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Longitudinal changes in abdominal fat distribution with menopause

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Abstract

Increases in abdominal fat have been reported with menopause, but the impact of menopause on abdominal fat distribution (visceral vs subcutaneous) is still unclear. The objective of the study was to determine if abdominal fat content (volume) or distribution is altered with menopause. Magnetic resonance imaging was used to quantify total abdominal, subcutaneous, and visceral fat in 8 healthy women, both in the premenopausal state and 8 years later in the postmenopausal state. Physical activity (PA) and blood lipids were also measured. Body weight and waist circumference did not change with menopause (pre- vs postmenopause: body weight, 63.2 ± 3.1 vs 63.9 ± 2.5 kg; waist circumference, 92.1 ± 4.6 vs 93.4 ± 3.7 cm); however, total abdominal fat, subcutaneous fat, and visceral fat all significantly ($P < .05$) increased with menopause (pre- vs postmenopause: total, 27 154 ± 4268 vs 34 717 ± 3272 cm^3; subcutaneous, 19 981 ± 3203 vs 24 918 ± 2521 cm^3; visceral, 7173 ± 1611 vs 9798 ± 1644 cm^3). Although absolute adiposity changed with menopause, relative fat distribution was not significantly different after menopause (pre- vs postmenopause: subcutaneous, 73% ± 3% vs 71% ± 3%; visceral, 26% ± 3% vs 28% ± 3%). Lean mass, fat mass, and PA, along with total cholesterol and triglyceride levels, did not change with menopause. High-density lipoprotein and low-density lipoprotein both increased ($P < .05$), and the ratio of total cholesterol to high-density lipoprotein decreased ($P < .05$) with menopause. As measured longitudinally with magnetic resonance imaging, total abdominal fat content increased with menopause despite no change in PA, body weight, or waist circumference; however, menopause did not affect the relative abdominal fat distribution in these women.

1. Introduction

Abdominal obesity is a well-accepted risk factor for cardiovascular and metabolic diseases [1-4]. Research has revealed that regional distribution of fat in the visceral abdominal region increases the risk for hypertension, diabetes, cardiovascular disease, etc, culminating in metabolic syndrome when compared with abdominal fat stored in the subcutaneous region [1,2,5]. Past literature has suggested that body fat shifts from peripheral stores to abdominal stores with aging [6]; and it is speculated that more fat becomes deposited in the visceral depot, thereby increasing the aforementioned health risks.

With menopause, an increase in abdominal fat accumulation has been reported to occur. Using dual-energy x-ray absorptiometry (DEXA) scans, both Ley et al [7] and Tremollieares et al [8] found that postmenopausal women had greater proportion of andriod fat when compared with premenopausal women in cross-sectional design studies. Likewise, in a 1-year longitudinal study, using waist to hip ratio, Reubinoff et al [9] reported a significant shift from gynoid to andriod fat distribution after 1 year in early postmenopausal women. These studies, however, could not determine if changes in abdominal fat distribution occurred in the visceral and subcutaneous abdominal depot because of the techniques used. Several cross-sectional investigations have compared premenopausal to postmenopausal women using computed tomography (CT) and have reported an increase in *absolute* visceral abdominal fat in the postmenopausal women [5,10,11], whereas others have found an increase in *relative* visceral abdominal fat in postmenopausal women [5,10,12]. Only 1 longitudinal study has investigated the change in abdominal fat distribution with menopause. Lovejoy et al [13] reported an increase in absolute visceral abdomenal fat with menopause, using single-slice CT. However, because CT scanning results in radiation exposure, typically only 1 abdominal slice is obtained; and this 1 slice

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is assumed to represent the entire abdomen of the individual [5,10,11]. It has previously been shown that fat deposition is not equal across the entire abdomen and that a single slice undersamples the whole abdominal area [14,15]. Although the study by Lovejoy et al [13] is strong because of the large subject population, a weakness is the single-slice CT.

