Regional Postprandial Fatty Acid Metabolism in Different Obesity Phenotypes

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To examine if postprandial splanchnic/hepatic free fatty acid (FFA) delivery is increased in upper-body (UB) obesity, and to determine the adipose tissue depots responsible for the greater postprandial FFA availability, we measured systemic and regional uptake and release of FFAs ([1-^{14}C]palmitate) before and during a 5-h frequent-feeding mixed meal in eight UB and eight lower-body (LB) obese women. Postabsorptive FFA flux and splanchnic FFA delivery were not different in UB and LB obese women; however, postprandial FFA concentrations (257 ± 45 vs. 81 ± 12 µmol/l, $P < 0.0001$), FFA flux (8.5 ± 1.2 vs. 3.9 ± 0.8 µmol · kg^{-1} fat-free mass · min^{-1}, $P < 0.0001$), splanchnic FFA delivery (275 ± 45 vs. 88 ± 24 µmol/min, respectively, $P < 0.005$), and estimated hepatic FFA delivery were greater in UB than LB obese women. Nonsplanchnic UB adipose tissue FFA release was greater in UB than in LB obese women (276 ± 71 vs. 97 ± 37 µmol/min, respectively, $P < 0.05$) and accounted for the greater postprandial FFA availability in UB obesity. Postprandial leg glucose uptake was less in UB than in LB obese women (8.4 ± 5.1 vs. 22.9 ± 2.6 µmol · kg^{-1} leg fat-free mass · min^{-1}, $P < 0.05$). We conclude that the elevated postprandial FFA release observed in UB obese women originates from the nonsplanchnic UB fat, not visceral fat. These results suggest that visceral fat may be a marker for, but not the source of, excess postprandial FFAs in obesity. *Diabetes* 48:1586–1592, 1999

Obese humans with an upper-body (UB) (1) or visceral (2–4) fat distribution are at increased risk for type 2 diabetes, hyperlipidemia, and hypertension. One potential mechanism linking UB obesity with these metabolic consequences is excess free fatty acid (FFA) availability. Abnormally elevated FFAs can produce hypertriglyceridemia (5), insulin resistance with respect to glucose uptake (6,7), decreased hepatic insulin clearance (8), and impaired endothelium-dependent vasodilation (9). UB obesity is associated with elevated post-absorptive (10) and postprandial (11) systemic FFA release.

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Received for publication 6 November 1998 and accepted in revised form 21 April 1999.

D.D.H. has received grant support from the Slim-Fast Institute and honoraria from Knoll Pharmaceutical.

FFA, free fatty acid; FFM, fat-free mass; GCRC, Mayo Clinic General Clinical Research Center; HPLC, high-performance liquid chromatography; LB, lower body; SA, specific activity; UB, upper body; WHR, waist-to-hip ratio.

It is now clear that different adipose tissue beds are heterogeneous with respect to their contribution to systemic lipolysis. Although the excess postabsorptive FFA release in UB obese women originates from nonsplanchnic UB fat (12), there are reasons to believe that other adipose depots may become dominant under other circumstances. For example, visceral fat adipocytes are more resistant than subcutaneous adipocytes to insulin's antilipolytic effects (13). In addition, even in nonobese adults with normal visceral fat stores, postprandial splanchnic FFA release (a minimum estimate of visceral adipose tissue lipolysis) increases relative to systemic FFA release compared with the postabsorptive state (14,15). Thus, differential insulin regulation of various adipose tissue depots appears likely, and could have important consequences following meal ingestion, when the insulin-mediated inhibition of FFA release contributes substantially to the suppression of hepatic glucose production (16) and VLDL secretion (17). Because of the portal venous drainage of omental and mesenteric adipose tissue, visceral obesity could result in substantially greater hepatic FFA delivery following meal ingestion if visceral adipose tissue lipolysis is, indeed, insulin resistant (18). In this case, splanchnic FFA release in UB obesity might become the major contributor to systemic FFA release. Thus, the postprandial period is an especially relevant condition to assess regional adipose tissue lipolysis in obesity because of the potential impact of FFAs on insulin action in different tissue beds.

