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Body composition and bone mineral density after ovarian hormone suppression with or without estradiol treatment

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Abstract

Suppression of ovarian hormones in premenopausal women with gonadotropin releasing hormone agonist therapy ($GnRH_{AG}$) can cause fat mass (FM) gain and fat-free mass (FFM) loss. It is unknown if this is specifically due to the decline in serum estradiol (E_2).

Objective—To evaluate the effects of $GnRH_{AG}$ with add-back of placebo (PL) or E_2 on FM, FFM, and bone mineral density (BMD). An exploratory aim evaluated the effects of resistance exercise on body composition during the drug intervention.

Methods—Seventy healthy, premenopausal women underwent 5 months of $GnRH_{AG}$ and were randomized to add-back of transdermal E_2 ($GnRH_{AG}$+E_2, n=35) or placebo ($GnRH_{AG}$+PL, n=35). As part of an exploratory aim to evaluate whether exercise can minimize effects of hormone suppression, some women within each drug arm were randomized to a resistance exercise program ($GnRH_{AG}$+E_2+Ex, n=12; $GnRH_{AG}$+PL+Ex, n=12).

Results—The groups did not differ in age (mean±SD) (36±8yr, 35±9yr) or BMI (both 28±6kg/m^2). FFM declined in response to $GnRH_{AG}$+PL (mean; 95% CI) (−0.6kg; −1.0, −0.3) but not $GnRH_{AG}$+E_2 (0.3kg; −0.2, 0.8) or $GnRH_{AG}$+PL+Ex (0.1kg;−0.6, 0.7). Although FM did not change in either group, visceral fat area increased in response to $GnRH_{AG}$+PL but not $GnRH_{AG}$+E_2. $GnRH_{AG}$+PL caused decreased BMD at the lumbar spine and proximal femur that

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AUTHOR CONTRIBUTIONS

Study design: WK, JK, RS, SV. Study conduct and data collection: KS, EG, AS. Data analysis: PW. Data interpretation: WK, KS, EM, PW, KG. Drafting manuscript: KS, KG, WK. Revising manuscript content: WK, KS, EM, KG, MW, PW.

were prevented by E_2. Preliminary data suggest that exercise may have favorable effects on FM, FFM, and hip BMD.

Conclusions—Suppression of ovarian E_2 resulted in loss of bone and FFM and expansion of abdominal adipose depots. Failure of hormone suppression to increase total FM conflicted with previous studies of the effects of $GnRH_{AG}$. Further research is necessary to understand the role of estrogen in the regulation of energy balance and fat distribution.

Keywords

body composition; bone mineral density; fat mass; fat-free mass; resistance exercise; menopause

INTRODUCTION

Obesity is a major public health problem in the U.S. and in developed countries worldwide. Although there are many behavioral, environmental and biological factors that contribute to the development of obesity,[1] there is evidence that the loss of ovarian hormones increases the propensity for weight gain in women. For example, fat mass (FM) increases in response to ovarian hormone suppression in premenopausal women [2-6] and estrogen-based hormone therapy (HT) attenuates weight gain in postmenopausal women.[7-18] Ovarian hormone deficiency may also alter fat distribution, resulting in a disproportionate increase in abdominal adiposity.[2,6,7,12,13,15] Because accumulation of abdominal fat increases the risk of obesity-related diseases (i.e., type 2 diabetes mellitus, coronary artery disease, hypertension),[19] it is important to understand how the loss of gonadal function influences regional adiposity and whether this is specifically related to the decline in serum estradiol (E_2).

There are well-known adverse effects of E_2 deficiency on bone mineral density (BMD).[20,21] Less well known is whether E_2 deficiency triggers a decline in lean tissue other than bone, such as skeletal muscle. The suppression of ovarian function in premenopausal women has been observed to result in a decline in fat-free mass (FFM) in some studies,[2,3,5,6] but it is not clear whether this is specifically related to the decline in serum E_2 concentration.

Collectively, evidence suggests that the menopausal transition is associated with unfavorable changes in body composition that include an increase in FM, particularly in the abdominal region, and decreases in FFM and BMD. Because the menopause is inextricably associated with age, it is challenging to isolate the independent effects of age or menopause from those of sex hormone deficiency *per se* in observational studies and this underscores the need for controlled studies of the effects of sex hormones on body composition. In this context, the aim of the present study was to evaluate the effects of 5 months of ovarian hormone suppression (gonadotropin releasing hormone agonist; $GnRH_{AG}$) on body composition (i.e., FM, FFM, BMD) in healthy, premenopausal women. To evaluate the mechanistic role of E_2, women were randomized to $GnRH_{AG}$+placebo (PL) or $GnRH_{AG}$+E_2. Our hypothesis was that $GnRH_{AG}$+PL would increase FM and decrease FFM and BMD and that these changes would be attenuated by E_2 add back.