In contrast, using a cross-sectional design and magnetic resonance imaging (MRI), we found that there was no difference in the absolute amount of visceral abdominal fat in pre- and postmenopausal women; but when observing relative visceral fat, we found that the percentage of visceral fat in the abdomen was higher in postmenopausal women [16]. These results lead us to postulate that menopause does not impact absolute fat distribution, but may impact relative fat distribution. To date, there are no published studies that have used a longitudinal design with imaging of the entire abdomen to quantify compartmentalization of abdominal fat with menopause.

The purpose of this study was to determine if changes in abdominal fat volume occur with menopause and if these changes occur in the visceral or the subcutaneous fat depots. We hypothesized that, with menopause, there would be an increase in abdominal fat volume, such that there would be greater relative increases in the visceral abdominal fat when compared with the subcutaneous abdominal fat.

2. Methods

2.1. Participants

Approximately 8 years after initial premenopausal testing [16], the 23 women from our previous study were contacted by investigators (via a recruitment letter) to participate in a subsequent study to repeat all initial measurements in the postmenopausal state. The objective of the initial cross-sectional study [16] was to determine the impact of menopausal status (pre- vs postmenopausal with and without hormone replacement therapy) on abdominal fat distribution using MRI. In addition, the initial study investigated the influence of abdominal fat distribution on blood lipid profiles and leptin concentrations. The groups were matched for weight (mean of premenopausal group = 66.1 ± 1.9 kg) and body mass index (BMI) (mean of premenopausal group = 25.1 ± 0.7 kg/m^2). Of the 23 women from the initial study, we were able to contact 12 women (the remaining women did not respond to the recruitment letter); and 8 women agreed to participate, whereas the remaining 4 women had either moved or were still in the premenopausal state. All volunteers signed a consent form that was approved by the Syracuse University Institutional Review Board and the State University of New York Upstate Medical University Institutional Review Board. Each subject completed a medical screening questionnaire, along with a physical activity (PA) questionnaire [16].

All women recruited for this study had been *postmenopausal* for more than 1 year (defined as subject self-report of no menses for 1 year [17]) and went through menopause naturally. All women, both in the premenopausal state and in the postmenopausal state, had a BMI of less than 32 kg/m^2 (range, 19-31 kg/m^2). Overall, the women were healthy and were free of known cardiovascular disease and other metabolic disease. All subjects were nonsmokers and were weight stable for at least 2 months before testing.

2.2. Experimental design

The following experimental design was conducted twice: once in the premenopausal state and then repeated in the postmenopausal state 8 years later. Visit 1 assessed fasting blood lipids and body composition. On visit 2, an MRI scan of the abdomen, from the midchest to midthigh region, was performed. The first and second visits were separated by approximately 1 to 2 weeks, depending on the subject's schedule and MRI availability.

2.3. Body composition

In the premenopausal state, total body fat was determined using underwater weighing. Body density was measured with the underwater weight taken simultaneously with measurement of residual lung volume [18]. Percentage of body fat was calculated according to the equations of Brozek et al [19]. In the postmenopausal state, total body fat was determined using the BodPod (Life Measurements, Concord, CA) because of mechanical problems with the underwater weighing system. This is justified because hydrostatic weighing and air displacement plethysmography have been shown to not be significantly different [20]. Body mass index was also determined in both the pre- and postmenopausal states. Waist circumferences were calculated at the umbilicus from the transverse MRI scans by manually drawing a line of circumference around the abdominal area using ImageJ software (National Institutes of Health, Bethesda, MD).