Postprandial fatty acid metabolism is also of interest because it is the only circumstance that changes adipose tissue from a net exporter to a net importer of fatty acids. During meal ingestion, regional differences in the balance between triglyceride fatty acid uptake (via chylomicron clearance) and FFA release influence body fat distribution. Mårin et al. (19) used radioisotope tracers to assess the uptake of fatty acids in a meal by intra-abdominal and peripheral adipose tissue in men undergoing elective surgery; significantly greater uptake was found in visceral fat, which could contribute to the greater visceral fat mass in men. Consistent with this hypothesis, we observed greater splanchnic chylomicron clearance in men than in women (14). That finding, however, might be attributed to sex, as opposed to fat distribution, factors. The present studies offered the opportunity to examine regional chylomicron uptake in groups of obese women with different amounts of visceral fat to determine whether differences in regional meal fatty acid uptake are associated with regional fat mass differences within the same sex.

We recently used a frequent feeding regimen to create a postprandial metabolic steady state (14), allowing the measurement of both regional FFA release and meal triglyceride

fatty acid uptake. The studies presented herein adapted the same approach to address three research questions regarding fatty acid metabolism in premenopausal UB and lower-body (LB) obese women. One goal was to determine whether splanchnic and hepatic FFA delivery is increased in UB obese women compared with LB obese women during meal ingestion. A second major goal was to test the hypothesis that the excess postprandial FFA availability in UB obese women (11) originates from the splanchnic bed. If this were observed, it would provide the first evidence that visceral adipose tissue lipolysis can contribute directly to the abnormal hepatic glucose and lipid metabolism reported in UB obesity. Finally, the opportunity to examine regional chylomicron (meal) and nonchylomicron triglyceride metabolism might lead to further insights into the mechanisms that contribute to different body fat distribution patterns in humans.

RESEARCH DESIGN AND METHODS

Subjects. Informed, written consent was obtained from 16 obese women who were selected to include an UB obesity (waist-to-hip ratio [WHR] >0.85) and a primarily LB obesity (WHR <0.80) phenotype. Three UB obese women were hypertensive (diastolic blood pressure >90 mmHg) but not on treatment at the time of recruitment, and one UB obese woman received insulin for management of type 2 diabetes. She was withdrawn from insulin for 2 weeks before the study. All volunteers had maintained a stable weight for >2 months before the study. To further ensure stable weight and consistent macronutrient intake, each participant consumed all meals in the Mayo Clinic General Clinical Research Center (GCRC) for 10 days before the study. The meal portions were adjusted, if necessary, to keep the volunteer's weight stable (±0.1 kg) and provided 20% of energy as protein, 40% as fat, and 40% as carbohydrate.

Materials and assays. [1-^{14}C]palmitate was purchased from Amersham (Arlington Heights, IL) and bound to human serum albumin as previously described (20). Chemical and isotopic purity were determined by high-performance liquid chromatography (HPLC) (20). Indocyanine green (Cardio-Green; Becton Dickinson, Cockeysville, MD) was used to measure leg and splanchnic plasma flow.

Plasma palmitate and total FFA concentrations and specific activity (SA) were determined by HPLC (20) using [$^{2}H_{31}$]palmitate as internal standard (21). Plasma chylomicron and nonchylomicron triglyceride concentrations were measured using an enzymatic method (22). Plasma glucose concentrations were measured with a glucose analyzer (Beckman Instruments, Fullerton, CA), and plasma insulin was measured by radioimmunoassay (23). Plasma epinephrine and norepinephrine were measured by HPLC with electrochemical detection (24).

Body fat and fat-free mass (FFM) as well as leg fat and leg FFM were measured by dual-energy X-ray absorptiometry (Lunar Radiation, Madison, WI) (25). A single-slice abdominal computed tomography scan at the L_{2-3} interspace was obtained on all subjects to measure abdominal subcutaneous and visceral fat area (26). Plasma indocyanine green concentrations were measured on the day of the study by spectrophotometry at 810 nm.