If ovarian hormone suppression does result in adverse changes in body composition and BMD, there is little knowledge as to whether such changes can be prevented by exercise training. Therefore, an exploratory aim was to determine if resistance exercise attenuates the effects of ovarian hormone suppression on body composition and BMD.

METHODS

This was a randomized controlled trial in which premenopausal women were randomized to undergo 5 months of $GnRH_{AG}$+PL or $GnRH_{AG}+E_2$. The study was approved by the Colorado Multiple Institutional Review Board (COMIRB) and all volunteers provided written informed consent to participate.

Study participants

Participants were healthy, premenopausal women aged 20 to 49 y with normal menstrual cycle function, defined as no missed cycles in the previous year and cycle length 28±5 days. Only non-smokers were enrolled. Volunteers were screened for eligibility through a review of medical and menstrual cycle history, physical examination, assessment of depressive symptoms, blood chemistries (metabolic panel, complete blood count), measurement of BMD, and a graded exercise test (GXT). Exclusion criteria included: use of hormonal contraception, oral glucocorticoids, or diabetes medications; history of cardiovascular, renal, or hepatobiliary disease; history of breast cancer, other estrogen-dependent neoplasms, or venous thromboembolic events; uncontrolled thyroid disease (ultrasensitive thyroid stimulating hormone <5 mU/L or >10 mU/L); uncontrolled hypertension (systolic >150 mmHg or diastolic >90 mmHg); symptoms of depression (CES-D score ≥16 or BDI-II score >18); lactation, pregnancy, or intent to become pregnant; renal (serum creatinine >1.3 mg/dL) or hepatic dysfunction (ALT, AST >1.5x upper limits of normal); hematocrit <33%; proximal femur or lumbar spine BMD T score <−2.0; body mass index >39 kg/m^2; and abnormal ECG responses to exercise, confirmed by follow-up evaluation by a cardiologist, that contraindicated vigorous exercise.

Intervention and procedures

Participants underwent baseline testing during days 2 to 6 of the menstrual cycle, although some women were tested later in the follicular phase due to scheduling challenges. $GnRH_{AG}$ therapy (leuprolide acetate 3.75 mg; TAP Pharmaceutical Products, Inc; Lake Forest, IL) was initiated at the beginning of the menstrual cycle; subsequent injections were delivered at 4-week intervals for 20 weeks. Absence of pregnancy was confirmed by a urine pregnancy test before each injection.

Participants were randomized to receive transdermal E_2 ($GnRH_{AG}+E_2$; Bayer HealthCare Pharmaceuticals, Berkeley, CA) 0.075 mg/d or placebo patches ($GnRH_{AG}$+PL). The E_2 regimen was expected to maintain serum E_2 concentration in the mid-follicular phase range. Some participants in each drug group were also randomized to progressive resistance exercise training ($GnRH_{AG}+E_2$+Ex, n=12; $GnRH_{AG}$+PL+Ex, n=12). The goal of this exploratory aspect of the study was to generate preliminary data on the effectiveness of

exercise to prevent changes in body composition and BMD during ovarian hormone suppression.

Exercise intervention

The progressive resistance exercise intervention included 4 d/wk of supervised exercise for 18 weeks (i.e., ended 2 weeks before the completion of the $GnRH_{AG}$ intervention), with 2 sessions per week focused on upper-body exercises (chest press, lat pulldown, overhead press, seated row, chin-ups/dips on a weight-assisted machine) and 2 on lower-body exercises (leg press, knee extension and flexion, hip abduction and adduction, squats on a Smith machine). Participants performed 3 sets of 12 repetitions of each exercise for the first 2 weeks at a light intensity to learn how to perform the exercises. Over weeks 3 to 6 the intensity was increased to ~70% of 1 repetition maximum (RM), such that muscle fatigue occurred in 8-12 repetitions. Thereafter, intensity was increased to ~80% of 1RM (5-8 repetitions per set).

Body composition and BMD

Body composition (total mass, FM, FFM) and total body, lumbar spine (L_1-L_4), and proximal femur (total hip, femoral neck, trochanter, subtrochanteric region) BMD were measured by DXA at baseline and week 18 of the intervention using a Hologic Discovery-W instrument (software v11.2, Waltham, MA). Regional FM and FFM (i.e., trunk and leg) measurements were obtained from the total body DXA scan. Intra-instrument CVs for scans completed on women <50 yr of age are: − 0.8% total mass, 2.6% FM, 1.1% FFM; 0.8% lumbar spine BMD, 0.9% total hip BMD, 1.9% femoral neck BMD, 1.1% trochanter BMD, and 0.99% subtrochanteric BMD. Scans in the current study were completed by two trained and experienced technicians and reviewed by one of the investigators to insure appropriate data acquisition and image analysis.

