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Regional body fat distribution and metabolic profile in postmenopausal women

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Abstract

The aim of the study was to examine how body fat distribution variables were associated with metabolic parameters in a sample of 113 postmenopausal women not receiving hormone therapy (56.9 ± 4.4 years, 28.4 ± 5.1 kg/m^2). Body fat distribution variables (visceral adipose tissue [AT], subcutaneous AT, and total midthigh AT) were measured using computed tomography; body fat mass was assessed by hydrostatic weighing; insulin sensitivity was determined with the euglycemic-hyperinsulinemic clamp; fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) concentrations were measured by a 75-g oral glucose load; and (high-sensitivity) C-reactive protein (hs-CRP) was measured using a highly sensitive assay. After controlling for fat mass, visceral AT was positively associated with plasma triglyceride, hs-CRP, FPG, and 2hPG, and negatively associated with high-density lipoprotein cholesterol (HDL-C) and insulin sensitivity. Total midthigh AT was negatively associated with apolipoprotein B, FPG, and 2hPG, and positively associated with insulin sensitivity. Stepwise multiple regression analyses including abdominal visceral AT, subcutaneous AT and total midthigh AT as independent variables showed that abdominal visceral AT best predicted the variance in plasma triglyceride, HDL-C, low-density lipoprotein peak particle size, hs-CRP, FPG, 2hPG, and insulin sensitivity. Abdominal subcutaneous AT was a significant predictor of only insulin sensitivity, whereas total midthigh AT predicted HDL-C, low-density lipoprotein peak particle size, and apolipoprotein B. These multivariate analyses also indicated that total midthigh AT was favorably related to these outcomes, whereas abdominal visceral AT and subcutaneous AT were unfavorably related. These results confirmed that abdominal visceral fat is a critical correlate of metabolic parameters in postmenopausal women. In addition, a higher proportion of AT located in the total midthigh depot is associated with a favorable metabolic profile.

1. Introduction

Menopause is associated with a body fat redistribution toward an increase in the accumulation of abdominal adipose tissue (AT), more specifically visceral AT [1,2]. Menopause-related central body fat accumulation potentially contributes to the increased incidence of type 2 diabetes mellitus and cardiovascular disease observed in postmenopausal women compared with premenopausal women [2]. Aging has also been found to be associated with a preferential accumulation of abdominal visceral AT in women [3]. The importance of the site of abdominal AT accumulation in relation to the metabolic risk profile is still a matter of some debate. Several authors have suggested that abdominal subcutaneous AT may also play an important role [4-6]. However, many investigators have hypothesized that abdominal visceral AT alone is responsible for the metabolic complications of obesity [7]. In this regard, excess visceral AT accumulation has been associated with a cluster of high-risk features such as dyslipidemia, insulin resistance, hypertension, and a prothrombotic-proinflammatory state, now defined as the

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metabolic syndrome [8-11]. More specifically, high visceral fat accumulation has been associated with several cardiovascular disease risk markers such as an increased plasma apolipoprotein (apo) B [12], oxidized low-density lipoprotein (LDL) [13], and C-reactive protein (CRP) concentrations [14], and a decrease in LDL peak particle size [15]. The vascular anatomy and the metabolic activity of visceral AT may be key factors predisposing to obesity complications [16].

Although the importance of abdominal AT in mediating the health risk of obesity is well accepted, there are limited data regarding the specific role of peripheral AT in postmenopausal women. There is some evidence that peripheral AT is actually protective against cardiovascular and type 2 diabetes mellitus risk, rather than being simply less harmful. Peripheral AT seems to confer a protective effect on cardiovascular and type 2 diabetes mellitus risk, as suggested by the observations that the adverse effects of a high waist-to-hip or waist-to-thigh ratio can be due not only to larger waist but also to smaller hip [17-20] or thigh [19,21,22] circumferences. Previous studies have also shown that a high thigh or hip girth was associated with a more favorable cardiovascular risk profile [20,22-24], and a reduced risk for ischemic heart disease [25] and type 2 diabetes mellitus [18,26]. Recently, Van Pelt et al [27,28] have shown that a high accumulation of leg fat as determined by dual-energy x-ray absorptiometry was associated with reduced cardiovascular risk in postmenopausal women.

