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Age-and menopause-related differences in subcutaneous adipose tissue estrogen receptor mRNA expression

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Abstract

Objectives—Changes in estrogen receptor (ER) expression likely underlie differential metabolic effects of estrogen in pre-and postmenopausal women. The aim of the current study was to determine whether ER gene expression in abdominal and femoral subcutaneous adipose tissue (SAT) was associated with age, menopause, or regional adiposity.

Methods—We studied pre-and post-menopausal (n=23 and 22, respectively; age 35–65 y) normal weight (mean±SD; BMI 23.7±2.5 kg/m^2) women with similar total fat mass. Abdominal and femoral SAT ERα *(ESR1)* and ERβ *(ESR2)* mRNA expression was determined by qPCR.

Results—Total fat mass did not differ between pre-and postmenopausal women (22.7±5.3 vs. 21.7±5.3 kg). Compared to premenopausal women, *ESR1* and the ratio of *ESR1* to *ESR2* were lower ($p \leq 0.05$) in postmenopausal abdominal and femoral SAT. *ESR1* and *ESR1:ESR2* were inversely associated with age in abdominal SAT ($r=-0.380$ and $r=-0.463$, respectively; $p<0.05$) and femoral SAT ($r=-0.353$ and $r=-0.472$, respectively; $p<0.05$). *ESR2* was not related to age or menopause. The inverse association between *ESR1* and age persisted after adjusting for trunk fat mass, estradiol, or leptin.

Conclusion—Among healthy pre-and postmenopausal women, increased age was associated with a decreased balance of ERα to ERβ in abdominal and femoral subcutaneous adipose tissue.

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None of the authors have any competing interests.

Keywords

Aging; menopause; adipose tissue; estrogen receptor gene expression

Introduction

The majority of women spend more than a third of their life postmenopausal. Aging in women typically leads to adverse changes in regional adiposity (i.e., increasing abdominal and decreasing femoral fat mass) and increased cardiometabolic risk [1]. The extent to which the age-related changes in adiposity and cardiometabolic risk in women are mediated by the loss of endogenous estrogens remains elusive. Estrogens exert their biological effects through two estrogen receptor (ER) isoforms: ERα and ERβ [2–4]. Both ER subtypes appear to be present in most, if not all, tissues in the body, with different tissues displaying varying degrees of relative expression [5]. Gene expression of ERα *(ESR1)* is reportedly higher than ERβ *(ESR2)* in subcutaneous adipose tissue (SAT) [2]. Studies of ER receptors in tissues other than SAT suggest there may be declines in ER expression with increasing age [4], but age-related reductions in ER have not yet been reported in human SAT. In fact, one study reported higher, not lower, abdominal SAT ERβ expression in postmenopausal compared to premenopausal women [6]. Such menopause-related differences in ER expression could be the result of aging, estrogen deficiency, or changes in body fat distribution, but to our knowledge this has not yet been studied. Age-or menopause-related changes in ERs could have profound effects on estrogen physiology and the progression of metabolic syndrome [1]. ERα and ERβ have distinct, often opposing, actions suggesting the relative proportions of ERα and ERβ are important to the tissue-specific response to estrogen [2, 5]. Globally knocking out *ESR1* in rodents promotes fat accumulation and metabolic impairments (e.g., insulin resistance, glucose intolerance) whereas knocking out *ESR2* has none of these effects [3]. On the other hand, knocking out *ESR1* specifically from adipocytes does not invoke the same metabolic impairments as seen in global knockouts, but results in adverse changes in adipose tissue function (e.g., inflammation, fibrosis); in the absence of *ESR1, ESR2* plays a protective role [7]. Such preclinical observations highlight the importance of studying the relative balance of ERα and ERβ in specific tissues and across the lifespan in women. The aims of the current study were to: 1) compare abdominal and femoral SAT *ESR1* and *ESR2* expression in pre-and postmenopausal women, and 2) determine the independent contribution of age and regional adiposity.

