Original Article

Regional Differences in Adipose Tissue Metabolism in Women

Minor Effect of Obesity and Body Fat Distribution

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Studies comparing adipose tissue metabolism in central versus peripheral fat depots have generated equivocal data. We examined whether regional differences in abdominal subcutaneous and omental adipose tissue metabolism in women exist and whether they persist across the spectrum of body fatness and abdominal adiposity values. We measured adipocyte size; lipoprotein lipase (LPL) activity; and basal, isoproterenol-, forskolin-, and dibutyryl cAMP–stimulated lipolysis in adipose tissue or mature adipocytes isolated from the omental and subcutaneous fat depots in a sample of 55 healthy women undergoing elective gynecological surgery. Measures of body fat mass and body fat distribution were also obtained by dual-energy X-ray absorptiometry and computed tomography. Subcutaneous adipocytes were significantly larger than omental adipocytes ($P < 0.0001$). LPL activity expressed as a function of cell number was significantly higher in subcutaneous versus omental adipose tissue ($P < 0.0001$). Basal, isoproterenol-stimulated, dibutyryl cAMP–stimulated (10^{-3} mol/l) and forskolin-stimulated (10^{-5} mol/l) lipolysis (expressed as a function of cell number) were all significantly higher in subcutaneous versus omental adipocytes ($P < 0.05$ to $P < 0.0001$). However, the response of omental adipocytes to lipolytic stimuli tested (fold increase over basal level) was significantly greater in magnitude compared with subcutaneous adipocytes ($P < 0.01$). These differences were relatively constant across total body fat mass and visceral adipose tissue area tertiles. In conclusion, compared with adipocytes from the omental fat compartment, subcutaneous adipocytes are larger, have higher LPL activity, and are more lipolytic on an absolute basis, which may reflect a higher fat storage capacity in this depot in women. In contrast, omental adipocytes display greater relative responsiveness to both adrenergic receptor– and postreceptor-acting agents compared with subcutaneous adipocytes. Overall and visceral obesity have only minor effects on regional differences in adipose tissue metabolism.
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Excess accumulation of adipose tissue within the abdominal cavity, or visceral obesity, has been associated with a cluster of metabolic alterations, which includes insulin resistance, hyperinsulinemia, elevated triglyceride levels, low HDL cholesterol, and hypertension as its main features (1,2). In many instances, the association between visceral adipose tissue accumulation and metabolic alterations has been found to be independent of differences in total adiposity, suggesting that the presence of large intra-abdominal fat stores is a critical determinant of obesity-related metabolic complications (2–4).

The physiological basis of this well-documented association has been intensely investigated in recent years, and one of the prevailing theories put forth, the portal vein theory, is related to the particular characteristics and anatomical location of visceral fat depots and their venous drainage by the portal vein system (5). Intra-abdominal adipocytes are generally believed to be hyperlipolytic by being highly responsive to catecholamine stimulation and poorly responsive to lipolysis inhibition by insulin (2,6–8). According to the portal vein theory, the specific propensity of visceral adipocytes to generate a high–free fatty acid flux in the portal vein would be critical in the appearance of obesity-related complications by increasing triglyceride-rich lipoprotein synthesis in the liver, by stimulating hepatic gluconeogenesis, by reducing insulin clearance, and also by eventually leading to ectopic fat accumulation (5,6).

Despite the prevalent idea that adipocytes from visceral fat depots are hyperlipolytic, a close survey of the literature indicates that relatively few studies have directly compared lipolysis in adipocytes or adipose tissue from intra-abdominal fat depots (mainly omentum) to that of adipocytes from other more peripheral depots (7–21). Interestingly, findings of these studies are not at all unanimous. Several reasons could potentially explain these discrepancies. Studies may have been plagued by methodological limitations including low sample size, differences in the sites of tissue sampling, and combining males and females, obese and nonobese, or omental and subcutaneous samples from distinct populations. Most importantly, differences in lipolysis units chosen (per lipid weight, per cell number, and per cell surface) and selective

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emphasis on given parameters (absolute glycerol release, cell sensitivity to agonists, responsiveness, and percent response) greatly contributed to obscure previous literature on regional differences in lipolysis. Most studies using either isolated adipocytes or tissue explants have shown higher basal lipolysis in subcutaneous versus omental adipocytes (8–12,15,18,21), with few exceptions reporting the opposite (16). The absolute lipolytic rate under maximal stimulation by the β-adrenergic agonist isoproterenol was also found to be higher in subcutaneous versus omental adipocytes in several studies (8,9,11,12,15). On the other hand, incremental lipolytic responses above basal level to isoproterenol (18,21) or other catecholamines (8,17) were reported to be higher in omental versus subcutaneous fat tissue or cells. Among all these studies, only one (17) specifically examined the question of whether regional differences were found both in obese and nonobese subjects. These results indicated that omental adipocyte catecholamine-induced lipolysis (expressed in percent response) was higher than that of subcutaneous adipocytes but only in obese subjects (17).