Axial CT images were obtained through the center of the L_2-L_3 and L_4-L_5 inter-vertebral disc spaces for measurement of abdominal fat areas and 20 cm superior to the distal edge of the lateral condyle of the right femur for measurement of thigh muscle and fat areas (120 kVp, 200-300 maS, and 10 mm slice thickness; General Electric instrument; Waukesha, WI). Images were analyzed by the technicians at the CT Scan Reading Center. Adipose tissue areas were determined using a CT intensity range (−190 to −20 Hounsfield units) that was defined by image-generated histograms of adipose and soft tissue regions. The visceral fat areas (cm^2) were manually outlined by tracing the muscles of the abdominal wall. Fat in the bowel was subtracted from the visceral fat area. The subcutaneous fat areas (cm^2) were calculated by subtracting the visceral and bowel fat areas from the total abdominal fat area. Thigh muscle area was separated from subcutaneous fat area by manually tracing along the deep fascial plane surrounding the muscles. Abdominal fat areas were averaged over the two abdominal slices and thigh muscle over the right and left thigh slices. Threshold for inclusion of repeat thigh scans was ±1 cm of baseline scan location. Analysis programs were developed by the University of Colorado CT Reading Center using IDL software (RSI, Inc., Boulder, CO) on a Sparc 20 workstation (Sun Microsystems, Sunnyvale, CA). Scans in the current study were completed by two trained and experienced technicians and reviewed by one of the investigators to insure appropriate data acquisition and image analysis.

Sex hormones

Blood samples for sex hormones were collected during baseline testing and during week 20 of the intervention. Collection samples were stored at −80°C until analysis. Estrone (E_1), E_2, and progesterone (P) were determined by radioimmunoassay (RIA, Diagnostic Systems Lab, Webster, TX). Respective intra-and inter-assay CVs were 8.7% and 8.6% for E_1, 6% and 11% for E_2, and 7.5% and 10.2% for P. Total testosterone (T) was analyzed by chemiluminescence immunoassay (Beckman Coulter, Inc. Fullerton, CA; 2.1% and 5.1%) and sex hormone-binding globulin (SHBG) by immunoradiometric assay (Diagnostic Systems Laboratory; 5.1% and 12%).

Statistical methods

The primary analysis compared the $GnRH_{AG}$+E_2 and $GnRH_{AG}$+PL groups, pooled across exercise status. It was acknowledged that the inclusion of exercisers could minimize the effects of $GnRH_{AG}$, but would be reflective of the effects of ovarian hormone suppression in sedentary and active women. Baseline differences in all variables between the $GnRH_{AG}$+E_2 and $GnRH_{AG}$+PL groups were evaluated using two-group *t* tests and changes within each group in response to intervention were evaluated with paired *t* tests. Differences in change over time between groups were tested using an ANCOVA model conditioned on baseline. The study was not powered to detect differences among the 4 treatment groups for the exploratory exercise intervention aim. Therefore, only descriptive statistics and within-group changes are presented. All analyses were done using SAS 9.2 (SAS Institute, Cary, NC). Data are reported as mean and 95% CI unless otherwise specified.

RESULTS

Seventy-nine women were randomized and 9 participants were lost to follow-up (personal reasons, 4; lack of time, 3; side effects of $GnRH_{AG}$, 1; uncontrolled hypertension; 1). Of the 70 women who completed the intervention, 35 were randomized to $GnRH_{AG}$+E_2 and 35 to $GnRH_{AG}$+PL. There were no significant differences in the characteristics of the drug groups at baseline (Table 1).

Sex hormones

There were significant decreases in serum E_1, E_2, P, T, and SHBG in response to $GnRH_{AG}$+PL. $GnRH_{AG}$+E_2 resulted in significant decreases in P and T, non-significant increases in E_1 and E_2, and no change in SHBG. The changes in E_1, E_2, and SHBG were significantly different between the groups (Table 2).

Body composition and BMD

There was a decline in FFM in response to $GnRH_{AG}$+PL that was significantly different from the gain in response to $GnRH_{AG}$+E_2; the loss was distributed across the trunk and leg regions (Table 3, Figure 1A). Thigh muscle area, as measured by CT, decreased after $GnRH_{AG}$+PL, but not $GnRH_{AG}$+E_2 (Figure 2). After adjustment for baseline value, there was a difference between the add-back groups in the change in thigh muscle area (−3.27 cm^2 (95% CI, −5.86, −0.68); p=0.01).

There were no significant changes in total FM in either drug group (Table 3, Figure 1A). However, there were significant increases in both subcutaneous and visceral abdominal fat areas by CT in the $GnRH_{AG}$+PL group but not in the $GnRH_{AG}+E_2$ group (Figure 2). Leg fat, as measured by DXA (Table 3, Figure 1A) and thigh fat as measured by CT (Figure 2), did not change (Figure 2). The decreases in spine and hip BMD in response to $GnRH_{AG}$+PL were significantly different (except at the subtrochanteric region) from the changes in response to $GnRH_{AG}+E_2$ (Table 3, Figure 3A).

Effects of resistance exercise training

FFM decreased in the $GnRH_{AG}$+PL+NoEx group, was preserved in the $GnRH_{AG}$+PL+Ex and $GnRH_{AG}+E_2$+NoEx groups, and increased non-significantly in the $GnRH_{AG}+E_2$+Ex group (Table 4, Figure 1B). There were no significant changes in FM in any of the groups, but FM tended to increase in non-exercisers and decrease in exercisers.