Experimental

Participants

We retrospectively analyzed baseline tissue samples collected in healthy non-obese (BMI<30kg/m^2) premenopausal (n=23, age 35–50y, regular menstrual cycles; 28±3d and early follicular follicle-stimulating hormone [FSH] 5–25 IU/L) and postmenopausal (n=22, age 48–60y, no menses ≥ 6mo or, if hysterectomized, FSH >30 IU/L) women previously enrolled in a study conducted by our laboratory [8]. None of the women used any type of oral contraceptive or postmenopausal hormone treatment. All participants provided written

informed consent to participate in the study, which was approved by the Colorado Multiple Institutional Review Board.

Body composition

Total, trunk, and leg fat mass and fat-free mass were measured by dual-energy X-ray absorptiometry (DXA, Hologic Delphi-W, software v11.2, Hologic, Inc., Bedford, MA), using manufacturer's recommendations to define the trunk and leg regions. Abdominal subcutaneous (SFA) and visceral (VFA) fat areas, femoral SFA and intramuscular fat area (IMFA) were determined by computed tomography as previously described [9].

Adipose Tissue Biopsies

Aspiration biopsies of abdominal and femoral SAT were collected in the fasted state using a mini-liposuction technique as previously described [10]. Collected adipose tissue was separated from the fluid and immediately flash frozen in liquid N_2.

Quantification of Estrogen Receptor mRNA by Quantitative PCR (qPCR

Total RNA was isolated with the QIAGEN RNeasy (Lipid) Tissue Mini Kit (Qiagen, Inc., Valencia, CA). qPCR analysis was done as follows: 1) total RNA was analyzed and quantitated (Experion System, Bio-Rad, Hercules, CA); 2) 100 ng total RNA was reverse transcribed (iScript cDNA synthesis kit, Bio-Rad); 3) qPCR was performed in duplicate (primers: *ESR1* 5′AGATCTTCGACATGCTGCTGGCTA, 3′AGACTTCAGGGTGCTGGACAGAAA; *ESR2* 5′TTGGTTTGGGTGATTGCCAAGAGC, 3′ATGTTGAGCAGATGTTCCATGCCC; *RPL13A* 5′CCTGGAGGAGAAGAGGAAAGAGA, 3′TTGAGGACCTCTGTGTATTTGTCAA; iQ SYBR Supermix, Bio-Rad) following manufacturer's protocol on an iQ5 Real-Time PCR Detection System (Bio-Rad) along with a no-template control per gene. *RPL13A* was used as an endogenous control; and RNA expression is expressed as $2^{\Delta CT}$ (ΔCT = RPL13A CT -gene of interest CT). Validation experiments confirmed that efficiencies of target and reference genes were approximately equal.

Bloodwork

Fasting serum samples were stored at −80°C and analyzed in batch. Leptin was assayed by radioimmunoassay (EMD Millipore, Corp., Billerica, MA), and estradiol (E_2) by chemiluminescence (Beckman Coulter, Inc., Indianapolis, IN).

Data analysis

Pearson correlations were used to evaluate the associations among measures of ER, age, total and regional adiposity. Partial correlations tested whether the associations of ER with age remained after controlling for potential confounding variables (adiposity, E_2, leptin). All statistical analyses were performed using SPSS software (IBM SPSS Statistics version 21.0). Data are presented as mean ± SD unless otherwise specified. Level of significance was set at $p<0.05$.

Results

Participant characteristics

Postmenopausal women were 13 years older than premenopausal women, and 7 years past menopause in average (Table 1). Participants were normal body weight (BMI 23.7±2.5 kg/m^2). Total adiposity (i.e. %fat) was similar between pre-and postmenopausal women. Although total and trunk fat mass did not differ, postmenopausal women had less leg fat mass and fat free mass than premenopausal women. Abdominal SFA and VFA did not differ between groups, but femoral SFA was lower in postmenopausal compared to premenopausal women (Table 1).