Lipoprotein separation. Plasma chylomicrons were isolated by ultracentrifugation of 2 ml of plasma at 780,000*g* in a 50.3 Ti rotor (Beckman Instruments, Spinco Division, Palo Alto, CA). The supernatant was aspirated with a modified Pasteur pipette. The triglyceride content of both the supernatant (chylomicron) and the infranatant (nonchylomicron) were measured. The triglyceride content of the supernatant was corrected for the presence of nonchylomicron triglycerides in the aspirate volume by correcting for the concentration in the infranatant and by handling the baseline plasma samples in the same manner as the meal samples. The plasma samples of two UB obese women were exceedingly lipemic after the initial ultracentrifugation, which prevented us from cleanly aspirating the chylomicron layer from each of the samples. Because of this technical problem, we believed the triglyceride analysis results from these two volunteers' samples, especially those obtained during meal ingestion, to be unreliable. The regional triglyceride uptake and release data from these two subjects are therefore not included in this report.

Protocol. All subjects were admitted to the GCRC the evening before the study. An 18-gauge infusion catheter was placed in a forearm vein and infused with 0.45% NaCl at 20 ml/h. The next morning, before arising from bed, each subject's resting energy expenditure was measured (DeltaTrac Metabolic Cart; SensorMedics, Yorba Linda, CA) and blood was sampled for construction of the indocyanine green calibration curve and for background plasma FFA SA. The volunteers were then transferred to the Vascular Radiology Laboratory for placement of infusion and sampling catheters into the right femoral artery, the right femoral vein, and the right hepatic vein as previously described (14). The remainder of the study was completed in the GCRC.

The experimental meal was provided using a liquid feeding formula (Ensure Plus; Ross Products Division, Abbott Laboratories, Columbus, OH) that contains 53% of energy as carbohydrate, 32% as fat, and 15% as protein. The study meal provided 40% of resting daily energy expenditure as determined by indirect calorimetry (see above) and was measured accurately (±2 ml) for each subject.

After returning to the GCRC, the subjects rested in bed for 90 min before beginning to consume the experimental meal. An infusion of [1-^{14}C]palmitate (0.3 μCi/min) was begun through the forearm vein infusion catheter 30 min before the first blood sample was taken. At the same time, the indocyanine green (220 μg/min) was started through the femoral artery sheath for measuring leg and splanchnic plasma flow rates. Arterial, femoral venous, and hepatic venous blood samples were collected at 15-min intervals over a 45-min baseline period before meal consumption began. After the basal blood samples were obtained, the [^{14}C]palmitate and indocyanine green infusions were discontinued and the subjects began consuming the experimental meal. Meal aliquots were provided at 20-min intervals over the next 5 h, beginning with priming (double) doses for the 1st h to more readily achieve steady-state chylomicronemia, followed by equal portions for the remainder of the study. The [^{14}C]palmitate and indocyanine green infusions were restarted 60 min before the second series of blood samples, which were collected at 15-min intervals over the final hour of meal ingestion. After completion of the study, all catheters were removed and local hemostasis was obtained. The subjects remained in the hospital under observation until the following morning.

Calculations. Systemic FFA flux during baseline and meal intervals was calculated using the [1-^{14}C]palmitate infusion rate divided by the steady-state palmitate SA and relating the palmitate concentration to total FFA concentration as previously described (27).

Regional (splanchnic and leg) FFA uptake and release were calculated using the mean steady-state arterial, hepatic venous, and femoral venous plasma FFA concentrations and SA values for each individual (12) combined with the leg (28) and splanchnic (29) plasma flow. UB nonsplanchnic FFA release was calculated by subtracting the sum of leg FFA release multiplied by 2 and splanchnic FFA release from systemic FFA flux (14).

To estimate whether splanchnic tissues in UB and LB obese women were exposed to different amounts of FFAs, splanchnic FFA delivery was calculated as the product of splanchnic plasma flow and arterial plasma FFA concentration. Because excess FFAs are believed to affect hepatic glucose and triglyceride metabolism, measurement of hepatic FFA delivery, some of which is derived from visceral adipose tissue lipolysis, would be valuable. It is not possible to measure visceral adipose tissue FFA release into the portal vein, however, because both uptake and release of FFA occur in the splanchnic bed; uptake occurs in extrahepatic tissues and liver (30), and release occurs from omental and mesenteric fat. Maximum and minimum hepatic FFA delivery values can be derived by modeling the sites of splanchnic FFA uptake (31).