Regional differences in lipoprotein lipase (LPL) activity have also been examined in a number of studies (10,13,14,16,22–24). Similar to lipolysis data, findings were equivocal. Two studies reported higher LPL activity in subcutaneous fat (10,23), two studies reported higher activity in omental fat (16,24), and three studies reported no difference (13,14,22). Again, low sample sizes were examined, and obese and lean or males and females were often combined in the analyses. Sex- or obesity-related differences in adipocyte size, a variable generally used in the calculation of LPL activity, could also have contributed to confound these data. Interestingly, adipocyte size is an important determinant of adipocyte function. Large adipocytes synthesize more triglycerides than smaller adipocytes and also release more fatty acids through lipolytic pathways (21,25). Studies have consistently reported that subcutaneous adipocytes are larger than omental adipocytes (9,11,13), which would indirectly suggest higher lipolysis rates as well as LPL activity in these adipocytes, and apparently contradict the widely accepted notion that omental adipocytes are hyperlipolytic and have a higher rate of triglyceride turnover.

The present study was aimed at examining whether regional differences in abdominal subcutaneous and omental adipose tissue LPL activity and lipolysis in women indeed exist and whether they persist across the spectrum of body fatness and abdominal adiposity values. We examined adipocyte size and LPL activity as well as basal, isoproterenol-, forskolin-, and dibutyryl cAMP–stimulated lipolysis in omental and subcutaneous fat biopsies surgically obtained from a sample of 55 women undergoing elective gynecological surgery. Detailed measures of body fat accumulation and body fat distribution were also obtained (dual-energy X-ray absorptiometry and computed tomography, respectively). We tested the hypothesis that omental adipocyte lipolysis rates are higher than those of subcutaneous adipocytes and that these differences are observed across the spectrum of total and visceral adiposity values.

RESEARCH DESIGN AND METHODS

Women of this study were recruited through the elective surgery schedule of the Gynecology Unit of the Laval University Medical Center. The study included 55 healthy women aged 39.6–61.7 years undergoing abdominal gynecological surgery. Women of the study elected for total (n = 53) or subtotal (n = 2) abdominal hysterectomies, some with salpingo-oophorectomy of one (n = 11) or two (n = 18) ovaries. Reasons for surgery included one or more of the following: menorrhagia/menometrorrhagia (n = 26), myoma/fibroids (n = 40), incapacitating dysmenorrhea (n = 8), pelvic pain (n = 2), benign cyst (n = 11), endometriosis (n = 6), adenomyosis (n = 2), pelvic adhesions (n = 4), benign cystadenoma (n = 1), endometrial hyperplasia (n = 4) or polyp (n = 2), and ovarian thecoma (n = 1). Menstrual status could be obtained for 54 women, and plasma follicle-stimulating hormone (FSH) was measured in 51 women. Eleven women were identified as ovarian hormone deficient. This subgroup included six women who had stopped bleeding naturally for at least 4 months and had elevated FSH levels (>30 IU/ml), two women using a GnRH agonist, and three having irregular menstrual bleeding and elevated FSH levels. Seven women were using hormonal supplements including oral contraceptives, hormone replacement, or phytoestrogen supplements. The remaining women (n = 34) were grouped into the pre- and perimenopausal category. These women had FSH values <30 IU/ml and reported the presence of menstrual cycles. This study was approved by the medical ethics committees of Laval University and Laval University Medical Center. All subjects provided written informed consent before their inclusion in the study.

Body fatness and body fat distribution measurements. These tests were performed on the morning of or within a few days before or after the surgery. Measures of total body fat mass, fat percentage, and fat-free mass were determined by dual-energy X-ray absorptiometry using a Hologic QDR-2000 densitometer and the enhanced array whole-body software V5.73A (Hologic, Bedford, MA). Measurement of abdominal subcutaneous and visceral adipose tissue cross-sectional areas was performed by computed tomography as previously described (26), using a GE Light Speed 1.1 CT scanner (General Electric Medical Systems, Milwaukee, WI). Subjects were examined in the supine position with arms stretched above the head. The scan was performed at the L4-L5 vertebrae level using a scout image of the body to establish the precise scanning position. The quantification of visceral adipose tissue area was done by delineating the intra-abdominal cavity at the internal-most aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body using the ImageJ 1.33u software (National Institutes of Health). Adipose tissue was highlighted and computed using an attenuation rage of −190 to −30 Hounsfield units. The coefficient of variation between two measures from the same observer (n = 10) were 0.0, 0.2, and 0.5% for total, subcutaneous, and visceral adipose tissue areas, respectively.

Plasma lipid-lipoprotein measurements. Blood samples were obtained after a 12-h fast on the morning of surgery. Cholesterol and triglyceride level measurements in plasma and lipoprotein fractions were performed with a Technicon RA-analyzer (Bayer, Etobicoke, Canada) using enzymatic methods, as previously described (27). Plasma VLDLs were isolated by ultracentrifugation, and the HDL fraction was obtained by precipitation of the LDLs from the infranatant with heparin and $MnCl_2$ (28). The cholesterol content of the infranatant was measured before and after precipitation, and the concentration of LDL cholesterol was obtained by difference.

Adipose tissue sampling. Subcutaneous adipose tissue was collected at the site of surgical incision (lower abdomen), and omental adipose tissue was collected from the distal portion of the greater omentum (epiploon). Samples were collected during the surgical procedure and immediately carried to the laboratory in 0.9% saline preheated at 37°C. Adipocyte isolation was performed with a portion of the fresh biopsy, and the remaining tissue was immediately frozen in liquid nitrogen and stored at −80°C for subsequent analyses.

