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A randomized trial of estrogen or raloxifene during postmenopausal weight loss: Adiposity and cardiometabolic outcomes

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Abstract

Objective—Estrogen-based hormone therapy (HT) attenuates abdominal fat gain after menopause, but whether HT improves abdominal fat loss during weight loss is unknown. We hypothesized that HT or a selective estrogen receptor modulator (raloxifene) would augment reductions in abdominal visceral fat during weight loss when compared to placebo, potentially increasing improvements in glucose tolerance and lipid profile.

Design and Methods—Healthy postmenopausal women (n=119; age 50–70y) underwent a 6-month weight loss (primarily exercise) intervention with randomization to raloxifene (60mg/d), HT (conjugated estrogens, 0.625mg/d), or placebo. We measured changes in total and abdominal (visceral and subcutaneous) fat mass, lipid profile, and fasting and post-challenge glucose and insulin.

Results—Neither HT nor raloxifene augmented loss of total or abdominal fat mass during exercise-induced weight loss when compared with placebo. Weight loss-induced improvements in risk factors were similar among the three groups, except for a greater reduction in fasted glucose in the HT group (difference in change [95%CI] from placebo; -0.40 [$-0.76, -0.05$]) and greater reductions in LDL (-0.36 [$-0.63, -0.09$]) and increases in HDL (0.15 [$0.07, 0.24$]) in both treatment groups.

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COMPETING INTERESTS

There are no conflicts of interest to disclose.

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Conclusions—Postmenopausal HT and raloxifene did not increase abdominal fat loss during weight loss, but did improve some cardiometabolic outcomes.

Keywords

weight loss; postmenopausal hormone therapy; cardiometabolic risk

INTRODUCTION

Excess fat stored in the abdomen, particularly in the visceral region, is associated with increased risk for heart disease, glucose intolerance, insulin resistance, Type 2 diabetes, and hypertension¹. Menopause appears to diminish the protection women are afforded from abdominal obesity prior to menopause. Evidence suggests estrogen deficiency in women after menopause promotes positive energy balance and increased fat mass, particularly in the abdominal region²⁻⁴. Treating postmenopausal women with estrogen-based hormone therapy (HT) attenuates fat gain, when compared with placebo^{5,6}. Further, a large meta-analysis of randomized placebo-controlled trials demonstrated that postmenopausal HT reduced abdominal fat by 6.8% and improved cardiometabolic outcomes associated with central adiposity (e.g., insulin sensitivity, new-onset diabetes, lipids, blood pressure)⁷. However, it is not known whether postmenopausal HT augments total and abdominal fat loss under conditions of negative energy balance. Moreover, weight loss itself is known to improve cardiometabolic risk factors (e.g., glucose tolerance, insulin sensitivity, lipids), but whether HT augments or attenuates weight-loss mediated improvements is not known.

Although the use estrogen-based HT after menopause for the prevention of cardiovascular disease has been the subject of much debate over the past decade, the quest to elucidate the physiological effects of estrogens remains highly important. Selective estrogen receptor modulators (SERM) were developed as an alternative postmenopausal HT because they act as both estrogen receptor agonists and antagonists, depending on the tissue. For example, raloxifene is an agonist in bone and an antagonist in breast tissue and the only SERM currently approved for the prevention of osteoporotic fractures and estrogen receptor-positive breast cancer⁸. It is not known whether raloxifene acts as an estrogen receptor agonist or antagonist in adipose tissue, but raloxifene has been shown to improve some markers of cardiometabolic risk⁹. Whether raloxifene augments or attenuates weight-loss mediated improvements is not known.

The primary aim of the study was to determine whether HT (oral conjugated estrogens) or a SERM (raloxifene) exaggerated abdominal fat loss during weight loss in postmenopausal women. The secondary aim was to determine whether weight-loss induced improvements in cardiometabolic outcomes were augmented or attenuated by HT or SERM treatment. To meet these aims, we induced weight loss through a 6-month program of supervised exercise training plus mild intermittent caloric restriction in postmenopausal women randomized to treatment with HT, raloxifene, or placebo. We hypothesized that reductions in total fat mass and total abdominal and visceral fat would be greater during weight loss in women treated with HT or raloxifene compared to placebo. We further hypothesized that the greater

improvements in abdominal fat would augment improvements in cardiometabolic outcomes (glucose tolerance, insulin sensitivity, and lipid profiles).

METHODS AND PROCEDURES

Study participants

Study participants were healthy, sedentary postmenopausal women aged 50 to 70 y who had not used menopausal HT in the previous 6 months. Inclusion and exclusion criteria for the study population were previously reported¹⁰. Briefly, women were overweight to moderately obese, non-smokers, and did not have diabetes or cardiovascular disease. Postmenopausal status was defined as the absence of menses for 1 year or a serum FSH >30 IU/L in women who had undergone a hysterectomy without oophorectomy. The study was approved by the Colorado Multiple Institutional Review Board and all volunteers provided written informed consent to participate. Of the 588 postmenopausal women who inquired about the study, 209 underwent informed consent and, of those, 119 were randomized into a 6-month weight loss intervention with three drug treatment arms (Figure 1).