Menopause-related differences

Postmenopausal women had lower *ESR1* expression than premenopausal women in abdominal SAT (0.96±0.58 vs. 1.58±1.17, $p<0.05$) and femoral SAT (0.97±0.49 vs. 1.44±0.98, $p=0.05$; Figure 1). *ESR2* did not differ between pre-and postmenopausal women in either abdominal SAT (1.17±0.70 vs. 1.22±0.64) or femoral SAT (1.09±0.68 vs. 1.25±0.71). Postmenopausal women had lower ratio of *ESR1:ESR2* than premenopausal women in both abdominal SAT (0.89±0.55 vs. 1.47±0.71, $p<0.01$) and femoral SAT (0.87±0.37 vs. 1.143±0.85, $p<0.01$; Figure 1).

Regional adipose tissue differences

Measures of abdominal adiposity (i.e., trunk fat mass and abdominal VFA) were weakly inversely related to *ESR1* and *ESR1:ESR2* in abdominal and femoral SAT ($r=-0.23$ to -0.27, $p\leq0.15$), but this did not reach statistical significance (Table 2). Measures of femoral adiposity (i.e., leg fat mass and femoral SFA) were not related to gene expression in either abdominal or femoral SAT. Serum E_2 was positively associated with the ratio of *ESR1:ESR2* in femoral SAT ($r=0.496$, $p<0.01$) but not abdominal SAT ($r=0.258$, $p=0.15$). Leptin, which was highly correlated with all measures of adiposity (data not shown), was inversely related to *ESR1* in femoral SAT (-0.294, $p<0.05$; Table 2).

Age-related differences

Among all women *ESR1* and *ESR1:ESR2*, but not *ESR2*, were inversely associated with age in abdominal and femoral SAT (Table 2). In this cohort, age was inversely correlated with serum E_2 ($r=-0.496$, $p<0.001$), fat free mass ($r=-0.475$, $p<0.01$), and positively correlated with abdominal VFA ($r=0.301$, $p<0.05$; data not shown). The inverse association of *ESR1* and *ESR1:ESR2* with age remained after adjusting for trunk fat mass, but was no longer significant in femoral SAT after accounting for variability in E_2 (Table 2). While leptin was not correlated with age or E_2 in this cohort (data not shown), the inverse associations of *ESR1* and *ESR1:ESR2* with age were strengthened after adjusting for leptin (Table 2).

Discussion

The primary new finding of the study was that there were menopause-and age-related differences in mRNA expression of ERα and ERα:ERβ, but not ERβ, in abdominal and femoral SAT. The inverse association of ERα and ERα:ERβ with age were independent of t

otal and regional adiposity. Serum E_2 was lower with increasing age in this cohort, but this did not appear to account for the lower ERα and ERα:ERβ with age.

Important role of ERα:ERβ

The relative expression of ERα and ERβ in adipose tissue has significant clinical relevance to women's health via their regulation of adipose tissue distribution and function [1]. Presumably, maintenance of metabolically healthy SAT along with an adequate balance of ERs allows for efficient storage of potentially toxic lipids away from other important insulin-sensitive organs (i.e. skeletal muscle or liver). Alterations of ERα and ERβ in adipose tissue appears to affect adipose tissue inflammation and fibrosis irrespective of circulating E_2 [7] with broad implications for the development of cardiometabolic disease [11, 12]. Thus, determining whether adipose tissue ER expression changes with aging or menopause (i.e., estrogen deficiency) in women is essential to: 1) understanding the progression of cardiometabolic risk after menopause; and 2) the development of safe and effective estrogen-based hormone therapies to attenuate risk.

It has been more than two decades since ERs were identified in human SAT [13], yet little is known about how expression of ERs changes with age or hormone exposure. Both ERα and ERβ are present in SAT in men and women, and while there do not appear to be sex differences in the expression of ERα, ERβ expression is higher in women than men [2]. ERα appears to regulate SAT homeostasis via growth and proliferation of adipocytes, whereas ERβ appears to regulate the sex-specific distribution of SAT [14]. While ERα expression is typically higher than ERβ, ERβ modulates ERα, and thus cellular estrogen sensitivity, highlighting the importance of ERα:ERβ [15].