Adipocyte isolation, lipolysis, and LPL activity. Tissue samples were digested for 45 min at 37°C with collagenase type I in Krebs-Ringer-Henseleit buffer (25 mmol/l HEPES, 125 mmol/l NaCl, 3.7 mmol/l KCl, 5 mmol/l $CaCl_2$, 2.5 mmol/l $MgCl_2$, and 1 mmol/l K_2HPO_4, pH 7.4) supplemented with 5 mmol/l glucose, 0.1 μmol/l adenosine, 0.1 mg/ml ascorbic acid, and 4% electrophoresis grade, delipidated BSA (SIGMA A7906) according to a modified version of the Rodbell method (29). Adipocyte suspensions were filtered through nylon mesh and washed three times with the buffer. For cell size measurements, mature adipocyte suspensions were visualized using a contrast microscope attached to a camera and computer interface. Pictures of cell suspensions were taken, and the Scion Image software was used to measure the size (diameter) of 250 adipocytes for each tissue sample.

Lipolysis experiments were performed by incubating isolated cell suspensions for 2 h at 37°C in Krebs-Ringer Henseleit buffer, with or without β-adrenergic receptor agonist isoproterenol in concentrations ranging from 10^{-10} to 10^{-3} mol/l or postreceptor-acting agents dibutyryl cAMP (10^{-3} mol/l) and forskolin (10^{-5} mol/l). Cell suspensions were diluted to ~5,000 cells per condition (30 μl). Glycerol release in the medium was measured by bioluminescence using the nicotinamide adenine dinucleotide-linked bacterial luciferase assay (30,31), a Berthold Microlumat plus bioluminometer

(LB 96 V), and the WinGlow software (EG&G, Bad Wildbad, Germany). In our conditions, adenosine deaminase (0.03–1.5 IU/ml) had no detectable effect on basal lipolysis rates. Intra- and interassay coefficients of variation for glycerol release measurements were 5.9 and 13.9%, respectively. Lipid weight of the cell suspension used in lipolysis experiments was measured by performing Dole's extraction. Average adipocyte weight and cell number in the suspensions were calculated using lipid weight, average cell volume, and the density of triolein. Lipolysis results were expressed in nanomoles glycerol per milligrams lipids in suspension per 2 h, in μmoles per 10^6 cells per 2 h, as fold-over basal lipolysis, or in nanomoles glycerol per μm^2 cell surface $\times 10^8$ per 2 h.

Heparin-releasable LPL activity was determined in 30- to 50-mg frozen adipose tissue samples by the method of Taskinen et al. (32). Tissue eluates were obtained by incubating the sample in Krebs-Ringer phosphate buffer and heparin at 37°C for 90 min. The eluates were then incubated with excess concentrations of unlabeled and ^{14}C-labeled triolein in a Tris-albumin buffer emulsified with ultrasound. The reaction was carried out at 37°C for 60 min with agitation. The resulting free fatty acids liberated from triolein by the LPL reaction were isolated by the Belfrage extraction procedure. Porcine plasma was used as a source of Apo-CII to stimulate LPL activity and unpasteurized cow's milk as an internal LPL activity standard for interassay variations. Activity results were expressed in nanomoles oleate per 10^6 cells per hour.

Statistical analyses. Omental versus subcutaneous differences in adipocyte size, adipocyte lipolysis, or adipose tissue LPL activity were tested using paired t tests either in the entire sample or within total body fat mass or visceral adipose tissue area tertiles. Repeated-measures analyses were also used to evaluate the significance of the [isoproterenol dose × fat depot] interaction. Pearson correlation coefficients were computed to quantify associations between adiposity variables and adipose tissue/adipocyte measures. Variables that were not normally distributed based on a significant Shapiro-Wilk test ($P < 0.05$) were $\log_{10}$ transformed in statistical analyses. Age- and total body fat mass–adjusted visceral adipose tissue area was computed using multiple regression analysis. All statistical analyses were performed using the JMP statistical software (SAS Institute, Cary, NC).

RESULTS

Characteristics of the study sample of 55 women are shown in Table 1. Women were 47.3 years old and were slightly overweight according to their mean BMI value (27.1 ± 5.2 kg/m^2). Adiposity values covered a wide spectrum, with body fat percentages ranging from 19.6 to 47.5%. Women of the study had a normal lipid profile on average. Three women were characterized by high plasma cholesterol values, two women had slightly low HDL cholesterol values, and 11 women had elevated triglyceride levels according to current clinical guidelines (1). Women with painful or premalignant conditions were not different from the remainder of the sample for any of the variables examined.

Table 2 shows regional differences in adipocyte size and LPL activity in the entire sample of women. Adipocyte size and weight were significantly lower in omental versus subcutaneous fat by 18 and 20%, respectively ($P < 0.0001$ for both). LPL activity expressed as a function of cell number was significantly higher in subcutaneous compared with omental fat (34% difference, $P < 0.0001$).