BMD decreased at all sites in the $GnRH_{AG}$+PL+NoEx group, but only at the lumbar spine in the $GnRH_{AG}$+PL+Ex group (Table 4, Figure 3B). BMD was preserved in all regions in both the $GnRH_{AG}+E_2$+NoEx and the $GnRH_{AG}+E_2$+Ex groups.

DISCUSSION

The primary aims of this study were to determine whether suppression of ovarian function with $GnRH_{AG}$ adversely affected body composition and BMD and whether changes were specifically related to the suppression of E_2. In support of our hypotheses, we observed that ovarian hormone suppression resulted in decreases in FFM and lumbar spine and proximal femur BMD that were prevented by E_2 add-back therapy. Unexpectedly, we did not find an increase in FM in response to $GnRH_{AG}$+PL, as has been observed by others,[2,3,5,6] but there was an increase in abdominal adiposity as measured by CT.

Effects of the drug intervention on FFM

To our knowledge, there have been 5 previous studies of the effects of $GnRH_{AG}$ therapy of at least 4 months in duration on body composition in premenopausal women.[2,3,5,6,22] Previous studies included women with uterine leiomyoma,[2,3,5,6,22] or endometriosis.[5] All of these studies found increases in FM and decreases in FFM although not all changes were statistically significant. The current study was the first to isolate the role of E_2 in mediating these changes in body composition by randomizing women to $GnRH_{AG}$+PL versus $GnRH_{AG}+E_2$.

The finding that ovarian hormone suppression caused a decrease in FFM was consistent with previous observations.[2,3,5,6] However, because none of the previous studies included E_2 add-back therapy, it was not clear whether the decline in FFM was related to the suppression of estrogens or androgens by $GnRH_{AG}$. In the current study, there were similar nonsignificant decreases in serum testosterone concentration in both the $GnRH_{AG}$+PL and $GnRH_{AG}+E_2$ groups, but FFM was decreased only in the former. This suggests that the loss of FFM in the $GnRH_{AG}$+PL group was mechanistically linked with the suppression of E_2, either through direct actions of E_2 on skeletal muscle or indirect effects of E_2 on other anabolic factors (e.g., insulin-like growth factor I). In laboratory animals, estrogens play a

key role in the maintenance of skeletal muscle mass and function.[23,24] There is also growing evidence that estrogen-based hormone therapy helps to preserve muscle mass, strength, and function in postmenopausal women.[23,25] Muscle mass, per se, was not measured in the current study, but the changes in thigh muscle area were consistent with the changes in FFM. These findings suggest that the loss of E_2 in women accelerates the loss of muscle mass. Importantly, the use of transdermal E_2 in the current study likely resulted in a smaller decrease in bioavailable androgens than if oral therapy had been used. Oral estrogens were found to increase SHBG and decrease free testosterone, whereas transdermal E_2 did not.[26] It is not clear whether oral estrogens would be as effective in preserving FFM as transdermal E_2. *Effects of the drug intervention on FM*

Multiple studies of premenopausal women treated with $GnRH_{AG}$ therapy found increases in FM.[2,3,5,6] In these studies, fat mass increased by 0.9 to 1.9 kg in response to 16 to 24 weeks of $GnRH_{AG}$ therapy. There was also a shift in fat distribution toward abdominal accumulation in response to ovarian hormone suppression, as evidenced by an increase in trunk-to-leg fat ratio after 4 months of $GnRH_{AG}$ therapy.[2,6] Based on the energy content of the fat gains in the four previous studies that involved 16 or 20 weeks of $GnRH_{AG}$ therapy,[2,3,5,6] the magnitude of disruption in energy balance was roughly equivalent to +90 to +130 kcal/d.

Suppression of gonadal hormones also promotes fat gain in men. In healthy men aged 20 to 50 years who underwent 16 weeks of $GnRH_{AG}$ and add-back placebo or testosterone therapy, with or without an aromatase inhibitor to block the conversion of testosterone to estrogens, FM increased in men on placebo add-back and this was exaggerated by aromatase inhibition.[27] These findings suggest that E_2 is mechanistically linked with the regulation of energy balance and fat gain in women and men. This is consistent with the observation that estrogen receptor alpha deficiency causes excess fat gain in both female and male mice.[28]

In the current study, we did not observe the increase in total FM that has been observed in other studies of gonadal hormone suppression.[2,3,5,6,22] A potential factor that may have contributed to the minimal fat gain in the current study was that the consenting process included a discussion of weight gain as a risk of the study. Thus, participants may have been sensitized to the possibility of weight gain and compensated by making behavioral changes. This may not have been the case in previous studies of the effects of $GnRH_{AG}$ therapy on body composition because they were observational studies of patients undergoing treatment for endometriosis[5] or uterine leiomyomas.[2,3,5,6,22] The exercise intervention in a subset of participants in the current study also attenuated the magnitude of fat gain. It was not clear whether the previous studies of the effects of $GnRH_{AG}$ therapy on body composition included active and/or sedentary women.