Few studies have investigated the associations between abdominal and peripheral AT distribution and the metabolic profile in postmenopausal women not receiving hormone treatment (HT). The favorable associations of peripheral AT with cardiovascular risk factors after controlling for the deleterious effects of abdominal visceral AT in postmenopausal women remain to be elucidated. Thus, our objective was to determine the respective contribution of abdominal and midthigh AT accumulation to the determination of the metabolic profile, using criterion methods to measure insulin sensitivity, plasma lipid-lipoprotein profile, and inflammatory markers in postmenopausal women not receiving HT.

2. Research design and methods

2.1. Subjects

This study was conducted in a sample of 113 postmenopausal women (aged between 46 and 68 years) recruited through the media in the Quebec City metropolitan area. Each woman was individually interviewed to evaluate if she corresponds to the study's criteria for age, menopausal status, HT, and other medication. Women were asked about their menstrual cycle. Those reporting that they did not had their menses for at least 1 year were considered as postmenopausal and were included in the study. A measure of the follicle-stimulating hormone was used to confirm the postmenopausal status (follicle-stimulating hormone value between 28 and 127 UI/L). All women included in our study were not using any type of HT and were not under treatment of coronary heart disease, diabetes, dyslipidemias, or endocrine disorders (except stable thyroid disease). Five women included in our study were smokers. None of the participants had received a diagnosis of type 2 diabetes mellitus before the study. Systolic and diastolic blood pressures were measured in the right arm of seated resting participants, as previously described [29]. All participants signed an informed consent document before entering the study, which was approved by the Laval University Medical Center, and Laval University Research Ethics Committees.

2.2. Anthropometric measurements

Body density was estimated by the hydrostatic weighing technique [30]. The mean of 6 valid measurements was used to calculate the percentage of body fat from body density with the equation of Siri [31]. Fat mass was calculated from the derived percentage of body fat and total body weight. Height, body weight, body mass index (BMI), and waist and hip circumferences were determined following the procedures recommended at the Airlie Conference [32]. Height was measured to the nearest millimeter with a stadiometer, and body weight was measured to the nearest 0.1 kg on a calibrated balance. Waist circumference was measured in duplicate at the mid distance between the iliac crest and last rib margin while the woman was in a standing position, and the measurement was recorded to the nearest millimeter. The hip circumference measurement was performed at the level of the greatest gluteal protuberance. Participants were wearing a swimming suit and were asked to remove their shoes for these last measurements.

2.3. Computed tomography

Measurements of abdominal AT areas were performed by computed tomography (CT) with a GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) with the procedures of Sjöström et al [33], as previously described [34]. Briefly, women were examined in the supine position with both arms stretched above the head. The CT scan was performed at the abdominal level between the L4 and L5 vertebrae. A radiograph of the skeleton was used as a reference to establish the position of the scan to the nearest millimeter. Total abdominal AT area was calculated by delineating the abdominal scan with a graph pen and then by computing the AT surface using an attenuation range of −190 to −30 HU [35]. Abdominal visceral AT area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal subcutaneous AT area was calculated by subtracting the visceral AT area from the total abdominal AT area.

Computed tomography was also used to measure total midthigh AT areas. For each subject, a single 10-mm–

thick CT image was obtained in the midthigh at the midpoint between the inguinal crease and superior edge of the patella.

2.4. Oral glucose tolerance test

A 75-g oral glucose tolerance test was performed in the morning after an overnight fast. Blood samples were collected in EDTA-containing tubes (Becton Dickinson, Franklin Lakes, NJ) through a venous catheter from an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 minutes for the determination of plasma glucose, insulin, and C-peptide concentrations. Plasma glucose was measured enzymatically, whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation [36,37]. Plasma C-peptide levels were measured by a modification of the method of Heding [38] with polyclonal antibody A-4741 from Ventrex (Portland, ME) and polyethylene glycol precipitation [36]. The interassay coefficient of variation was 1.0% for a basal glucose value set at 5.0 mmol/L.