Intervention

Study Drug—Women were randomized in a double-blinded manner to placebo, raloxifene, or HT. The HT was 0.625 mg/d conjugated estrogens (Premarin®, Pfizer Inc.); women with an intact uterus also received 5 mg/d medroxyprogesterone acetate (MPA) for 13 consecutive days trimonthly. This HT regimen was selected to minimize exposure to progestins while still protecting the endometrium. Raloxifene (Evista®, Eli Lilly) treatment was 60 mg daily and placebo treatment was a daily placebo tablet; women in these groups with an intact uterus also received cyclic placebo MPA. All study drugs and placebo tablets were purchased through a local pharmacy (Belmar Pharmacy, Lakewood, CO). Compliance to study drug was estimated from pill counts on returned bottles, study exit surveys, and serum estradiol and raloxifene concentrations measured at the baseline and 6-month study visits.

Weight Loss—All 119 women were enrolled in a 6-month weight loss intervention. Weight loss was primarily exercise-induced, but also included 1 week of caloric restriction during months 1, 3 and 5 of the supervised exercise intervention to boost weight loss. The supervised endurance exercise program was designed to increase energy expenditure by approximately 400 kcal per session. Women were asked to attend supervised exercise sessions 4 days per week, which would generate a weight loss of ~4.5 kg. They were also encouraged to do additional exercise at home. All exercise, including any done at home, was recorded in exercise logs. Mode of exercise (e.g., treadmill, elliptical, rowing ergometer), duration of activity (minutes), workload (speed, grade), and intensity (heart rate monitors, Polar Electro Inc) were used to quantify caloric expenditure for each session. Exercise intensity was progressively increased during the first few weeks until women were exercising at 70 to 80% of maximal heart rate for 45 to 60 minutes per day. Because weight loss with exercise occurs slowly¹¹, the 6-month program included 1-week periods of reduced-calorie diets provided by the Clinical and Translational Research Center (CTRC)

Metabolic Kitchen during months 1, 3 and 5. Energy intake was reduced to 25 kcal per kg fat-free mass per day, but not less than 1200 kcal per day, with 60% of the energy as carbohydrate, 25% as protein, and 15% as fat. Of the 119 women enrolled, 98 completed the 6-month weight loss intervention and body composition assessment.

Procedures

Body composition—Total body and regional (trunk, arm, and leg) fat mass (FM) and fat-free mass (FFM) were measured by dual-energy x-ray absorptiometry (DXA) at baseline and 6 months using either a Lunar DPX-IQ (n = 72; Lunar Co., Madison, WI, software version 4.38) or a Hologic Delphi-W (n = 47; Hologic, Inc., Bedford, MA, software version 11.2) instrument. The recommendations of the manufacturers were used to define the trunk, arm and leg regions. The use of two DXA instruments could not be avoided, but each participant had baseline and 6-month measurements on the same instrument. The within-instrument coefficients of variation (CV) for FM and FFM were $1.1\pm 0.9\%$ and $0.5\pm 0.4\%$, respectively.

Abdominal visceral and subcutaneous fat areas were determined by computed tomography (CT) using a General Electric (Waukesha, WI) High Speed CT. Single axial CT images (120 kVp, 200–300 mAs, 10-mm slice thickness) were acquired at the levels of the L₂-L₃ and L₄-L₅ intervertebral spaces; the areas for the 2 slices were averaged. Adipose tissue areas were determined using a CT intensity range from image-generated histograms of adipose and soft tissue regions. The abdominal visceral fat areas (VFA; cm²) were manually outlined by tracing the muscles of the abdominal wall. Abdominal subcutaneous fat areas (SFA; cm²) were calculated by subtracting the visceral fat areas from the total abdominal fat area.

Oral Glucose tolerance test (OGTT)—A 75-g OGTT was administered in the morning after an overnight fast. Blood samples were obtained before and 30, 60, 90, and 120 min after glucose ingestion for glucose and insulin determinations. The total areas under the glucose (GLU_A) and insulin (INS_A) curves were calculated using the trapezoidal rule. The INS_A and fasted insulin (INS₀) were used as indices of hyperinsulinemia and the product of the insulin and glucose areas (INS_A × GLU_A) was calculated as an estimate of peripheral insulin resistance (i.e., Matsuda Index) as previously described¹². The areas and products were left as conventional (non SI) units for consistency with previous studies.

Hormones and metabolites—Blood samples were stored at –80° C and analyzed in batch by the CTRC Core Laboratory. Serum insulin concentrations were determined with a double-antibody radioimmunoassay (Diagnostic Systems Laboratory, Webster, TX). Serum glucose was measured using a hexokinase assay on a Cobra Mira Plus instrument (Roche Diagnostic Systems, Indianapolis, IN). Intra- and inter-assay coefficients of variation were 5.2% and 9.8% for insulin measurements; and 1.1% and 3.6% for glucose determinations.

Blood lipids and lipoproteins—Measurements of serum lipid and lipoprotein concentrations were done by the CTRC Core Laboratory. Total cholesterol (C), High-density lipoprotein-C (HDL-C) and triglycerides (TG) were measured by automated enzymatic commercial kits on a Cobra Mira Plus instrument (Roche Diagnostic Systems,

Indianapolis, IN). Intra- and inter-assay coefficients of variation were as follows: 1) TC, 5.1% and 2.4%; 2) TG, 1.4% and 3.3%; 3) HDL, 4.5% and 2.9%. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.