Despite the lack of change in FM in the current study, there were significant increases in both subcutaneous and visceral abdominal fat areas in the $GnRH_{AG}$+PL group but not in the $GnRH_{AG}$+E_2 group. This finding was consistent with the observation that abdominal fat areas, particularly visceral, increase dramatically during the menopausal transition.[29] It has been observed that the level of abdominal visceral adiposity in women aged 42 to 52 y is

linked more closely with androgens than estrogens,[30] but the current observations suggest that it is the loss of E_2 that triggers the expansion of abdominal fat depots in women.

Effects of the intervention on BMD

As expected, BMD decreased at most skeletal sites in the $GnRH_{AG}$+PL group and this was prevented by E_2. $GnRH_{AG}$ therapy has been observed to cause decreases in BMD of 4 to 5% at the lumbar spine after 6 months of treatment.[31-33] The severity of bone loss depends on the $GnRH_{AG}$ dose, length of treatment, and participant characteristics.[34] When duration of treatment is less than 6 months, the bone loss has been found to be reversible.[35-38]

Effects of the exercise intervention

Subsets of women in each drug treatment arm also underwent concurrent resistance training. The intent was to generate preliminary evidence regarding whether exercise can prevent or attenuate body composition changes that occur in response to ovarian hormone suppression. Because the study was not powered for between-group comparisons, only within-group changes were evaluated. The findings suggest that resistance exercise may be helpful in attenuating the decline in FFM that occurred in response to the suppression of ovarian hormones. Resistance exercise also appeared to mitigate at least some of the decline in BMD at the proximal femur, but not lumbar spine. These encouraging preliminary data suggest that regular exercise training may be particularly important during the menopausal transition to minimize bone loss and unfavorable changes in body composition.

A strength of this study was the randomized controlled design that provided robust experimental control over the sex hormone environment by using pharmacologic suppression of endogenous sex hormones (“medical menopause”) and add-back E_2 or placebo. The potential confounding effects of age were minimized by studying premenopausal women. However, the use of the “medical menopause” model was also a limitation of the study because it does not simulate all the aspects of “natural menopause” (e.g., more abrupt hormone withdrawal, suppression rather than elevation of gonadotropins). Other limitations were that potential effects of route of E_2 delivery (oral vs. transdermal), E_2 dose, or combined E_2+P add-back were not evaluated.

CONCLUSIONS

Large randomized controlled trials of the risks and benefits of HT in postmenopausal women[39-41] have increased awareness that benefits of HT may not outweigh the risks for some women. The current study demonstrated that the suppression of ovarian hormones in premenopausal women caused decreases in FFM and BMD and that these changes were specifically related to the suppression of E_2. Our preliminary data further suggests that resistance exercise may help to maintain FFM and BMD during ovarian hormone suppression, but further research will be needed to confirm this potential benefit. It is not clear whether the findings from this study of ovarian hormone suppression in premenopausal women reflect changes that occur in response to the natural menopause transition. Future studies using this methodologic approach should be carried out in women who are approaching menopause to determine if there is an independent effect of age.

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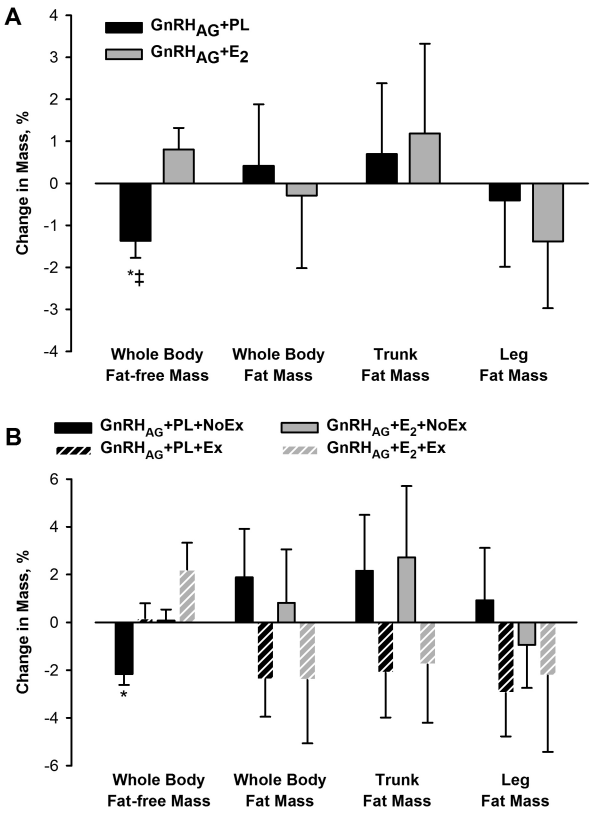

Figure 1.

