast with prior observations that higher androgen levels are associated with increased lean body mass and fat mass, particularly among postmenopausal women.(13) Other studies have found that T do not predict weight or WC changes but vice-versa,(12) and that sex steroids and WC associations were of significance primarily among normal weight women.(14) Of note, our results represent overweight, dysglycemic women over a fairly short period of time and thus may conflict with reports from healthier populations of postmenopausal women.

Among women with polycystic ovary syndrome (PCOS), manipulation of steroid levels with flutamide may decrease improvements in weight apart from a hypocaloric diet.(15) However, we did not find strong evidence that serum sex steroid levels would further potentiate weight loss interventions, or that additional manipulation of serum sex steroid levels would further aid weight loss. While the populations of estrogen users and non-users were not directly comparable since estrogen use was elective, both groups of women experienced similar magnitudes of weight loss and reductions in waist circumference dissociated with serum sex steroid levels. While some observational studies consistently document strong associations between weight and sex steroid levels, the nature of the relationship is complex and probably bidirectional.(12, 16-21) Adipose tissue may manufacture sex steroids, suggested by studies demonstrating that weight reduction in obese women leads to declines in T,(16) increases in WC in the late menopausal transition precede increases in E2,(12) and hepatic steatosis is associated with declines in SHBG manufacture. (17, 18) Conversely, estrogen use,(19) androgen use,(20) and other menopause-related sex hormone changes may influence fat mass and location.(12, 21)

Strengths of our report include its randomized study of weight loss interventions which led to significant changes in weight, as well as measurement of serum sex steroid levels. Limitations include lack of more detailed body composition measures that would be allowed us to examine changes in visceral adiposity and adipose tissue volume more accurately. Although we used mass spectrometric assays which may be more sensitive for the low sex steroid levels typically observed in postmenopausal women, variance was still high at lower levels and may have biased estimates towards the null. For associations that were not statistically significant, the point estimates were close to 0 and the confidence intervals narrow with several exceptions, suggesting that these results may have been underpowered: the association between total estradiol and changes in weight among non-estrogen users, and the association between DHEA and changes in waist circumference among estrogen users. Finally, this study was a secondary analysis of a randomized trial not designed a priori to assess the interaction between sex steroids upon response to weight loss interventions in small subsets. Such a study which randomized women to estrogen therapy as well as to weight loss would be unlikely to be performed today due to logistics, cost, and ethical concerns.

We conclude that among estrogen users, baseline sex steroid levels were not associated with intervention response, suggesting that exogenous estrogen does not potentiate weight loss interventions by altering serum sex steroid levels. Lower androgen levels may predict gain in adiposity, although not response to interventions. We also did not find consistent associations between baseline E2 and intervention responses among women who did not use estrogen. Further exploration of the interaction between exogenous estrogen and its impact on metabolic markers should explore other pathways aside from alterations in sex steroid and SHBG levels.

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What is already known about this subject

- Randomized trials of estrogen therapy suggest that it has neutral or favorable effects on weight loss in overweight or obese postmenopausal women.
- Reports on whether estrogen therapy can potentiate or interfere with weight loss interventions are few, and contradictory.
- Reports to date have not measured sex steroid levels.

What this study adds

- Postmenopausal using and not using estrogen therapy both lost significant amounts of weight compared to placebo.
- Among non-estrogen users and estrogen users, baseline sex hormone levels had minimal impact upon anthropometric changes associated with interventions.
- These results suggest that change in sex steroid levels was not the mechanism through which weight loss was enacted.

Table 1

Characteristics of postmenopausal women by oral estrogen therapy (ET) use. Means (SD) or percentages shown; medians (interquartile ranges or IQR) shown for sex hormones.