Regional differences in basal, isoproterenol-, forskolin-, and dibutyryl cAMP–stimulated lipolysis in the entire sample of women are shown in Fig. 1. When data were expressed as a function of lipid weight in the adipocyte suspension, basal lipolysis and the response to the lowest isoproterenol dose examined (10^{-10} mol/l) were significantly higher in subcutaneous adipocytes. No other significant difference was found between the two depots (Fig. 1*A*). Lipolysis values expressed per cell number are shown in Fig. 1*B*. Using these units, the response of subcutaneous adipocyte suspensions to all conditions examined (basal, isoproterenol, and postreceptor-acting agents) was significantly higher than that of omental adipocytes with the exception of the 10^{-8} mol/l isoproterenol stimulation, which only tended to be higher in subcutaneous versus omental adipocytes. Adipocyte suspension responses to lipolytic stimuli expressed in fold-over basal levels are shown in Fig. 1*C*. Omental adipocytes displayed significantly greater responses to isoproterenol starting at doses greater or equal to 10^{-8} mol/l. In addition, omental adipocytes had greater responses than subcutaneous adipocytes when stimulated with postreceptor-acting agents (Fig. 1*C*). EC50 values for isoproterenol stimulation were computed, and the slight differences observed did not reach statistical significance (Fig. 1). When expressing our data as a function

TABLE 1
Characteristics of the study sample of 55 women

Variable	Mean ± SD (range)
Age (years)	47.3 ± 4.9 (39.6–61.7)
Weight (kg)	71 ± 16 (49–111)
BMI (kg/m^2)	27.1 ± 5.2 (17.2–41.3)
SBP (mmHg)	127 ± 12 (100–159)
DBP (mmHg)	75 ± 0 (49–92)
Total body fat mass (kg)	25.2 ± 9.6 (10.0–50.8)
Fat-free mass (kg)	43.1 ± 6.8 (32.5–63.0)
Percent fat	34.7 ± 6.3 (19.6–47.5)
Abdominal adipose tissue areas (cm^2)	
Total	422 ± 184 (128–991)
Visceral	96 ± 46 (34–233)
Subcutaneous	326 ± 145 (94–759)
Lipid profile (mmol/l)*	
Cholesterol	4.83 ± 0.65 (3.43–6.12)
LDL cholesterol	2.75 ± 0.60 (1.31–3.96)
HDL cholesterol	1.49 ± 0.38 (0.81–2.69)
Triglycerides	1.29 ± 0.64 (0.51–2.99)
Cholesterol/HDL cholesterol	3.42 ± 0.86 (1.64–5.42)

*n = 50 women for variables of the lipid profile. DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 2
Regional difference in adipocyte size, weight, and adipose tissue LPL activity

Variable	Subcutaneous adipose tissue	Omental adipose tissue
Adipocyte size (μm)	98 ± 13	80 ± 16*
Adipocyte weight (μg/cell)	0.51 ± 0.18	0.30 ± 0.16*
LPL activity (nmol oleate/h × 10^6cell)	16.68 ± 7.75	11.05 ± 5.68*

Data are means ± SD. n = 53 women for adipocyte size and weight, and n = 52 for LPL activity. *$P < 0.0001$.