Percent change from baseline in fat-free mass and fat mass measured by DXA in response to 5 months of $GnRH_{AG}$ therapy with placebo or estradiol treatment (Panel A) and resistance exercise training or no exercise (Panel B). * $p<0.05$, within-group change; ‡ $p<0.05$, between-group difference.

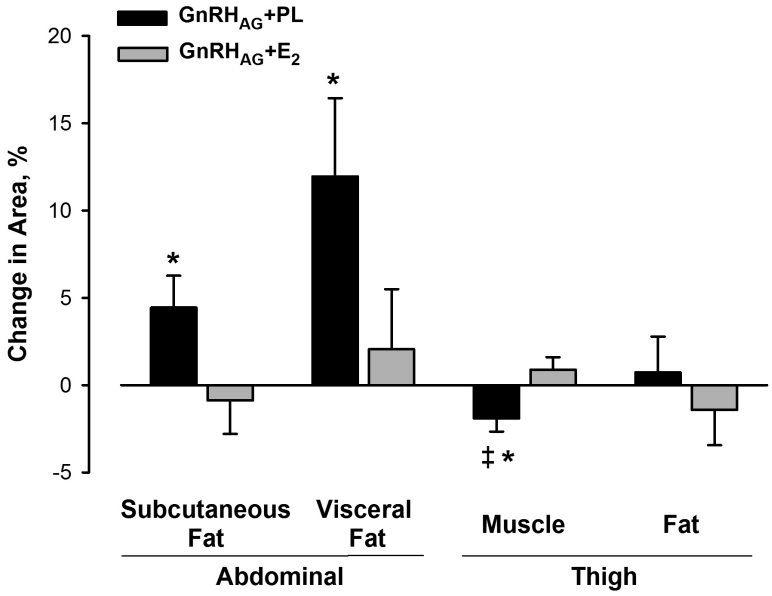

Figure 2.

Percent change in area of abdominal subcutaneous and visceral fat and thigh muscle and fat measured by CT in response to 5 months of $GnRH_{AG}$ therapy with placebo or estradiol treatment. * $p<0.05$, within-group change; ‡ $p<0.01$, between-group difference.

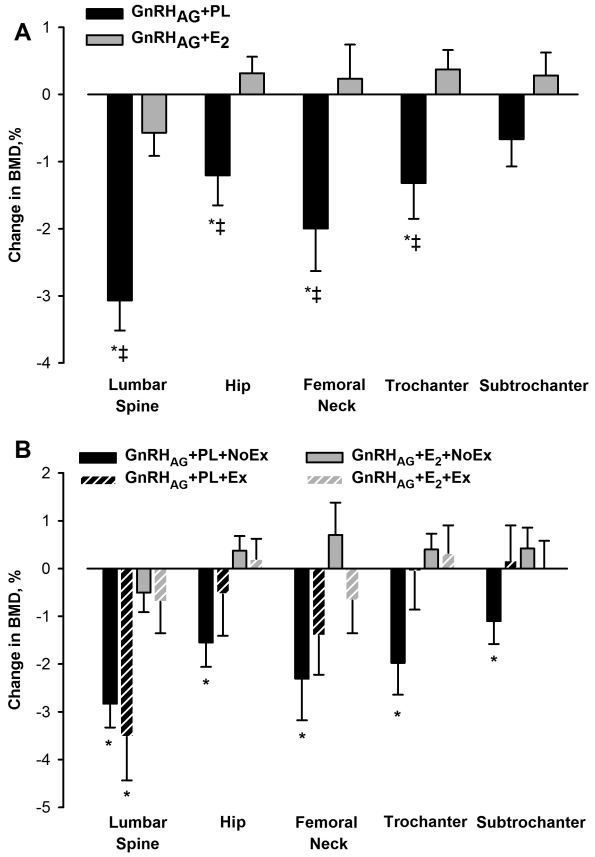

Figure 3.

Percent change from baseline in bone mineral density in response to 5 months of $GnRH_{AG}$ therapy with placebo or estradiol treatment (Panel A) and resistance exercise training or no exercise (Panel B). * $p < 0.05$, within-group change; ‡ $p < 0.05$, between-group difference.

Table 1

Baseline characteristics of participants randomized to gonadotropin releasing hormone agonist ($GnRH_{AG}$) therapy plus placebo (PL) or estradiol (E_2) treatment. Values are n (%) or mean ± SD.