	Non-users n=382	Estrogen users n=324	p-value
Randomization arm (%)			
Intensive lifestyle change	35	33	0.26
Metformin	32	38	
Placebo	33	29	
Age (years)	58.7 (9.0)	56.5 (7.6)	<0.01
Race/ethnicity (%)			<0.01
Caucasian	53	66	
African-American	28	16	
Hispanic	16	13	
Asian	3	4	
Type of menopause (%)			<0.01
Bilateral oophorectomy	20	42	
Natural menopause	67	39	
Age > 55 years and hysterectomy	14	19	
Years since final menstrual period	15 (10)	14 (9)	0.34
Baseline weight (kg)	91.0 (19.7)	87.6 (17.8)	0.04
Baseline waist circumference (cm)	104 (14)	101 (14)	<0.01
Baseline BMI (kg/m ²)	34.6 (6.8)	33.3 (6.5)	0.01
Baseline fasting insulin levels (IU/l)	26.4 (16.0)	23.4 (12.0)	<0.01
Baseline fasting plasma glucose (mg/dl)	107 (8)	104 (7)	<0.01
Baseline 2-hour glucose (mg/dl)	164 (17)	166 (18)	0.16
Baseline follicle stimulating hormone (IU/l)	55.3 (26.6)	34.8 (22.5)	<0.01
Baseline sex hormone binding globulin (nmol/l)	33.2 (18.3)	85.3 (77.0)	<0.01
Baseline total estradiol (pg/ml)	8.5 (8.0)	17.6 (14.8)	<0.01
Baseline total testosterone (pg/ml)	14.0 (13.0)	15.0 (11.0)	0.44
Baseline total dehydroepiandrosterone (ng/ml)	1.6 (1.3)	1.3 (1.2)	0.01
Baseline total testosterone:estradiol	0.023 (0.04)	0.018 (0.07)	<0.01

Table 2

Associations between baseline sex steroid and sex hormone binding globulin levels with change in weight (weight) and change in waist circumference (waist circumference) among women who did not use estrogen and estrogen users. * Standardized β -coefficients and 95% confidence intervals (CIs) shown; a negative β -coefficient indicates that a greater baseline hormone level is associated with greater declines in weight or WC. Bold type indicates a statistically significant association.

	Among women who did not use estrogen	Among women who used oral estrogen
	β -coefficient (95% CI)	β -coefficient (95% CI)
Sex hormone binding globulin (nmol/l)		
weight	0.16 (-0.66, 0.98) p=0.70	-0.20 (-1.25, 0.86) p=0.72
waist circumference	0.05 (-0.85, 0.94) p=0.92	0.70 (-0.62, 2.02) p=0.30
Total estradiol (pg/ml)		
weight	-1.3 (-2.93, 0.33) p=0.12	0.11 (-1.14, 1.35) p=0.86
waist circumference	-0.52 (-2.28, 1.24) p=0.56	-0.22 (-1.77, 1.34) p=0.78
Total testosterone (pg/ml)		
weight	-0.037 (-0.99, 0.92) p=0.94	-3.5 (-5.14, -1.83) p<0.01[†]
waist circumference	0.049 (-1.00, 1.10) p=0.93	-4.8 (-6.88, -2.74) p<0.01[†]
Dehydroepiandrosterone (ng/ml)		
weight	0.49 (-0.60, 1.59) p=0.38	-0.86 (-1.89, 0.16) p=0.10
waist circumference	-0.09 (-1.37, 1.17) p=0.88	-1.3 (-2.54, 0.02) p=0.054
Total testosterone:total estradiol		
weight	-0.31 (-1.51, 0.89) p=0.61	-1.5 (-2.15, -0.90) p<0.01[†]
waist circumference	-0.29 (-1.58, 0.99) p=0.65	-2.0 (-2.78, -1.20) p<0.01[†]

* Associations adjusted for randomization arm, age, race/ethnicity, baseline follicle stimulating hormone, and baseline anthropometric measure

[†] p<0.05 for interaction with randomization arm; association significant among women randomized to placebo but not among women randomized to lifestyle change or metformin.