Age-or menopause-related changes in ER expression

Studies assessing SAT ER expression across menopause are limited and data are conflicting. One study observed no menopause-or age-related difference in gene expression of either ER isoform in abdominal SAT from Korean women, nor any correlations between ER expression and anthropometric measures [16]. Others found an increase in abdominal SAT ERβ, but not ERα, with menopause, resulting in similar changes in ERα:ERβ observed in our study [6]. Discrepancies among studies may be complicated by racial differences in adipose tissue or hormone changes across menopause [17, 18]. We are the first to observe an age-related difference in gene expression for ERα and ERα:ERβ in human SAT from pre- and postmenopausal women not using any type of hormone therapy. Consistent with this, a study in rodents revealed a robust up-regulation of ERβ expression with age, regardless of estrogen status induced by ovariectomy [19]. However, the older rats were fatter than the young rats, making it difficult to separate the effects of chronological age from increased adiposity. It is generally believed that an increased fat mass might help to maintain local tissue production of estrogens due to aromatization of androgens [20]. Though evidence for this has yet to be demonstrated in human subcutaneous adipose tissue, elevated local estrogen production could in theory preserve or change ER in adipose tissue with aging. In the present study, pre-and postmenopausal women were similar in total adiposity, minimizing this potential confounding effect. Nevertheless, we evaluated whether regional adiposity was a predictor of estrogen receptor gene expression.

Relative expression of ER among adipose tissue depots

ER gene expression and protein content may differ across various SAT depots, but the data are mixed. One study reported no difference in gene expression for ERα, but lower ERβ, in abdominal compared to gluteal SAT from overweight premenopausal women [21]. Whereas another reported higher ERaα and lower ERβ protein in abdominal compared to gluteal SAT from overweight and obese premenopausal women [5]. In both reports, the balance of ERα:ERβ was higher in the abdominal compared to gluteal SAT depot. In contrast, the present study suggested no difference in ERα:ERβ between abdominal and gluteal SAT depot (p=0.86; data not shown). Our data are partially supported by an *in vitro* study [2] reporting that the gene expression for ERα and ERβ did not differ in mature adipocytes collected from abdominal subcutaneous and visceral adipose tissue. Ad ditional human studies are needed to confirm whether there are depot-specific differences in ER expression or the balance of ERα:ERβ.

Leptin and ER expression with age

Leptin is produced by adipocytes in response to AT expansion. Estrogen modulates leptin production and sensitivity to other organs in rodents and humans [22, 23]. Adjusting for leptin strengthened our observed inverse associations of ERα and ERα:ERβ with age, suggesting there may be bidirectional communication between leptin and ER in human SAT. This is partially supported by in vitro studies suggesting that stimulation of ERα increases leptin production, while stimulation of ERβ decreases it, in 3T3-L1 mature adipocytes [24]. Future studies are needed to further investigate the impact of circulating leptin on adipose tissue ER.

Study limitations

There are some limitations to the study that should be considered. First, the participants recruited in the study were non-obese and both groups had a similar BMI and adiposity. Increases in adiposity often occur with menopause; thus our outcomes may not be generalizable to women who become obese during the menopause transition. However, studying non-obese pre-and postmenopausal women matched for adiposity allowed us to investigate the effect of menopause and age independent of increased adiposity. Second, we did not collect muscle in this study. Although we recruited pre-and post-menopausal women having a similar adiposity, fat-free mass was lower in postmenopausal women. Future studies are needed to determine whether this loss of lean mass is accompanied by changes in muscle ER expression with age or menopause. Third, the present study only assessed gene expression. It will be important to measure protein content to further interrogate changes in ERs with age and menopause. Fourth, the present study used whole adipose tissues for mRNA analysis. There is a possibility that the cellular composition of the tissue (i.e. the proportion of adipocytes and stromal cells) varied by age or menopausal status, which may have influenced our results. Fifth, there may be differences in the association between ER and adipo sity within the pre-and postmenopausal groups that cannot be evaluated due to the limited sample size; larger studies are warranted. Lastly, postmenopausal women in the current study were relatively early postmenopausal (~7 years since menopause on average). Future studies should include women who are more years past menopause to investigate

whether duration of estrogen deficiency (i.e. time since menopause) further contributes to age-related declines in ER expression.