Statistics—Statistical power was based on a previous study wherein exercise-induced fat loss was preserved by HT¹³. In that study, the 6-month changes in trunk fat in the HT group and control group during the period of weight regain following completion of the exercise intervention were 0.3 ± 1.6 kg and 1.5 ± 1.7 kg, respectively, suggesting that 30 women per group would provide 80% power to detect a 1.2 kg difference between groups in a two-sided level $\alpha=0.05$ *t* test.

Participant characteristics at baseline were compared across groups by one-way ANOVA for continuous measures or chi-squared tests of equal proportions for categorical variables. The effects of treatment and weight loss were addressed using a statistical model that regressed the change from baseline in the outcome measure on the corresponding baseline value and an indicator for treatment group. Baseline was included to increase the efficiency (increase power) of the estimates. The model was parameterized so that 3 statistical tests (contrasts) could be evaluated to compare the effect of HT vs. placebo, raloxifene vs. placebo, and the average of the two treatments vs. placebo. Both absolute and relative (i.e., percent of total fat mass) changes in regional adiposity were evaluated but results did not differ, so only absolute changes are presented. Likewise, the results of intent-to-treat and compliance (drug and exercise) analyses did not differ appreciably, so only the intent-to-treat results are presented. Data are presented as mean \pm SD unless otherwise specified.

RESULTS

Study cohort

The three groups of postmenopausal women randomized to HT, raloxifene or placebo, were similar with respect to age, number of years since menopause, hysterectomy status, past exposure to HT, aerobic fitness, and degree of obesity (Table 1). Of the 119 women randomized into the study, 98 women completed the exercise and weight loss intervention and 6-month follow-up body composition assessment by DXA (primary outcome). The 21 non-completers did not significantly differ from the 98 completers in any of the outcomes (data not shown) with the exception that the drop-outs had a significantly ($p<0.05$) larger waist girth (97 ± 13 vs 91 ± 12 cm) at baseline. Of the 98 completers, 93 had paired OGTT and lipid profiles and 85 had paired abdominal CT data. Missing follow-up data were primarily due to the inability to schedule tests within one month of completing the weight loss intervention. Additional CT data were lost to incorrect scan levels being obtained at either baseline or follow-up. Exercise volume, intensity and energy expenditure were similar among the 3 groups (Table 2). At study entry, groups were similar for total adiposity and regional adipose deposition, with a propensity for abdominal adiposity as evidenced by the high waist girths and visceral fat areas (Table 3).

Body composition changes following intervention

For all 3 groups weight loss and fat loss during the 6-month exercise intervention averaged -3.7 ± 3.4 kg and -3.5 ± 3.4 kg, respectively (Table 3, Figure 2). Trunk and leg fat decreased by -1.6 ± 2.0 kg and -1.5 ± 1.4 kg, respectively, while fat-free mass was maintained (-0.2 ± 1.4 kg). Fat loss from the abdominal compartment (as measured by CT) was highly variable, with an average decrease in fat area of -34.9 ± 37.6 cm² from the subcutaneous region and -15.4 ± 21.3 cm² from the visceral region (Table 3, Figure 3). There were no differences in total body and regional fat loss among the 3 drug treatment groups.

Cardiometabolic changes following intervention

Exercise-induced weight loss resulted in significant decreases in fasted, 2-hour, and area under the curve for glucose and insulin, but the improvements were similar among the HT, raloxifene and placebo groups (Tables 4 and 5). Insulin sensitivity ($INS_A * GLU_A$) was equally improved in all groups after 6 months of weight loss. The only significant difference among the groups was a greater reduction in fasted glucose in HT compared with placebo ($p < 0.05$).

In general, exercise-induced weight loss improved lipid profiles, but effects differed among the three treatment groups (Tables 4 and 5). Compared with placebo, LDL-cholesterol was decreased ($p < 0.05$) and HDL-cholesterol increased ($p < 0.05$) in the HT and raloxifene groups following intervention; the decrease in total cholesterol was similar for all groups. There was a non-significant trend ($p = 0.09$) for HT to attenuate the weight loss-induced decrease in fasting TG observed in the placebo group.

DISCUSSION

To our knowledge, this was the first randomized, controlled trial in postmenopausal women to determine the effects of HT and raloxifene on regional fat distribution and cardiometabolic risk (glucose tolerance and lipid profiles) in response to exercise-induced weight loss. In contrast to the hypothesis, neither HT nor raloxifene exaggerated the decrease in total or abdominal fat mass during exercise-induced weight loss when compared with placebo. Treatment with either HT or raloxifene during weight loss had some additional beneficial effects on cardiometabolic outcomes when compared with placebo. HT, but not raloxifene, improved fasted glucose compared to placebo. LDL- and HDL-cholesterol were also improved to a greater extent in response to HT or raloxifene when compared with placebo.

Energy imbalance, fat accumulation, and estrogens

Several lines of evidence suggest that estrogen deficiency disrupts energy balance in a manner that increases propensity for weight gain. Preclinical studies have demonstrated an accelerated weight gain following ovariectomy, which is prevented with estradiol or raloxifene administration¹⁴⁻¹⁶. Menopause also appears to trigger an energy imbalance that increases propensity for weight and fat gain²⁻⁴. The menopause-related change in energy balance appears to be mediated, at least in part, by declines in ovarian hormones because GnRH agonist suppression of ovarian function has been shown to increase fat mass^{17,18}.