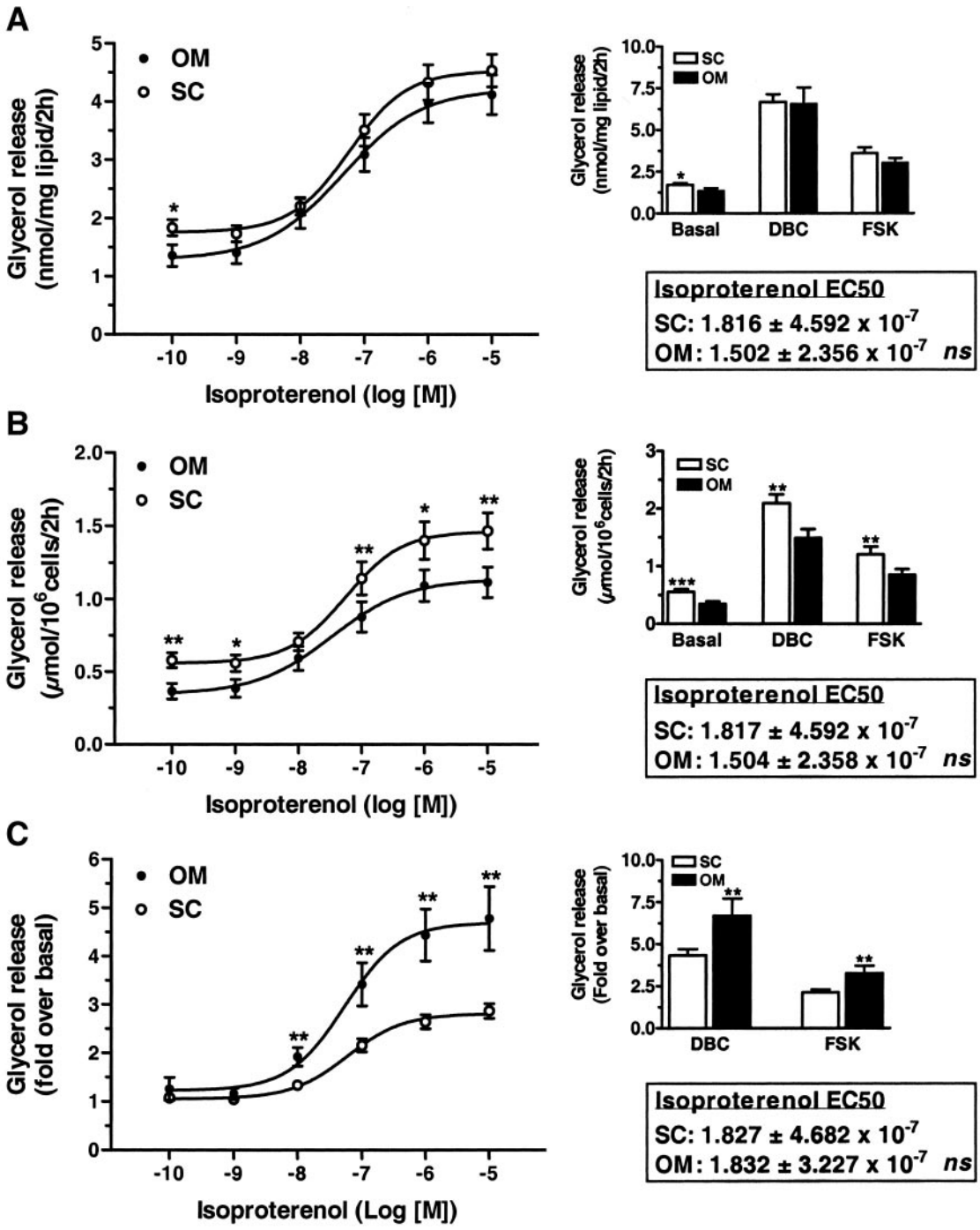

FIG. 1. Regional differences in basal, isoproterenol-, dibutyryl cAMP (DBC)-, and forskolin (FSK)-stimulated lipolysis in mature adipocytes isolated from omental (OM) and subcutaneous (SC) adipose tissue expressed as a function of lipid weight (*A*), cell number (*B*), or fold-over basal (*C*). Number of subjects were $n = 48$ for isoproterenol, $n = 50$ for basal and FSK, and $n = 51$ for DBC (*A*) and (*B*); and $n = 46$ for isoproterenol, $n = 49$ for DBC, and $n = 48$ for FSK in (*C*). *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$. *P* values for the [isoproterenol dose × fat depot] interaction tested by repeated-measures analysis were $P = 0.24$, $P = 0.07$, and $P < 0.05$ for *A*, *B*, and *C*, respectively.

of cell surface (nanomoles glycerol per μm^2 cell surface × 10^8 per 2 h), no significant depot difference was detected in any of the lipolytic conditions tested (not shown). Statistically significant depot differences in adipocyte size, LPL activity, or lipolysis were also significant when examining ovarian hormone–deficient women and pre-/perimenopausal women separately (see RESEARCH DESIGN AND METHODS).

Correlations between adiposity measures examined in this study and average adipocyte diameter in each depot are shown in Table 3. Subcutaneous and omental adipocyte diameter were both strongly and positively correlated with all adiposity measures, including BMI and total body fat mass as well as computed tomography–measured adipose tissue areas. Subcutaneous adipocyte diameter was most strongly associated with total abdominal adipose tissue area ($r = 0.80$, $P < 0.0001$). Omental adipocyte diameter was most strongly associated with visceral adipose tissue area ($r = 0.80$, $P < 0.0001$). As a result, several highly significant positive correlations were observed be-

TABLE 3
Pearson correlation coefficients between adiposity measures and omental or subcutaneous adipocyte diameter

	Subcutaneous adipocyte size	Omental adipocyte size
BMI	0.70	0.65
Fat mass*	0.78	0.74
Percent fat	0.75	0.76
Abdominal adipose tissue areas		
Total*	0.80	0.76
Subcutaneous*	0.76	0.72
Visceral*	0.78	0.80

*Calculations performed with $\log_{10}$-transformed variables; $n = 53$ women for subcutaneous adipocyte size. $P < 0.0001$ for all variables.

tween adiposity measures and both omental and subcutaneous LPL activity or adipocyte lipolysis expressed as a function of cell number (not shown). Visceral adipose tissue area adjusted for age and total body fat mass was only associated with omental adipose tissue/cell measures (not shown).

We then examined whether regional differences in adipocyte diameter, LPL activity, and lipolysis persisted across tertiles of total body fat mass and visceral adiposity values. As shown in Fig. 2, subcutaneous adipocyte size was significantly higher in all tertiles of total body fat mass. In addition, subcutaneous LPL activity and basal lipolysis expressed as a function of cell number were higher in every fat mass tertile, with the exception of basal lipolysis in the lowest fat mass tertile, which only tended to be different. Isoproterenol-stimulated lipolysis (10^{-5} mol/l), when expressed in fold-over basal, was significantly higher in omental versus subcutaneous adipocytes for the mid–fat-mass tertile, whereas it tended to be higher in other tertiles (Fig. 2). The same analysis was performed in visceral adipose tissue area tertiles and generated similar results (Fig. 3). Adipocyte size, basal lipolysis, and LPL activity in the subcutaneous fat depot were significantly higher across all tertiles of visceral adipose tissue area, with the exception of basal lipolysis in the first visceral adipose tissue area tertile, which only tended to be different. Isoproterenol-stimulated lipolysis (10^{-5} mol/l) expressed in fold-over basal was significantly higher in omental versus subcutaneous adipocytes for the mid- and upper-visceral adipose tissue area tertiles, and a trend for higher omental lipolysis was found for the lowest tertile (Fig. 3). Stratifying the sample into tertiles of age- and total body fat mass–adjusted visceral fat area led to differences that were similar to those observed in Fig. 3, with the exception of the omental isoproterenol fold-response, which only tended to be higher than the subcutaneous response in the lower tertiles (not shown).