2.4. Magnetic resonance Imaging

Regional fat distribution was quantified using MRI (premenopausal images: 1.5-T whole-body scanner, General Electric, Waukesha, WI; postmenopausal images: 1.5-T whole-body scanner, Philips Intera, Andover, MA) standard spin echo imaging with respiratory time recovery = 400, echo time = 20, field of view = 40 to 48, 256 × 256, and number of excitation = 1. Slice thickness was 1 cm, with approximately 30 to 40 consecutive slices per scan. The images were analyzed using an automated fat segmentation program (WinVessel Version 1.05, Michigan State University, East Lansing, MI) to avoid investigator bias. The program used a fully automated global thresholding technique for fat segmentation and a manual option technique to determine subcutaneous from visceral abdominal adipose tissue [16]. To reduce error, images were analyzed twice with the program operator blinded to subject name and menopausal status [16]; and both the pre- and postmenopausal images were handled and analyzed by 1

researcher. Total abdominal fat was calculated in the region beginning at the superior portion of the head of the femur and continued up to the most inferior portion of the kidneys. Total abdominal fat was determined by adding together all fat components of all slices. For each slice area, visceral fat was determined; and this was subtracted from the total fat in that slice to calculate the subcutaneous fat.

2.5. PA questionnaire

In both the pre- and postmenopausal states, the women were categorized on their PA level into 1 of the following groups: (1) inactive, (2) active daily life (no outside exercise), (3) moderately active daily life (formal exercise <3 times per week), and (4) active daily life (formal exercise >3 times per week). The PA questionnaire was a composite of a number of questions from other questionnaires to address daily activity and exercise activity and was identical to the form used 8 years prior [16]. These questionnaires targeted leisure activities, home activities, and work demands. Two investigators reviewed these questionnaires and provided a score (PA score) [16]. If there were discrepancies in more than 1 category, these were discussed.

2.6. Blood sampling and assays

In both in the pre- and postmenopausal states, after a 12-hour overnight fast and a 24-hour period of no exercise, at 7:00 AM, a blood sample was taken for measurement of blood lipid concentrations. The lipid profile of the subject's whole blood was analyzed by the Cholestech LDX (Hayward, CA) [21]. The lipid profile included high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), TC/HDL ratio, and triglycerides (TRG).

2.7. Statistical analysis

A paired *t* test for descriptive characteristics of the women pre- and postmenopause was conducted. An additional paired *t* test was also done to observe the pre- and postmenopausal differences in the absolute and relative total, visceral, and subcutaneous fat contents. All data were analyzed using SPSS (Chicago, IL) software (Version 14) and are expressed as mean ± SEM. An α level of .05 was used, and power was calculated to be 0.95 to 0.98.

Table 1
Subject characteristics

	Premenopausal	Postmenopausal
Age (y)	49.3 ± 0.6	57 ± 0.8*
Height (cm)	162.2 ± 2.1	162.2 ± 2.1
Weight (kg)	63.2 ± 3.1	63.9 ± 2.5
BMI (kg/m^2)	24.1 ± 1.4	24.3 ± 1
Body fat (%)	29.6 ± 3.4	34.7 ± 2.3
Fat mass (kg)	19.3 ± 3.1	22.1 ± 1.8
Lean mass (kg)	43.9 ± 1.2	40.7 ± 2.6
Waist circumference (cm)	92.1 ± 4.6	93.4 ± 3.7
TRG	92.4 ± 27.2	95.1 ± 35.1
TC (mmol/L)	196.1 ± 23.6	204.5 ± 15.4
HDL (mmol/L)	54.1 ± 2.9	69.9 ± 4.2*
LDL (mmol/L)	108.8 ± 10.9	127.3 ± 15.1*
TC/HDL ratio	3.2 ± 0.2	2.8 ± 0.2*
PA score	3.1 ± 0.4	3.1 ± 0.4

Values are mean ± SEM. n = 8. Physical activity score: 1 to 4 (1 = inactive, 4 = active).

* $P < .05$ between pre- and postmenopausal states.

3. Results

Body weight, BMI, waist circumference, fat mass, lean mass, and PA score did not change with menopause (Table 1). Percentage of body fat increased from 29.6% ± 3.4% to 34.7% ± 2.3%, although this increase was not statistically significant. There were increases ($P < .05$) in HDL and LDL concentrations and a decrease in TC/HDL ratio ($P < .05$) with menopause, although no change in TC and TRG concentration occurred with menopause (Table 1).