Whether the energy imbalance observed during estrogen deficiency can be explained by decreases in energy expenditure or an increase in energy intake remains unclear. We previously found that sex hormone suppression caused a decrease in resting energy expenditure¹⁹. It is not known whether this was specifically related to the suppression of ovarian estrogen secretion, but exogenous estrogen administration to postmenopausal women has been shown to attenuate weight and fat gain^{5,6}. Importantly, a meta-analysis of randomized trials suggests HT, compared to placebo or no treatment, reduces abdominal adiposity and improves markers of cardiometabolic risk⁷. However, previous studies were conducted in postmenopausal women not actively losing weight so prior to our study it was not known whether exogenous estrogen would augment fat loss (particularly in the abdominal region) under conditions of negative energy imbalance.

SERMs interact with estrogen receptors but can have either agonist or antagonist effects in different tissues. Raloxifene is reported to act as an agonist in bone, serum lipids, and arterial vasculature and as an antagonist in breast and uterine tissues. Whether raloxifene is an estrogen receptor agonist or antagonist in adipose tissue is not yet clear, but studies of ovariectomized rats suggest that raloxifene, like estrogen, attenuates body fat accumulation²⁰. Likewise, raloxifene was shown to attenuate fat gain in postmenopausal women^{21,22}. Nevertheless, raloxifene did not augment fat loss in the present study.

It is not clear why HT and raloxifene would attenuate fat gain during positive energy balance but have no effect on fat loss during negative energy balance. However, it could be argued that the lack of an effect of estrogens or raloxifene on total or regional fat loss was not surprising given that weight loss was achieved primarily through an exercise-induced increase in energy expenditure. If the mechanism by which estrogens attenuate fat gain during positive energy imbalance is through an increase in energy expenditure, it is possible that our exercise-related increase in energy expenditure masked an effect of estrogens on fat loss. Similarly, regarding the lack of an effect of HT on regional changes in adiposity, it is possible that exercise enhanced the reduction in abdominal fat, possibly via sympathetic nervous system activity, and masked potential effects of HT. Verification of this hypothesis would require a comparison of the effects of HT on reductions in regional fat in response to diet- versus exercise-induced weight loss. The different effects of estrogens under conditions of negative, compared to positive, energy imbalance suggests a mechanism that protects against weight gain, but does not influence weight loss.

Exogenous estrogens and cardiometabolic risk

Estrogen-based HT has been shown to increase²³⁻²⁵, not change^{26,27}, or decrease²⁸ the glucoregulatory action of insulin in postmenopausal women. Inconsistency among studies is likely due to widely varying types of HT regimens (e.g. varying duration of treatment, dose, route of administration, and opposition by progestins) and concurrent changes in body composition. Our previous studies of acute estrogen administration suggest estrogens can improve insulin-mediated glucose uptake in the absence of changes in body composition²⁹. However, the current study suggests that, in the context of equal weight loss among treatment groups, HT does not augment improvements in insulin action. On the other hand, there was a 7% (0.35 mmol/L, 6 mg/dL) reduction in fasting glucose in response to HT. This

is consistent with previous observations that both oral conjugated estrogens^{30,31} and transdermal estradiol³² reduce fasting glucose in postmenopausal women. While fasting glucose may not be linearly related to cardiovascular outcomes, these small improvements were sufficient to restore fasting glucose to the low risk range (3.9–5.6 mmol/L) for these women³³. Previous studies of postmenopausal women randomized to raloxifene or placebo observed no change³⁴ or worsened³⁵ insulin action following raloxifene treatment. However, in the current study raloxifene did not diminish weight loss-induced improvements in insulin action.

Oral conjugated estrogens have generally been shown to decrease total and LDL-cholesterol and increase HDL-cholesterol and triglycerides in postmenopausal women^{7,36–38}. Raloxifene was also shown to improve total, HDL- and LDL-cholesterol⁹. Exercise-induced weight loss can similarly improve lipid profiles, but with the added benefit of reducing serum triglycerides³⁹. Our data suggest that both HT and raloxifene further augment weight loss-induced decreases in LDL-cholesterol and increases in HDL-cholesterol, but tend to lessen improvements in triglyceride. The average treatment-related (i.e., difference from placebo) increase in HDL of 0.15 mmol/L (5.8 mg/dL) and decrease in LDL of 0.36 mmol/L (13.9 mg/dL) are clinically meaningful³³ in this population and consistent with previous studies of HT treatment without exercise or weight loss^{7,9}.

Limitations

It is not known whether our results were affected by the type of HT or SERM used in the study. Because we used oral conjugated estrogens in combination with MPA, it is possible that the anti-estrogenic effects of the progesterone attenuated the effects of the estrogens. However, the MPA was administered only trimonthly and only in those women with an intact uterus, so any effect of MPA was likely minimal. A different dose and/or route of administration (e.g., transdermal) may also have had more of an effect on body composition, but the oral dose we used was previously found to attenuate fat accumulation in postmenopausal women⁷. It is not yet known whether raloxifene acts primarily as an estrogen agonist or antagonist in adipose tissue; it is possible that another SERM would have different effects on adipose tissue loss during negative energy balance.

It is also not known whether our results were affected by the type of weight loss intervention used in the study. We induced weight loss primarily through an increase in energy expenditure (daily exercise) with only a small decrease in energy intake (intermittent caloric restriction). It is possible that a greater emphasis on dietary restriction would have brought about greater improvements in fasting glucose, and LDL-cholesterol, compared to exercise-induced weight loss⁴⁰. Conversely, diet-induced weight loss might have had less impact on abdominal adiposity and insulin sensitivity than was observed with exercise-induced weight loss⁴⁰. Such differences might have altered the impact of HT and raloxifene on cardiometabolic improvements.