Conclusion

Among pre-and post-menopausal women, increasing age was associated with decreasing gene expression for ERα and ERα:ERβ in abdominal and femoral subcutaneous adipose tissue. This inverse correlation between ER and age was independent of adiposity and serum estradiol.

Acknowledgments

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Highlights

- Menopause-related decrease in mRNA expression of ERα and ERα:ERβ in adipose tissue
- Increasing age was associated with decreasing gene expression for ERα and ERα:ERβ
- Inverse correlation between ER and age independent of adiposity and serum estradiol

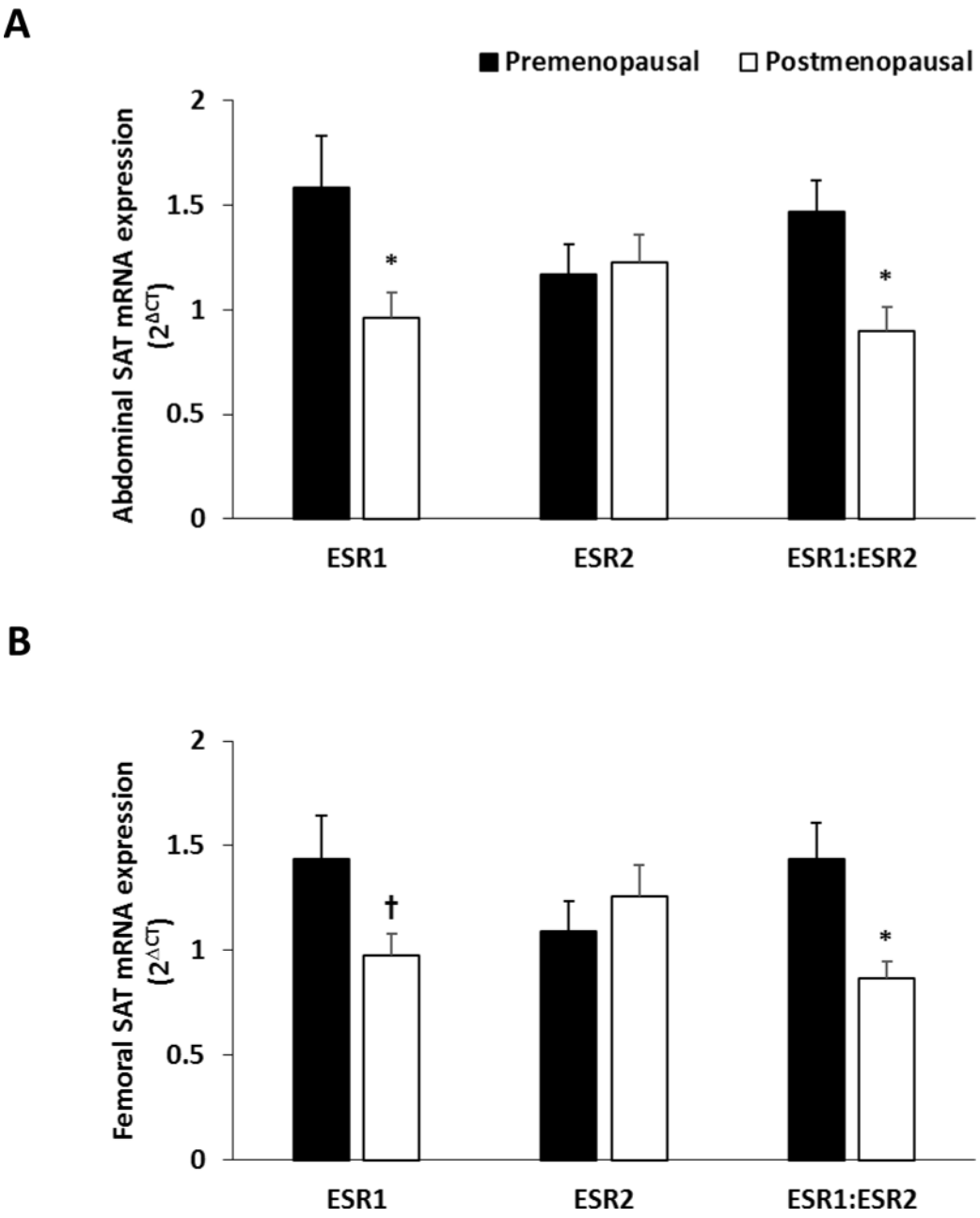

Figure 1.