	$GnRH_{AG}$+PL (n = 35)	**$GnRH_{AG}$+E_2 (n = 35)**	**p value**
Ethnicity			0.44
Hispanic or Latino	6 (17.1)	3 (8.6)	
Not Hispanic or Latino	27 (77.1)	31 (88.6)	
Unknown	2 (5.7)	1 (2.9)	
Race			0.06
White	24 (68.6)	25 (71.4)	
American Indian or Alaska Native	1 (2.9)	0 (0.0)	
Asian	2 (5.7)	0 (0.0)	
Black or African American	3 (8.6)	6 (17.1)	
Native Hawaiian or Pacific Islander	0 (0.0)	1 (2.9)	
More than one race	5 (14.3)	1 (2.9)	
Refused to answer	0 (0.0)	2 (5.7)	
Age (yr)	36 ± 8	35 ± 9	0.61
BMI (kg/m^2)	28 ± 6	28 ± 6	0.86
Body Composition (kg)			
Total mass	74.4 ± 15.8	76.6 ± 17.7	0.59
Fat mass	27.8 ± 11.1	28.2 ± 11.8	0.86
Fat-free mass	46.6 ± 6.2	48.3 ± 6.6	0.27
BMD (g/cm^2)			
Lumbar Spine	1.053 ± 0.109	1.083 ± 0.077	0.19
Total Hip	0.996 ± 0.117	0.984 ± 0.093	0.64
Femoral Neck	0.868 ± 0.107	0.871 ± 0.097	0.91
Trochanter	0.747 ± 0.105	0.738 ± 0.076	0.67
Subtrochanter	1.176 ± 0.142	1.157 ± 0.114	0.54
Serum Sex Hormones			
Estradiol (pg/mL)	85.8 ± 78.3	62.1 ± 45.5	0.17
Estrone (pg/mL)	56.7 ± 21.7	56.4 ± 18.5	0.95
Progesterone (ng/mL)	1.2 ± 1.6	0.8 ± 1.1	0.21
Testosterone (ng/dL)	32.1 ± 16.8	37.9 ± 13.2	0.19
SHBG (nmol/L)	49.2 ± 23.6	41.9 ± 16.3	0.18

Table 2

Serum sex hormone concentrations before and after 5 months of gonadotropin releasing hormone agonist plus placebo ($GnRH_{AG}$+PL) or estradiol ($GnRH_{AG}+E_2$) treatment. Values are mean (SEM or 95% CI).

	$GnRH_{AG}$+PL (n = 35)			$GnRH_{AG}+E_2$ (n = 35)			
	Before	**After**	**Within-group Change (95% CI)**	**Before**	**After**	**Within-group Change (95% CI)**	**Between-group Difference in Change[a] (95% CI)**
Estradiol, pg/mL	85.8 (14.3)	21.4 (1.5)	−64.4 (−94.1, −34.6)	62.1 (8.6)	93.6 (17.1)	32.1 (−8.7, 72.8)	−72.4 (−108, −37.0)
Estrone, pg/mL	56.7 (3.9)	37.0 (4.1)	−19.7 (−28.1, −11.4)	56.4 (3.4)	68.3 (6.1)	11.9 (−0.9, 24.7)	−31.5 (−45.3, −17.6)
Progesterone, ng/mL	1.2 (0.3)	0.3 (0.0)	−0.9 (−1.5, −0.3)	0.8 (0.2)	0.3 (0.0)	−0.5 (−0.9, −0.1)	0.0 (−0.1, 0.1)
Testosterone, ng/dL	32.1 (3.1)	27.1 (3.5)	−5.0 (−8.2, −1.8)	37.9 (2.8)	30.9 (2.6)	−7.0 (−10.5, −3.5)	1.3 (−3.3, 5.9)
SHBG, nmol/L	49.2 (4.2)	41.0 (3.8)	−8.2 (−12.9, −3.5)	41.9 (3.4)	43.1 (3.3)	1.2 (−3.4, 5.8)	−7.8 (−13.9, −1.7)

[a] Adjusted for baseline values

Table 3

Body composition and BMD before and after 5 months of gonadotropin releasing hormone agonist plus placebo ($GnRH_{AG}$+PL) or estradiol ($GnRH_{AG}$+E_2) treatment. Values are mean (SEM or 95% CI).