In summary, exercise plus intermittent caloric restriction effectively reduced fat mass and improved cardiometabolic outcomes in postmenopausal women irrespective of hormone treatment. Neither HT nor raloxifene augmented abdominal fat loss, but improvements in some indicators of cardiometabolic risk were exaggerated by HT and raloxifene treatment,

independent of fat loss. The apparent lack of an effect of HT or raloxifene to amplify reductions in abdominal adiposity during weight loss is seemingly in contrast with the effect of these treatments to minimize gains in abdominal adiposity in postmenopausal women who were weight stable or in mild positive energy balance. Better understanding of the mechanisms underlying the effects of estrogens on adipose tissue and energy metabolism are needed to explain these discrepant findings.

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What is already known about this subject

- Postmenopausal women treated with estrogen-based hormone therapy (HT) gain less fat, particularly in the abdominal region, than those treated with placebo.
- Postmenopausal HT improves insulin sensitivity and lipid profiles, when compared with placebo.

What this study adds

- HT does not augment abdominal fat loss during weight loss.
- HT augments improvements in fasting glucose, HDL and LDL during weight loss.
- A selective estrogen receptor modulator (raloxifene) does not augment abdominal fat loss during weight loss but augments improvements in HDL and LDL, when compared with placebo.

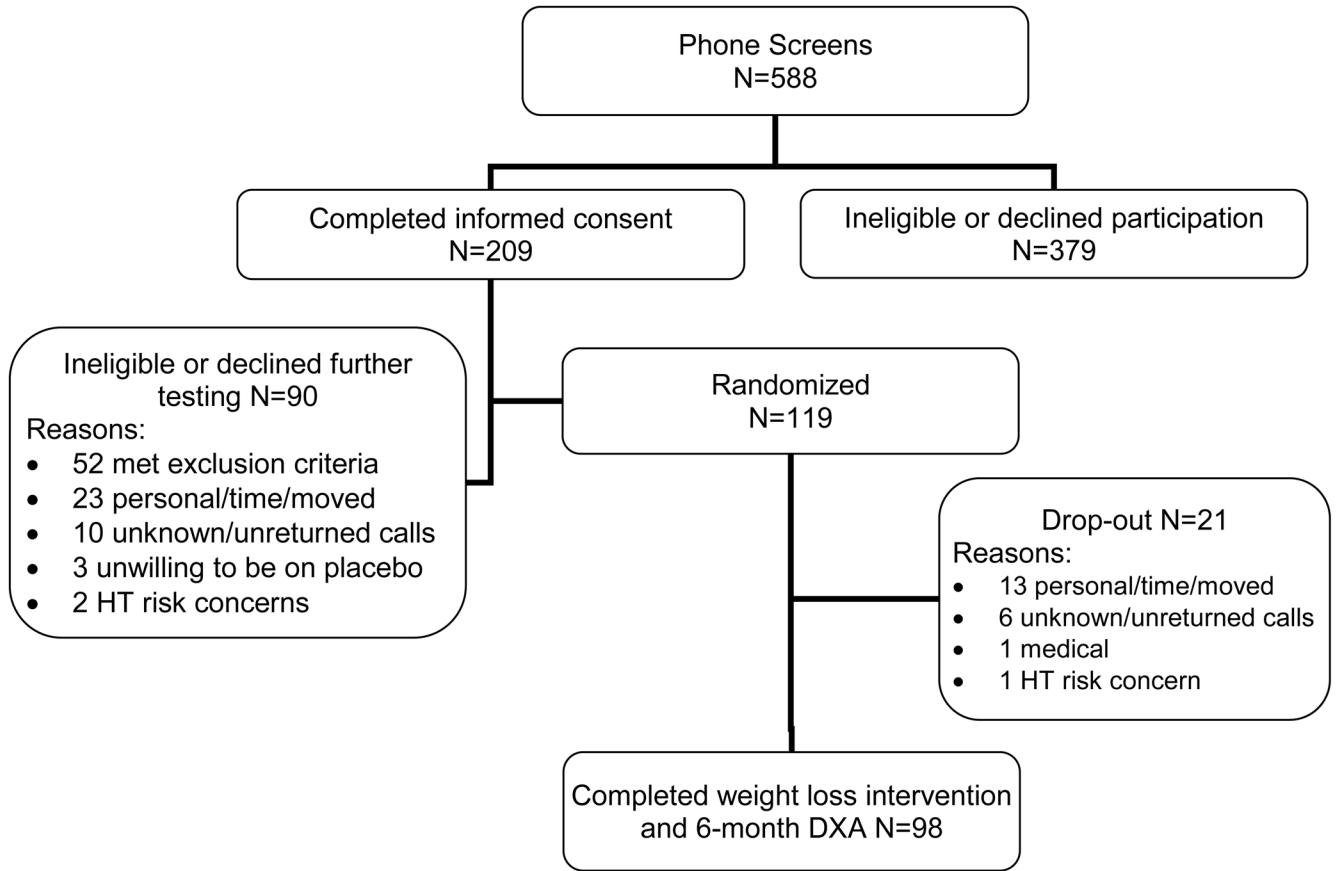


Figure 1.
Enrollment schematic

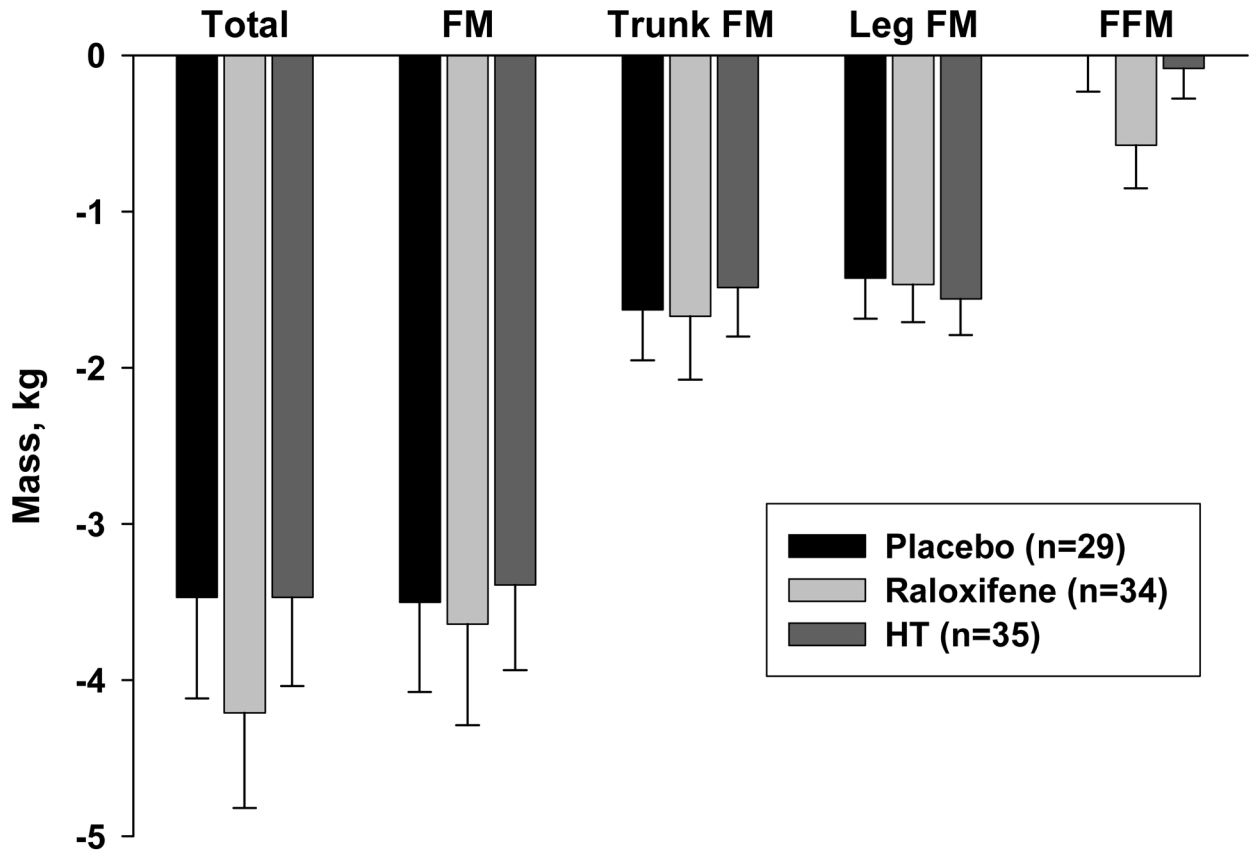


Figure 2. Six-month changes (n=98; mean±SE) in total and regional mass among postmenopausal women randomized to treatment with placebo, raloxifene, or estrogen-based hormone therapy (HT) during an exercise-induced weight loss intervention.