DISCUSSION

This examination of regional differences in omental and subcutaneous adipocyte metabolism was prompted by the apparent contradiction between the rather discordant literature available on this topic and the wide-spread belief

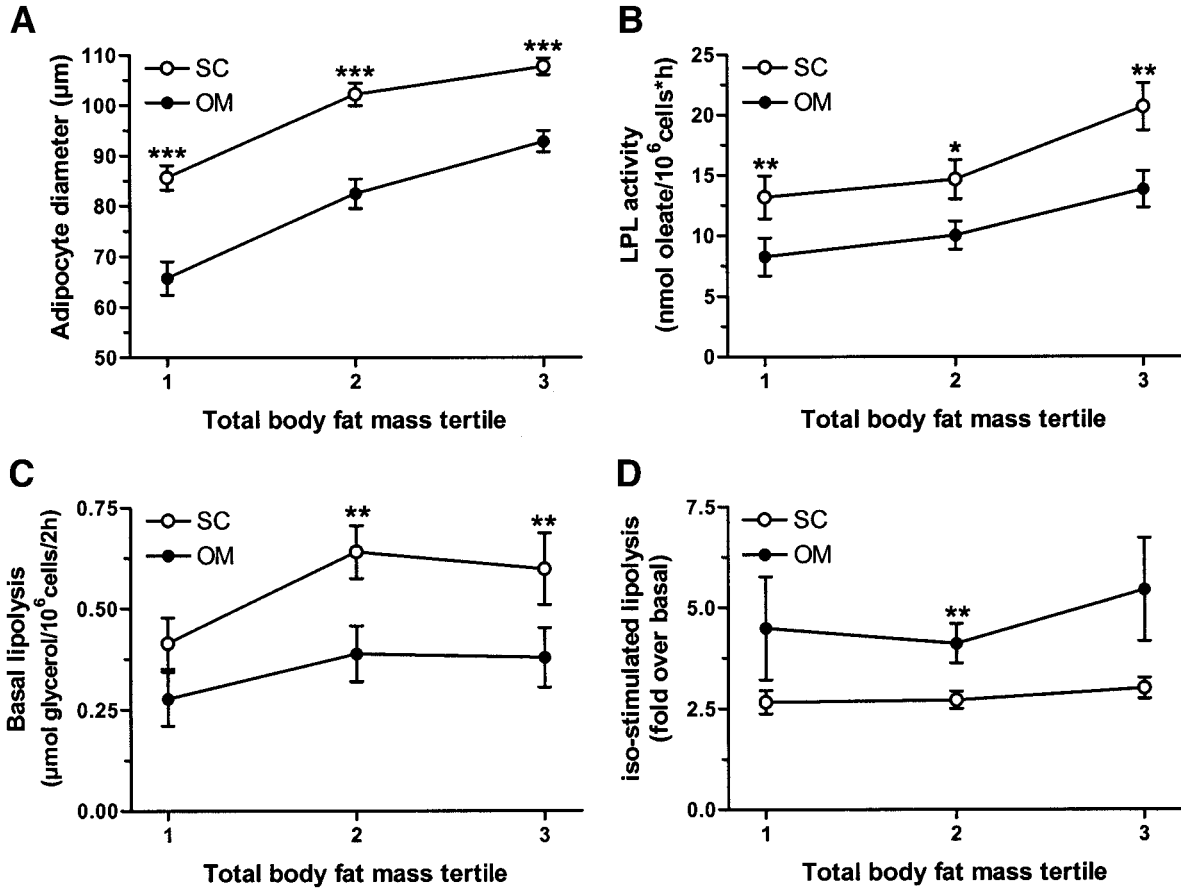

FIG. 2. Regional differences in adipocyte size (*A*), LPL activity (*B*), basal (*C*), and isoproterenol-stimulated (10^{-5} mol/l) (*D*) lipolysis in omental (OM) and subcutaneous (SC) adipocytes according to tertiles of total body fat mass. Mean total body fat mass by tertile: *1*) 16.1 ± 2.5 kg, n = 16; *2*) 24.1 ± 2.7 kg, n = 17; *3*) 36.6 ± 7.1 kg, n = 17, $P < 0.0001$. *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$.