There was a significant ($P < .05$) increase in total abdominal fat paralleled by an increase in subcutaneous and visceral abdominal fat with menopause (Fig. 1). When the absolute abdominal measurements for visceral and subcutaneous fat were expressed relative to total abdominal fat, there was no change in the percentage of subcutaneous abdominal fat and visceral abdominal fat with menopause (Fig. 2).

4. Discussion

This is the first longitudinal study, to our knowledge, to measure subcutaneous and visceral abdominal fat changes with menopause using multiple MRI slices of the abdominal region. Although we have a small sample of white women, our findings suggest that the relative amount of visceral fat does not increase with menopause; however, the absolute visceral volume increased, which may contribute to the increase in cardiovascular risk observed in women after menopause. Furthermore, these changes in body composition during the 8-year period were not reflected by changes in typical clinical markers: body weight, BMI, or waist circumference. The changes in total abdomenal fat mass in these women are due to changes in fat mass in both depots and possibly a decrease in abdominal muslce mass.

Total abdominal fat was approximately 35% higher in the postmenopausal state when compared with the premenopausal state in the women sampled despite no change in PA level or body weight. Subcutaneous abdominal fat increased approximately 32%, and visceral abdominal fat increased approximately 44%. Similarly, using a single CT scan slice and cross-sectional design, Hunter et al [5] reported an increase in both absolute visceral and subcutaneous abdominal fat with menopause. In addition, previous cross-sectional studies [5,10,16] have reported an increase in relative subcutaneous and visceral abdominal fat, expressed as either a percentage of visceral fat to total abdominal fat or as a ratio of subcutaneous to visceral abdominal fat. In a longitudinally designed study, Lovejoy

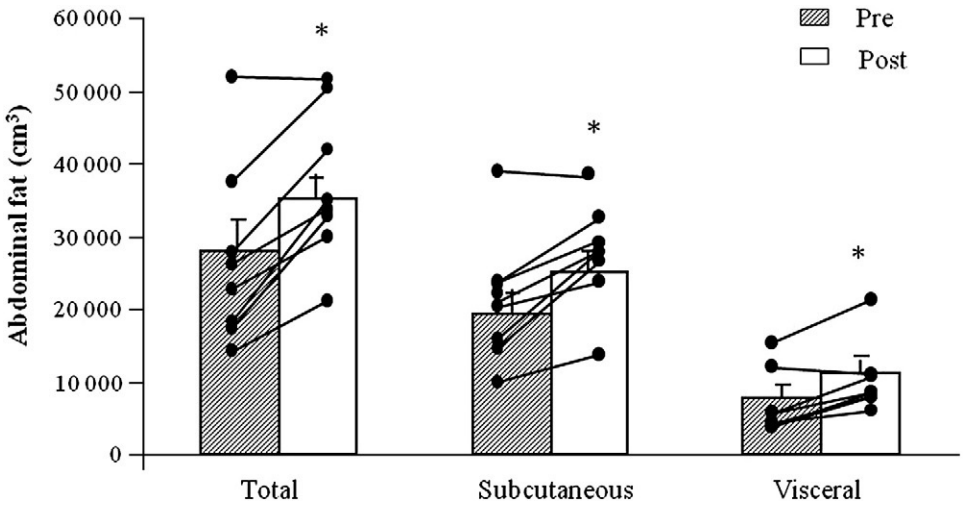

Fig. 1. Total, subcutaneous, and visceral abdominal fat differences with menopause. The data are presented in the pre- and postmenopausal states. Data are expressed as mean ± SEM. *$P < .05$ vs premenopausal state.

et al [13] also reported an increase in visceral adipose volume with menopause using CT scans to quantify abdominal adipose. Unlike most of the research that have been conducted in this area, the present study used a longitudinal design, rather than the frequently used cross-sectional design, and quantified the total abdominal region with MRI instead of a single CT scan slice.