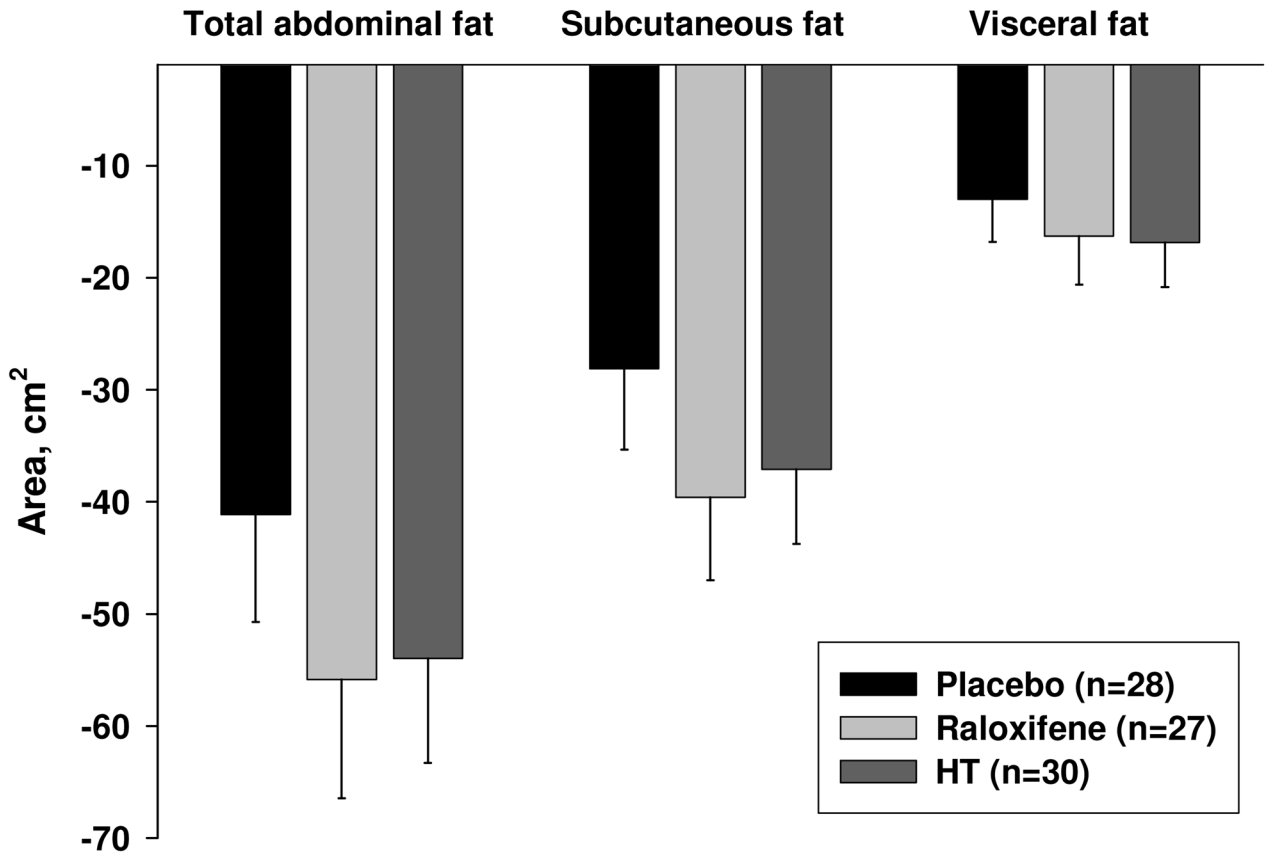


Figure 3. Six-month changes in CT abdominal fat (n=85; mean±SE) among postmenopausal women randomized to treatment with placebo, raloxifene, or estrogen-based hormone therapy (HT) during an exercise-induced weight loss intervention.

Table 1

Baseline characteristics of postmenopausal women randomized to placebo, raloxifene, or hormone therapy (HT).

	Treatment Group		
	placebo n = 38	raloxifene n =38	HT n =43
Age, yr	56±5	56±4	56±4
Age at menopause, yr	47±6	47±6	47±7
Time since menopause, yr	9.2±8.3	8.5±7.3	9.0±7.9
Hysterectomy, n (%)	13 (34%)	13 (34%)	14 (33%)
Time since last HT use, yr (n)	3.7±5.0 (28)	2.6±3.3 (21)	2.7±4.3 (26)
Duration of previous HT use, yr	4.7±7.9	5.8±7.0	4.5±4.8
VO ₂ peak, L/min	1.76±0.25	1.78±0.36	1.69±0.25
Height, cm	164.0±6.2	163.2±8.1	163.2±6.9
Weight, kg	80.8±12.3	81.4±13.2	78.7±12.6
BMI, kg/m ²	30.0±4.1	30.6±4.7	29.7±4.5

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Table 2

Volume of exercise performed during the 6-month exercise-induced weight loss intervention in women randomized to placebo, raloxifene, or hormone therapy (HT) who completed the 6-month intervention.

	Treatment Group		
	Placebo n=29	Raloxifene n=34	HT n=35
Days per wk	3.1±1.0	3.3 ± 1.1	3.0 ± 1.0
Minutes per wk	157.8±68.4	166.4±64.0	153.7±55.9
Average heart rate (beats/min)	133.4 ± 12.3	134.2±12.9	132.7±10.8
Exercise energy expenditure (kcal/wk)	1219.2±703.1	1266.9±608.4	1214.2±537.5

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Table 3

Baseline (mean±SD) and comparison of change in 6-month (difference [95%CI]) body composition in postmenopausal women treated with placebo, raloxifene, or hormone therapy (HT) who completed the intervention.

	Baseline		Difference in change from Placebo		
	Placebo	Raloxifene	HT	Raloxifene	HT
Anthropometric, n	28	34	34	34	34
Waist, cm	90.8±13.0	92.5±10.4	90.9±12.4	-1.9 [-4.6, 0.8]	0.3 [-2.4, 3.0]
Hip, cm	111.4±10.1	112.9±10.7	110.4±9.5	-1.5 [-4.1, 1.0]	-0.8 [-3.4, 1.7]
Thigh, cm	56.5±5.7	56.6±5.8	56.1±5.2	-0.4 [-1.9, 1.1]	-0.0 [-1.5, 1.5]
DXA, n	29	34	35	34	35
Weight, kg	79.5±11.7	81.4±13.0	79.2±12.9	-0.7 [-2.4, 1.1]	-0.0 [-1.7, 1.7]
FFM, kg	44.0±5.3	45.4±5.9	44.9±5.2	-0.5 [-1.2, 0.2]	-0.1 [-0.8, 0.6]
FM, kg	35.5±8.0	36.0±9.2	34.3±8.5	-0.1 [-1.8, 1.6]	0.0 [-1.7, 1.7]
Trunk FM, kg	17.3±4.2	17.8±4.1	16.8±4.4	-0.0 [-1.0, 1.0]	0.1 [-0.9, 1.1]
Leg FM, kg	13.4±3.3	13.2±4.74	12.8±3.7	-0.1 [-0.7, 0.6]	-0.2 [-0.9, 0.4]
CT, n	28	27	30	27	30
AFA, cm ²	473±109	487±143	479±134	-13.6 [-41.3, 14.1]	-12.3 [-39.2, 14.7]
SFA, cm ²	355±91	361±117	344±97	-10.9 [-30.6, 8.8]	-10.0 [-29.2, 9.2]
VFA, cm ²	118±55	126±40	135±55	-2.3 [-13.3, 8.8]	-1.6 [-12.5, 9.2]