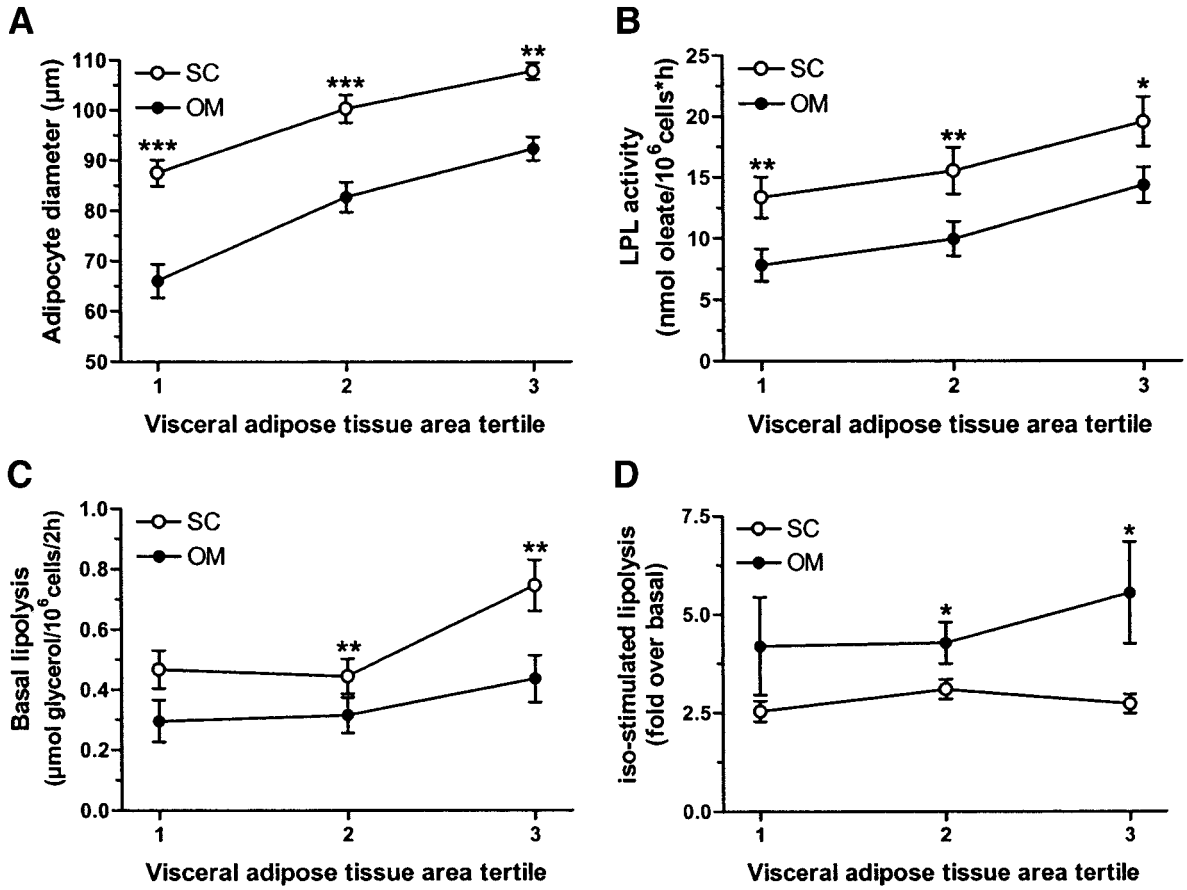

FIG. 3. Regional differences in adipocyte size (*A*), LPL activity (*B*), basal (*C*), and isoproterenol-stimulated (10^{-5} mol/l) (*D*) lipolysis from omental (OM) and subcutaneous (SC) adipose tissue according to tertiles of visceral adipose tissue area. Mean visceral adipose tissue area by tertile: *1*) 53 ± 11 cm^2, n = 16; *2*) 89 ± 14 cm^2, n = 17; *3*) 151 ± 35 cm^2, n = 17, $P < 0.0001$. *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$.

that omental adipocytes are hyperlipolytic. We tested the hypothesis that omental adipocyte lipolysis would be higher than that of subcutaneous adipocytes. The opposite was found. On an absolute basis, the subcutaneous fat depot clearly appeared as having larger adipocytes, higher lipolysis rates per cell, and higher LPL activity compared with omental fat. On the other hand, omental adipocytes appeared to be substantially more responsive than subcutaneous adipocytes to positive lipolytic stimuli including both a β-adrenergic receptor agonist and postreceptor acting agents. We also examined whether these differences would be observed across the spectrum of total and visceral adiposity values. Regional differences appeared as relatively constant for any adiposity level, suggesting that overall and visceral obesity have only minor effects on these regional differences in adipose tissue metabolism. This study is the largest to date on the issue of regional differences in adipocyte metabolism and the only one comparing visceral versus subcutaneous parameters across adiposity values evaluated with radiological imaging methods.

As a result of methodological differences and the numerous ways of expressing or presenting data, previous studies on the issue of lipolysis and LPL activity in omental and subcutaneous fat have been strikingly equivocal (7–17). The present study reconciles several apparent contradictions. First, the higher lipolysis and LPL activity found in subcutaneous adipocytes on a per-cell basis is highly consistent with the notion that larger adipocytes accumulate more triglycerides and also release more fatty acids than smaller adipocytes (21,25). Our finding of larger adipocytes in the subcutaneous fat depot is highly consistent with previous studies (9,11,13) and may reflect a higher fat storage capacity in individual cells from this depot in women. Second, our in vitro results may also be consistent with data obtained in vivo. Lipolysis measures performed in vivo with isotope dilution techniques by Jensen and colleagues (33–35) have been consistent in demonstrating that splanchnic fatty acid release, an indirect measure of portally drained lipolysis, is not the major contributor to whole-body circulating free fatty acids. The higher absolute lipolytic rates observed in subcutaneous adipocytes of the present study support the notion of a predominant contribution of subcutaneous lipolysis to the circulating free fatty acid pool. On the other hand, higher responsiveness (fold increase in glycerol release) of omental adipocytes to positive lipolytic stimuli has also been found in other studies (15) and may be consistent with the hypothesis that omental adipocytes contribute to the generation of a high–fatty acid flux to the liver, at least in physiological conditions of stimulated lipolysis. Conversely, subcutaneous adipose tissue metabolism would be less labile in such conditions, which may alter fat mobilization from this depot in weight loss.