2.5. Euglycemic-hyperinsulinemic clamp

Insulin sensitivity was determined with an euglycemic-hyperinsulinemic clamp previously described by DeFronzo et al [39]. The euglycemic-hyperinsulinemic clamp was performed after a 12-hour overnight fast. An antecubital arm vein was cannulated with a catheter for infusion of insulin and glucose (20% dextrose). A hand vein from the contralateral arm was cannulated to permit sampling of blood for the determination of plasma insulin and glucose concentrations. Fasting blood sample was drawn for baseline measurements. A primed continuous infusion of insulin (Humulin R, Eli Lilly Canada Inc, Toronto, Canada) (40 mU/[m^2 min]) was then started. Adjustments in glucose infusion rate were performed to reach the fasting plasma glucose (FPG) values and a steady-state of about 5.5 mmol/L for women with FPG greater than the reference range (FPG ≥6.1 mmol/L). Once the steady state of glucose concentration was reached, the insulin infusion was continued for a total of 2 hours. The duration of the insulin infusion was such that the rate of infused glucose reached a constant value during the last hour of the clamp. Blood samples were collected in EDTA-containing tubes from time −15 minutes and then every 5 minutes during the test to measure blood glucose concentration by using Glucometer Elite (number 3903-E; Bayer, Tarrytown, NY). Measurements of plasma glucose concentrations were then validated by an enzymatic method [37]. Plasma insulin concentrations were monitored from blood samples collected every 10 minutes and stored at −20°C, for later analyses using radioimmunoassay with polyethylene glycol separation [36]. The insulin-stimulated glucose disposal rate or *M* value was then calculated from the glucose infusion rate per kilogram of fat-free mass during the last 30 minutes of the clamp. Insulin sensitivity (*M*/*I*) was determined as the *M* value divided by the mean insulin concentration during the last 30 minutes of the clamp, as defined previously [39].

2.6. Plasma lipid-lipoprotein profile

On the morning of the euglycemic-hyperinsulinemic clamp, blood samples were collected to measure a complete plasma lipid-lipoprotein profile by standard methods. Blood samples were collected after a 12-hour overnight fast from an antecubital vein into vacutainer tubes containing EDTA. Cholesterol and triglyceride (TG) concentrations were determined enzymatically in plasma and lipoprotein fractions with a Technicon RA-500 analyzer (Bayer), and enzymatic reagents were obtained from Randox Laboratories (Crumlin, United Kingdom). Plasma very low-density lipoprotein (density <1.006 g/mL) was isolated by ultracentrifugation [40]. The high-density lipoprotein (HDL) fraction was obtained after precipitation of LDL in the infranatant (density >1.006 g/mL) with $MnCl_2$ and heparin [40]. The cholesterol and TG contents of the infranatant were measured before and after the precipitation step. Apolipoprotein B was measured by nephelometry (BN ProSpec; Dade Behring, Newark, DE) in plasma and lipoprotein fractions with reagents provided by this company (N Antisera to Human Apolipoprotein B). Nondenaturing 2% to 16% polyacrylamide gradient gel electrophoresis was used to characterize LDL peak particle size as previously described [41]. Oxidized LDL concentrations were measured using a commercial sandwich enzyme-linked immunosorbent assay according to the manufacturer's instructions (Alpco Diagnostics, Windham, NJ).

2.7. Inflammatory markers

Plasma CRP levels were measured in plasma stored at −80°C using the Behring Latex-Enhanced highly sensitive CRP (hs-CRP) assay on a Behring Nephelometer BN-100 (Behring Diagnostic, Westwood, MA) and the calibrators (N Rheumatology Standards SL) provided by the manufacturer.