In previous cross-sectional [5,7-10,22-25] and longitudinal [13] investigations, abdominal fat has been measured by CT, DEXA, and anthropometric measurements combined with prediction equations. Using waist to hip ratio over a 1-year period, Reubinoff et al [9] reported a shift from gynoid to android fat distribution in early postmenopausal women (baseline, 0.80 ± 0.01; 1 year later, 0.85 ± 0.01). Similarly, Ley et al [7] and Tremollieres et al [8] both reported more upper body fat in postmenopausal women compared with premenopausal women using DEXA scans. Although these studies using anthropometric measurements and DEXA scans showed that abdominal fat increases with menopause [7-9], these techniques are not able to directly quantify abdominal fat content. Computed tomography has the ability to measure both the visceral and subcutaneous fat distribution in the abdomen; however, the entire abdomen is not measured because of the radiation exposure. Although the 1-slice measurement is very precise, extrapolating these findings to the whole abdomen may skew the results [26]; and we have previously shown that 1-slice measurements does not reflect abdominal changes over time [15] or total abdominal fat content [14]. Unlike the CT scan, which is limited to single-slice acquisition, MRI uses multislice acquisition to quantify both total and regional differences in abdominal fat.

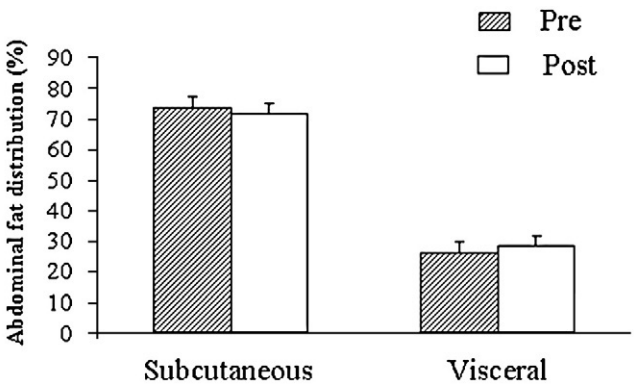

Fig. 2. Percentage of change of subcutaneous and visceral abdominal fat with menopause. The data are presented in the pre- and postmenopausal states. Data are expressed as mean ± SEM.

Increases in visceral adiposity are associated with insulin resistance, hypertension, and hyperlipidemia, as shown in past epidemiologic studies [1,27]. Because an increase in visceral fat is known to deliver higher free fatty acid levels to the portal circulation, visceral fat accumulation is thought to be more deleterious than subcutaneous abdominal fat accumulation. Furthermore, menopause is associated with increased cardiovascular and other health risks; thus, increases in the visceral depot have implications with the progression through menopause. Some researchers have shown that an increase in visceral fat may be due to a change in PA with menopause. Hunter et al [5] reported that PA was reduced in postmenopausal women compared with premenopausal women and that this reduction was associated with an increase in visceral abdominal fat. Similarly, Kanaley et al [16] found that PA was a significant predictor of visceral abdominal fat ($R^2 = 0.32$, $P > .001$) in pre- and postmenopausal women; and Lovejoy et al [13] found a reduction in PA 2 years before menopause. In contrast, in the current study, PA did not change with menopause; yet visceral abdominal fat still increased. This suggests that there are variables other than PA that influence visceral abdominal fat distribution with menopause, such as, but not limited to,

years in postmenopausal state, age, TC, HDL, LDL, TC/HDL, TRG, and postmenopause hormonal changes in leptin and estrogen.

As mentioned above, from our initial cohort of premenopausal women, we were able to locate and have 8 women repeat the testing. These women were somewhat similar to other women in the Upstate NY area, but also probably represent women who are more concerned with health-related issues. In addition, relative to other areas of the country, the dietary habits and PA levels may be quite different and may have impacted our results. Furthermore, all the women who returned in the present study are white women, which may also impact our findings. In the present study, the PA level of these women did not change with menopause, as others have reported [13,16]. However, we view this as a strength of our study, in that the PA was held constant, thus demonstrating that other variables are responsible for the changes in abdominal fat distribution with menopause.

In conclusion, although women going through menopause may not show weight gain or change in BMI, alterations in body composition are occurring such that both subcutaneous and visceral fat are increasing, but there is no change in the relative distribution of fat in the abdomen.

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