Our findings are consistent with several previous studies demonstrating, among others, that subcutaneous cell lipolysis is higher in the basal state (8–12,15,18,21) and when maximally stimulated with isoproterenol (8,9,11,12,15).

However, previous studies have suggested that regional variation in lipolysis may be explained by differential sensitivity and regulation of adrenergic receptors (8,10,12,17). Specifically, these studies demonstrated that the α-β-receptor balance may be lower in omental adipocytes, which would confer these cells a greater lipolytic response to catecholamines (8,10). Although α-adrenergic receptor modulation of lipolysis was not examined, our results do not support the idea that regional differences in lipolysis are driven by differential adrenergic receptor sensitivity. Indeed, we show that both β-adrenoceptor agonists (isoproterenol in our case) and postreceptor-acting agents induce a greater response in omental versus subcutaneous adipocytes. In addition, contrary to some (8,17) but not all (12) previous reports, we found that isoproterenol EC50 values were clearly not different between fat depots. The reason for this discrepancy is unclear. However, the previous studies reporting significant differences were performed in severely obese subjects in one study and in relatively small study samples (8,17). While an altered α-β-adrenergic balance in omental adipocytes cannot be excluded, our results suggest that regional lipolysis differences are at least partly independent from adrenergic receptor sensitivity, the postreceptor cellular machinery of omental adipocytes being also intrinsically highly responsive.

Our results demonstrate that regional differences between omental and subcutaneous adipocytes are relatively independent of the degree of total and visceral adiposity. However, one must keep in mind that the present sample did not include morbidly obese women. As a result, at all levels of obesity or abdominal obesity, subcutaneous adipocytes were larger on average than omental adipocytes. A close examination of Fig. 2 actually shows that the two slopes of adipocyte size seem to converge slightly as omental adipocyte size values increase with obesity. In our sample, only a few women had omental adipocytes as large as their subcutaneous cells. Examining women with higher BMI may have led to a higher number of women with omental and subcutaneous adipocytes of identical sizes, which may have affected our examination of differences in adipose tissue metabolism. We did not find any significant regional difference in lipolysis when expressing data as a function of cell surface, which supports the hypothesis that fat cell size is a critical determinant of regional differences in lipolysis.

As mentioned, LPL activity and lipolysis are coupled and vary strongly with adipocyte size (21,25). In our study, we found a positive correlation between lipolysis in a given depot and LPL activity of the same depot (not shown). Given the fact that most studies in women demonstrated that subcutaneous adipocyte size is in general larger than omental adipocyte size (9,11,13), it is not surprising that on an absolute basis (when expressed per cell number), subcutaneous tissue or cells exhibit both higher LPL activity and higher lipolytic rates compared with the omentum. We suggest that these results reflect a larger capacity to store fat in the subcutaneous compartment, at least in women. Men generally have twice as much visceral fat compared with women for any given fat mass value (36), and whether similar regional differences in LPL activity or lipolysis would be found remains to be determined.

Strong positive correlations were found between adipocyte size and measures of overall or visceral fat accumulation. These correlations contributed to the fact that in any fat depot, measures of adipocyte metabolism expressed as a function of cell number, a calculation based on cell size, were also strong, positive correlates of adiposity. These results suggest that as the size of a given fat compartment increases, adipocytes located within this compartment also enlarge and so does the fatty acid flux across their membranes, which is consistent with findings demonstrating a size-function relationship in adipocytes (11,21,25). The responsiveness of omental adipocytes (fold increase in glycerol release of a given stimuli over basal) were also significantly and positively correlated with visceral adipose tissue area as well as age- and fat mass–adjusted visceral adipose tissue area. In addition, we observed a larger absolute difference in omental versus subcutaneous isoproterenol responsiveness in the upper tertile of visceral adipose tissue area (and also in the upper tertile of age and fat mass–adjusted visceral adipose tissue area), which suggests that visceral obese women may have even greater omental adipocyte lipolytic responsiveness compared with individuals with low visceral fat accumulations. Accordingly, recent evidence obtained by the Jensen group demonstrated that visceral adipose tissue lipolysis accounts for an increasing proportion of hepatic free fatty acids as visceral fat accumulation increases (37).

Limitations of this study should be acknowledged. We investigated positive lipolytic stimuli, but negative stimuli were not examined. Resistance of adipocytes to insulin suppression of lipolysis is a key feature of omental adipocytes, and most likely contributes to the hepatic free fatty acid flux in postprandial conditions (6). In vitro examination of these parameters in the present study may have generated complementary results. However, we believe that our clear examination of positive stimuli combined with other strengths of the study, including the use of radiological imaging to measure adiposity and the relatively large sample size make our results relevant. The lack of morbidly obese women in our sample also appears as a limitation. As mentioned, regional differences in adipose tissue metabolism may be altered in this population. Further studies are required to clearly elucidate this issue.

In summary, in our sample of healthy women, subcutaneous adipocytes were characterized by higher rates of lipolysis and LPL activity, when these values were expressed as a function of cell number. However, omental adipocytes were more responsive to positive lipolytic stimuli compared with subcutaneous cells. Regional differences were relatively constant across the spectrum of adiposity values, suggesting that overall and visceral obesity have only minor effects on the regional differences in adipose tissue metabolism.

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