2.8. Statistical analyses

Statistical analyses were performed using software from the SAS Institute, Cary, NC (version 8.2). The visceral AT to total midthigh AT ratio (visceral-midthigh AT ratio) was also calculated. Pearson correlation coefficients were calculated to quantify the univariate associations between body fat distribution variables (visceral AT, subcutaneous AT, total midthigh AT, and visceral-midthigh AT ratio) and metabolic variables. Partial Pearson correlation coefficients were also calculated to control for overall adiposity (fat mass). Forward stepwise multiple regression analyses were performed to determine the best predictors among body fat distribution variables (visceral AT, subcutaneous AT, and midthigh AT) of the variance in metabolic variables. Regression analyses were also computed by adding fat mass into the models. The critical *P* value for significance was set at .05. Some variables were not normally distributed

Table 1
Areas and volumes of abdominal and peripheral AT measured by CT in postmenopausal women into study

Variables	Mean ± SD	Range
Age (y)	56.9 ± 4.4	(46.4–68.0)
BMI (kg/m^2)	28.4 ± 5.1	(19.0–48.2)
Waist circumference (cm)	91.1 ± 12.8	(65.9–125.7)
Hip circumference (cm)	107.1 ± 11.2	(82.0–150.5)
Body fat mass (kg)	29.3 ± 10.4	(7.6–67.3)
Fat mass (% of body weight)	39.2 ± 7.5	(14.9–55.2)
Abdominal AT areas (cm^2)		
Total	510.7 ± 170.6	(165.7–943.2)
Visceral	140.2 ± 56.3	(40.3–288.0)
Subcutaneous	370.5 ± 130.2	(103.5–736.0)
Midthigh AT area (cm^2)		
Total	181.1 ± 55.3	(59.1–312.5)

(BMI, FPG, TG, LDL peak particle size, oxidized LDL, and hs-CRP). For these variables, analyses were done on their log-transformed values.

3. Results

Variables related to body fat composition and distribution of postmenopausal women are presented in Table 1. Univariate correlation analyses indicated that abdominal visceral and subcutaneous AT areas were both significantly associated with many metabolic variables including TG concentrations, hs-CRP levels, FPG, 2hPG, and insulin sensitivity (Table 2). Abdominal visceral AT area was also correlated positively with total cholesterol (TC) to HDL cholesterol (HDL-C) ratio (TC/HDL-C ratio) and negatively with HDL-C concentrations and LDL peak particle size. On the other hand, total midthigh AT was only associated with hs-CRP. Similarly to visceral AT, the ratio of visceral-midthigh AT was significantly associated with TG, HDL-C, LDL peak particle size, and insulin sensitivity. The visceral-midthigh AT ratio was also correlated with apo B and oxidized LDL concentration. Visceral AT, subcutaneous AT, and midthigh AT were all positively associated with fat mass (respectively, $r = 0.66$, $r = 0.80$, and $r = 0.75$; $P < .0001$). Further adjustment for fat mass was performed to control for overall adiposity. Associations between visceral AT and metabolic variables remained significant, whereas associations between subcutaneous AT and metabolic variables were no longer significant (Table 3). Association between total midthigh AT and hs-CRP was no longer significant after adjustment for fat mass. Moreover, total midthigh AT became significantly associated with apo B ($r = -0.30$, $P = .002$), LDL peak particle size ($r = 0.29$, $P = .003$), oxidized

Table 2
Correlation coefficients for the associations of abdominal visceral and subcutaneous AT, total midthigh AT, and visceral-midthigh AT ratio with metabolic variables

	Body fat distribution variables			
	Visceral AT	Subcutaneous AT	Midthigh AT	Visceral-midthigh AT ratio
TG	0.41***	0.23*	0.08	0.34**
HDL-C	−0.39***	−0.17	−0.04	−0.30**
TC/HDL-C	0.32**	0.07	−0.07	0.40***
Hs-CRP	0.58***	0.53***	0.44***	0.18
LDL-C	0.01	−0.04	−0.13	0.19*
Apo B	0.16	0.01	−0.13	0.34**
LDL peak particle size	−0.19*	0.03	0.17	−0.33**
Oxidized LDL	0.12	−0.03	−0.11	0.23*
Fasting glycemia	0.35**	0.26**	0.08	0.33**
2-h plasma glucose	0.43***	0.29**	0.11	0.43***
Insulin sensitivity	−0.38***	−0.26**	−0.05	−0.40***

Significant correlation: *$P < .05$, **$P < .01$, ***$P < .0001$. LDL-C indicates LDL cholesterol.