	$GnRH_{AG}$+PL (n = 35)			$GnRH_{AG}$+E_2 (n = 35)			
	Before	**After**	**Within-group Change (95% CI)**	**Before**	**After**	**Within-group Change (95% CI)**	**Between-group Difference in Change[a] (95% CI)**
Total mass (kg)	74.4 (2.7)	73.8 (2.7)	−0.6 (−1.3, 0.2)	76.6 (3.0)	76.9 (3.0)	0.3 (−0.9, 1.5)	−0.9 (−2.3, 0.5)
FFM (kg)	46.6 (1.0)	46.0 (1.0)	−0.6 (−1.0, −0.3)	48.3 (1.1)	48.7 (1.1)	0.3 (−0.2, 0.8)	−1.1 (−1.7,- 0.4)
Trunk FFM (kg)	23.3 (0.5)	23.0 (0.5)	−0.3 (−0.5, 0.0)	23.9 (0.6)	24.0 (0.5)	0.2 (−0.2, 0.5)	−0.5 (−0.9, −0.1)
Leg FFM (kg)	15.2 (0.5)	14.9 (0.4)	−0.3 (−0.5, −0.1)	16.1 (0.5)	16.2 (0.5)	0.1 (−0.1, 0.3)	−0.5 (−0.8, −0.2)
FM (kg)	27.8 (1.9)	27.8 (1.9)	0.1 (−0.6, 0.8)	28.2 (2.0)	28.2 (2.1)	0.0 (−1.0, 0.9)	0.1 (−1.1, 1.3)
Trunk FM (kg)	13.6 (1.0)	13.7 (1.1)	0.1 (−0.3, 0.5)	13.4 (1.1)	13.5 (1.1)	0.1 (−0.4, 0.7)	0.0 (−0.7, 0.6)
Leg FM (kg)	10.4 (0.7)	10.3 (0.7)	0.0 (−0.3, 0.2)	11.0 (0.8)	10.9 (0.8)	−0.1 (−0.5, 0.2)	0.1 (−0.4, 0.5)
BMD (g/cm^2)							
Lumbar spine	1.053 (0.018)	1.021 (0.019)	−0.032 (−0.041, −0.023)	1.083 (0.013)	1.076 (0.012)	−0.007 (−0.015, 0.001)	−0.026 (−0.038, −0.014)
Total hip	0.996 (0.020)	0.984 (0.020)	−0.012 (−0.022, −0.003)	0.984 (0.016)	0.988 (0.016)	0.003 (0.002, 0.008)	−0.015 (−0.026, −0.005)
Femoral neck	0.868 (0.018)	0.850 (0.018)	−0.018 (−0.030, −.0006)	0.871 (0.016)	0.873 (0.017)	0.002 (−0.007, 0.011)	−0.020 (−0.035, −0.005)
Trochanter	0.747 (0.018)	0.738 (0.018)	−0.009 (−0.018, −0.001)	0.738 (0.013)	0.741 (0.014)	0.003 (0.002, 0.008)	−0.013 (−0.022, −0.003)
Subtrochanter	1.176 (0.024)	1.168 (0.024)	−0.008 (−0.019, 0.002)	1.157 (0.019)	1.160 (0.019)	0.003 (−0.005, 0.011)	−0.011 (−0.024, 0.002)

[a] Adjusted for baseline values; fat-free mass (FFM), fat mass (FM), bone mineral density (BMD)

Table 4

Changes in body composition and BMD in response to 5 months of gonadotropin releasing hormone agonist plus placebo ($GnRH_{AG}$+PL) or estradiol ($GnRH_{AG}$+E_2) treatment and resistance exercise training or no exercise. Values are mean (95% CI).

	$GnRH_{AG}$+PL		**$GnRH_{AG}$+E_2**	
	No Exercise n = 23	**Exercise n = 12**	**No Exercise n = 23**	**Exercise n = 12**
Total Mass (kg)	−0.6 (−1.6, 0.4)	−0.5 (−2.0, 0.9)	0.4 (−0.7, 1.4)	0.1 (−2.9, 3.2)
FFM (kg)	−1.0 (−1.5, −0.6)	0.1 (−0.6, 0.7)	−0.0 (−0.5, 0.4)	1.0 (−0.3, 2.2)
Trunk FFM (kg)	−0.5 (−0.8, −0.2)	0.2 (−0.2, 0.7)	0.1 (−0.2, 0.4)	0.2 (−0.7, 1.2)
Leg FFM (kg)	−0.4 (−0.7, −0.2)	−0.1 (−0.4, 0.3)	−0.0 (−0.3, 0.2)	0.4 (0.1, 0.8)
FM (kg)	0.5 (−0.5, 1.4)	−0.6 (−1.7, 0.5)	0.4 (−0.7, 1.5)	−0.8 (−2.9, 1.2)
Trunk FM (kg)	0.3 (−0.2, 0.8)	−0.3 (−0.9, 0.3)	0.4 (−0.3, 1.1)	−0.4 (−1.4, 0.7)
Leg FM (kg)	0.1 (−0.3, 0.5)	−0.3 (−0.7, 0.2)	0.0 (−0.3, 0.4)	−0.4 (−1.3, 0.5)
BMD (g/cm^2)				
Lumbar spine	−0.029 (−0.039, −0.019)	−0.037 (−0.058, −0.016)	−0.006 (−0.015, 0.004)	−0.008 (−0.024, 0.008)
Total hip	−0.015 (−0.026, −0.005)	−0.006 (−0.026, 0.014)	0.004 (−0.003, 0.010)	0.002 (−0.007, 0.011)
Femoral neck	−0.021 (−0.038, −0.004)	−0.012 (−0.027, 0.003)	0.006 (−0.006, 0.019)	−0.006 (−0.018, 0.006)
Trochanter	−0.014 (−0.024, −0.004)	−0.000 (−0.015, 0.014)	0.003 (−0.002, 0.008)	0.003 (−0.007, 0.013)
Subtrochanter	−0.013 (−0.026, −0.001)	0.001 (−0.019, 0.021)	0.005 (−0.006, 0.015)	0.000 (−0.014, 0.014)

Fat-free mass (FFM), fat mass (FM), bone mineral density (BMD)