AFA, abdominal fat area; FM, fat mass; FFM, fat-free mass; SFA, subcutaneous fat area, VFA, visceral fat area.

Table 4

Baseline (mean±SD) and comparison of change in 6-month (difference [95%CI]) oral glucose tolerance test (OGTT) and lipid data in postmenopausal women treated with placebo, raloxifene, or hormone therapy (HT) who completed the intervention and OGTT visit.

	Baseline			Difference in change from Placebo		
	Placebo	Raloxifene	HT	HT	Raloxifene	HT
OGTT, n	27	33	33	33	33	33
GLU ₀ , mmol/L	5.0±0.5	5.2±1.4	5.3±0.7	5.3±0.7	-0.06 [-0.41, 0.30]	-0.40 [-0.76, -0.05]*
GLU ₁₂₀ , mmol/L	6.7±2.2	7.5±3.5	7.2±2.5	7.2±2.5	0.70 [-0.27, 1.66]	0.56 [-0.40, 1.52]
GLU _A , *10 ³	16.5±3.3	17.7±5.9	17.0±3.9	17.0±3.9	0.75 [-0.81, 2.30]	0.46 [-1.08, 2.01]
INS ₀ , pmol/L	58.5±24.4	60.7±32.6	73.3±38.0	73.3±38.0	-10.0 [-24.0, 3.0]	-3.4 [-16.6, 9.7]
INS ₁₂₀ , pmol/L	328±253	404±294	421±306	421±306	-36 [-233, 162]	86 [-111, 284]
INS _A , *10 ³	6.3±3.2	6.8±3.7	7.0±4.0	7.0±4.0	-0.23 [-1.90, 1.43]	0.59 [-1.07, 2.26]
INS _A * GLU _A , *10 ⁸	1.0±0.6	1.2±0.7	1.2±0.6	1.2±0.6	0.03 [-0.32, 0.37]	0.18 [-0.17, 0.53]
Lipid profile, n	27	33	33	33	33	33
Total C, mmol/L	5.34±0.89	5.13±0.76	5.08±0.71	5.08±0.71	-0.17 [-0.51, 0.16]	-0.14 [-0.48, 0.19]
TG, mmol/L	1.99±1.18	1.84±0.63	2.02±0.68	2.02±0.68	0.11 [-0.21, 0.43]	0.28 [-0.05, 0.60]
HDL-C, mmol/L	1.33±0.44	1.26±0.27	1.17±0.38	1.17±0.38	0.16 [0.06, 0.25]*	0.15 [0.05, 0.25]*
LDL-C, mmol/L	3.33±0.79	3.24±0.72	3.21±0.77	3.21±0.77	-0.34 [-0.65, -0.03]*	-0.37 [-0.68, -0.06]*

0 subscript, fasting (0 min); 120 subscript, post-glucose challenge (120 min); A, area under the curve; C, cholesterol; HDL, high density lipoprotein; INS, insulin; LDL, low density lipoprotein;

* p<0.05.

Table 5

Six-month change (mean±SD) oral glucose tolerance test (OGTT) and lipid data in postmenopausal women treated with placebo, raloxifene, or hormone therapy (HT) who completed the intervention and OGTT visit.

	6-month Change		
	Placebo	Raloxifene	HT
OGTT, n	27	33	33
GLU ₀ , mmol/L	0.03±0.52	-0.02±0.85	0.35±0.61 *
GLU ₁₂₀ , mmol/L	-0.50±2.13	-0.04±2.30	-0.09±1.74
GLU _A , *10 ³	-0.86±2.42	-0.26±3.65	-0.46±2.79
INS ₀ , pmol/L	-5.57±25.2	-16.5±26.2	-15.2±32.9
INS ₁₂₀ , pmol/L	-51.0±181.5	-79.8±233.9	43.5±567.3
INS _A , *10 ³	-0.92±2.24	-1.17±3.13	-0.35±3.89
INS _A * GLU _A , *10 ⁷	-2.16±4.12	-2.05±6.31	-0.52±8.60
Lipid profile, n	27	33	33
Total C, mmol/L	-0.14±0.85	-0.23±0.62	-0.18±0.68
TG, mmol/L	-0.26±0.47	-0.11±0.58	0.02±0.83
HDL-C, mmol/L	-0.09±0.27	0.09±0.17*	0.12±0.22*
LDL-C, mmol/L	0.03±0.74	-0.28±0.59*	-0.30±0.61*

0 subscript, fasting (0 min); 120 subscript, post-glucose challenge (120 min); A, area under the curve; C, cholesterol; GLU, glucose; HDL, high density lipoprotein; INS, insulin; LDL, low density lipoprotein;

* p<0.05, different from placebo.