Table 3
Correlation coefficients for the associations of abdominal visceral and subcutaneous AT, total midthigh AT, and visceral-midthigh AT ratio with metabolic variables, adjusted for fat mass

	Body fat distribution variables		
	Visceral AT	Subcutaneous AT	Midthigh AT
TG	0.30**	0.03	−0.19
HDL-C	−0.34**	−0.06	0.14
TC/HDL-C	0.27**	−0.05	−0.28**
Hs-CRP	0.33**	0.18	0.12
LDL-C	0.05	0.01	−0.18
Apo B	0.14	−0.06	−0.30**
LDL peak particle size	−0.21*	0.15	0.29**
Oxidized LDL	0.14	−0.10	−0.20*
Fasting glycemia	0.24*	0.06	−0.23*
2-h plasma glucose	0.34**	0.08	−0.24*
Insulin sensitivity	−0.34**	−0.14	0.24*

Significant correlation: *$P < .05$, **$P < .01$.

Table 4
Multivariate regression analyses showing independent contributions of AT accumulation variables to the variance of metabolic variables in the sample of postmenopausal women

Dependent variable	Independent variable	Coefficient (β)	Partial ($R^2 \times 100$)	P
TG	Visceral AT	0.0032	16.7	<.0001
HDL-C	Visceral AT	−0.0030	14.9	<.0001
	Midthigh AT	0.0012	2.6	.07
TC/HDL-C	Visceral AT	0.0092	10.5	.0006
	Midthigh AT	−0.0057	6.0	.007
Apo B	Midthigh AT	−0.00097	5.1	.02
LDL peak	Midthigh AT	0.000063	8.5	.002
particle size	Visceral AT	−0.000066	3.8	.04
Hs-CRP	Visceral AT	0.0086	30.4	<.0001
	Midthigh AT	0.0049	5.6	.004
Fasting glycemia	Visceral AT	0.00082	12.2	.0002
2-h plasma glucose	Visceral AT	0.0244	21.4	<.0001
Insulin sensitivity (M/I)	Visceral AT	−0.000047	21.5	<.0001
	Subcutaneous AT	0.000030	9.5	.003

LDL ($r = -0.20$, $P = .04$), FPG ($r = -0.23$, $P = .02$), 2hPG ($r = -0.24$, $P = .01$), and insulin sensitivity ($r = 0.21$, $P = .04$) after adjustment for fat mass.

Stepwise multiple regression analyses including abdominal visceral AT, subcutaneous AT, and total midthigh AT as independent variables showed that abdominal visceral AT was the best predictor of TG, HDL-C concentrations, TC/HDL-C ratio, hs-CRP, FPG, 2hPG, and insulin sensitivity (Table 4). Abdominal subcutaneous AT only predicted insulin sensitivity. Total midthigh AT was the best predictor of apo B concentration as well as of LDL peak particle size and also predicted TC/HDL-C ratio and HDL-C. According to coefficients of regression, total midthigh AT was favorably related whereas abdominal visceral AT and subcutaneous AT were unfavorably related to metabolic variables studied. When stepwise analyses were repeated with adding fat mass as an additional independent variable, similar results were found except for hs-CRP, for which fat mass became the best predictor ($R^2 = 0.35$, $P < .0001$).

4. Discussion

Results of this study first confirmed those observed in other studies that showed that abdominal visceral AT was associated with deterioration in many components of the metabolic risk profile [10,11,42,43]. We have previously shown that visceral AT was associated with a deteriorated metabolic profile, particularly when an elevated visceral AT accumulation was combined with the presence of insulin resistance in postmenopausal women [44]. The present study extends these findings by showing that abdominal subcutaneous AT added little to the prediction of the metabolic outcomes after accounting for visceral AT. Furthermore, we showed that total midthigh AT not only entered as a significant predictor into many of the regression models, but was also found to be favorably related to the metabolic risk factors; that is, an increased proportion of fat located in the midthigh depot was associated with a more favorable metabolic profile.