Relative mRNA expression of estrogen receptor (ER). Panel A: mRNA expression of ESR1 (ERα), ERβ (ESR2), and the balance of ESR1:ESR2 in abdominal subcutaneous adipose tissue (SAT); Panel B: mRNA expression of ESR1, ESR2, and the balance of ESR1:ESR2 in femoral SAT from premenopausal (n=23) and postmenopausal (n=22) women. * $p<0.05$, † $p=0.05$ for pre-vs post-menopausal women.

Table 1

Participant Characteristics

	Premenopausal n=23	Postmenopausal n=22
Age (yr)	42 ± 4	55 ± 4 *
Years since menopause	n/a	7 ± 6
Weight (kg)	67.6 ± 8.4	62.1 ± 8.2
BMI (kg/m^2)	24.2 ± 2.5	23.3 ± 2.4
%fat	33.3 ± 4.8	34.5 ± 5.2
Total Fat Mass (kg)	22.7 ± 5.3	21.7 ± 5.3
Trunk Fat Mass (kg)	9.2 ± 2.6	9.7 ± 3.5
Leg Fat Mass (kg)	10.4 ± 2.5	8.8 ± 1.7 *
Fat-free mass (kg)	44.9 ± 4.6	40.5 ± 4.7 *
VFA	41 ± 25	58 ± 41
Abdominal SFA (cm^2)	229 ± 62	221 ± 71
Femoral SFA (cm^2)	212 ± 58	173 ± 40 *
Femoral IMFA (cm^2)	17 ± 9	15 ± 6
Estradiol (pg/mL)	91 ± 76	13 ± 6
Leptin (ng/mL)	13 ± 6	12 ± 8

* $p<0.05$; mean±SD; VFA = visceral fat area;

SFA = subcutaneous fat area, IMFA = intra-muscular fat area.

Table 2

Correlations of abdominal and femoral subcutaneous adipose tissue estrogen receptor alpha (ESR1) and estrogen receptor beta (ESR2) mRNA expression with age, fat mass, serum estradiol and leptin among pre-and postmenopausal women.

	ESR1		ESR2		ESR1:ESR2	
	Abdominal	**Femoral**	**Abdominal**	**Femoral**	**Abdominal**	**Femoral**
Pearson Correlations						
Age	**−0.380** *	**−0.353** *	0.014	0.137	**−0.463** **	**−0.472** **
%fat	−0.291 †	−0.219 †	−0.028	−0.053	**−0.359** *	−0.211 †
Total fat mass	−0.178	−0.160	−0.139	−0.061	−0.127	−0.156
Trunk fat mass	−0.270 †	−0.256 †	−0.162	−0.048	−0.247 †	−0.264 †
Leg fat mass	−0.007	−0.004	−0.078	−0.078	0.082	−0.029
VFA	−0.233 †	−0.248 †	−0.129	−0.055	−0.224	−0.229 †
Abdominal SFA	−0.155	−0.179	−0.038	−0.032	−0.296 †	−0.250 †
Femoral SFA	0.022	0.030	0.130	−0.038	−0.071	0.042
Serum E_2	0.155	0.148	−0.011	−0.123	0.258 †	**0.496** **
Serum Leptin	−0.248 †	**−0.294** *	−0.215	−0.082	−0.130	−0.218 †
Partial Correlations						
Age (adjusted for %fat)	**−0.336** *	**−0.320** *	−0.021	0.152	**−0.417** **	**−0.446** **
Age (adjusted for E_2)	**−0.361** *	**−0.327** *	0.010	0.085	**−0.398** *	−0.285 +
Age (adjusted for leptin)	**−0.417** **	**−0.405** **	−0.005	0.129	**−0.480** **	**−0.511** **

* p≤0.05;

** p≤0.01;

† p≤0.15;

VFA = visceral fat area; SFA = subcutaneous fat area; E_2 = estradiol.