Although the importance of abdominal AT depot in mediating the health risk of obesity is generally well accepted, it has been debated whether this association is determined by the accumulation of abdominal visceral AT or subcutaneous AT. Our results show that abdominal visceral AT area contributes to a larger extent to the deteriorated metabolic risk profile in postmenopausal women than abdominal subcutaneous AT. In fact, abdominal visceral AT independently contributes to the variance of all variables studied, except for apo B concentrations. Both visceral AT and subcutaneous AT predicted insulin sensitivity independently of fat mass when multivariate analyses were conducted. The contribution of visceral AT and/or subcutaneous AT on insulin resistance is not consistent. Some studies have found a positive association between subcutaneous fat and insulin resistance [11,45], whereas others found a strong positive correlation between visceral fat and insulin resistance and no association between subcutaneous fat and insulin resistance [46,47]. Moreover, other studies have shown that abdominal visceral AT confers a greater cardiovascular and type 2 diabetes mellitus risk than subcutaneous AT [10,24]. Univariate analyses also showed that total midthigh AT was positively correlated with hs-CRP levels. This apparently unfavorable association of midthigh AT accumulation with hs-CRP may be partly explained by the confounding effect of global adiposity found in women with increased midthigh AT levels. In fact, after further adjustment for fat mass, total midthigh AT was no longer positively associated with hs-CRP; and midthigh AT became negatively associated with apoB, FPG, and 2hPG concentration, and positively associated with insulin sensitivity. These observations were confirmed by performing stepwise multiple regression analyses. This suggests that women with a preferential accumulation of fat in the midthigh depot were characterized by a more favorable metabolic profile. However, the cross-sectional design of our study does not allow us to determine if this relationship is causal. These results support other studies performed in men and women relating to the protective effect of peripheral AT accumulation on metabolic risk profile [7,22,24,28,48].

It has been demonstrated that adipocytes from abdominal visceral AT depot are more sensitive to lipolytic activity and more resistant to suppression of lipolysis by insulin than are the adipocytes from the gluteal or femoral regions [49]. In contrast, the gluteal/femoral AT shows a low fatty acid turnover [50-52]. Pouliot et al [53] published evidence that midthigh AT accumulation was positively correlated with HDL2-C concentrations and with the HDL2-C/HDL3-C ratio, and that this relationship could be explained by the elevated midthigh AT lipoprotein lipase activity contributing to raise HDL2-C levels. Therefore, AT in the thigh region is more likely to take up free fatty acids from the circulation and store them, thereby protecting other organs such as the liver, skeletal muscle, and pancreas from high free fatty acid exposure [54]. In addition, AT produces many peptides such as interleukin-6, tumor necrosis factor–α, plasminogen activator inhibitor–1, leptin, and adiponectin [55] that in turn impact on metabolism. Regional differences in secretion of these peptides could potentially explain the direct and opposite effects of these AT depots on metabolic risk profile.

In conclusion, results of our study confirmed that abdominal visceral fat is a critical correlate of metabolic parameters in postmenopausal women not using any type of HT and that both visceral AT and subcutaneous AT were independent predictors of insulin resistance. Moreover, an increased proportion of fat located at midthigh levels protects postmenopausal women against deteriorations in the metabolic risk profile. Although the mechanisms for the distinct effects of abdominal vs peripheral adiposity on metabolic risk profile remain to be further determined, these findings provide further support for the concept that total adiposity

does not adequately indicate the extent of cardiovascular and type 2 diabetes mellitus risk in postmenopausal women. These observations reinforce the importance of considering body fat distribution (abdominal and peripheral AT accumulation) in the evaluation of cardiovascular and type 2 diabetes mellitus risk in postmenopausal women.

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