The maximum hepatic FFA delivery can be estimated using the following approach: if all splanchnic FFA uptake takes place in the liver, the fractional uptake of newly released FFA from visceral lipolysis is equal to the fractional splanchnic uptake of systemically delivered FFA (measured using the FFA tracer). Under these circumstances, the maximum estimate of visceral FFA release = splanchnic FFA release/(1 – fractional splanchnic FFA uptake). These conditions also define the maximum estimate of the hepatic exposure to systemic FFAs, because no extrahepatic FFA uptake is assumed. Thus, maximum hepatic FFA delivery = maximum visceral FFA release + splanchnic FFA delivery.

It is also possible to calculate the minimum estimate of visceral lipolysis and therefore minimum hepatic FFA delivery. If all splanchnic FFA uptake occurs in extrahepatic tissues (no hepatic FFA uptake), then splanchnic FFA release equals visceral FFA release. This scenario also defines the minimum hepatic delivery of systemic FFA: splanchnic FFA delivery × (1 – fractional splanchnic FFA uptake). Thus, minimum hepatic FFA delivery = splanchnic FFA release + [splanchnic FFA delivery × (1 – fractional splanchnic FFA uptake)]. If the minimum estimate of hepatic FFA delivery in one group exceeds the maximum estimate of hepatic FFA delivery in another group, it would provide strong evidence for greater hepatic FFA delivery in the first group.

The body mass of our volunteers differed sufficiently that liver size might also be different; we therefore chose not to compare the estimates of maximum and minimum hepatic FFA delivery on an absolute (μmol/min) basis. Liver mass appears to vary as a function of body mass, and lean tissue mass is suggested to be a better predictor of liver size (32,33). The between-group comparisons of the maximum and minimum hepatic FFA delivery were performed using values expressed relative to FFM.

The chylomicron (meal) triglyceride rate of appearance was taken to be equal to the triglyceride ingestion rate based on our previous findings (14) and the fact that chylomicron triglyceride concentration was relatively stable during the final hour of meal ingestion. Regional chylomicron triglyceride uptake was calculated using the following formula:

TABLE 1
Subject characteristics

	UB obese women	LB obese women	*P* value
Age (years)	40 ± 6 (33–49)	39 ± 6 (30–46)	NS
BMI (kg/m^2)	33.9 ± 2.7 (29.0–37.3)	33.6 ± 1.8 (30.4–35.6)	NS
Weight (kg)	93.8 ± 9.9 (78–107)	91.5 ± 8.4 (74–103)	NS
Body fat (%)	46 ± 4 (41–53)	52 ± 3 (50–58)	<0.05
WHR	0.90 ± 0.06 (0.85–1.00)	0.76 ± 0.02 (0.72–0.79)	
FFM (kg)	50.3 ± 4.1 (44.7–55.4)	43.7 ± 2.8 (37.4–46.1)	<0.05
Visceral fat (cm^2)	172 ± 48 (101–250)	104 ± 24 (72–138)	<0.005
Abdominal subcutaneous fat (cm^2)	332 ± 56 (230–379)	305 ± 83 (227–473)	NS
Leg fat (kg)	13.9 ± 3.7 (7.8–19.7)	17.4 ± 4.6 (11.4–24.2)	NS

Data are means ± SD (range). n = 8 UB and 8 LB obese women. WHR data are not subject to statistical comparisons because it is a variable used to select the volunteers. Visceral and abdominal subcutaneous fat areas were measured by single-slice computed tomography at the L_{2-3} level; percent body fat, FFM, and leg fat were measured by dual-energy X-ray absorptiometry.

$$\text{Regional chylomicron triglyceride uptake rate} = [(\text{chylomicron triglyceride})_{\text{arterial}} - (\text{chylomicron triglyceride})_{\text{venous}}] \times \text{regional plasma flow rate}$$

The regional chylomicron triglyceride uptake rate was divided by the meal triglyceride ingestion rate to estimate the relative contributions of the leg and splanchnic bed in clearing chylomicron triglycerides. The leg uptake and net splanchnic release of nonchylomicron triglycerides were calculated by multiplying the appropriate arteriovenous concentration differences by regional plasma flow rate.

Basal and steady-state meal leg glucose uptake was also measured. Plasma glucose concentrations were converted to whole blood glucose concentrations by multiplying the plasma value by 1 – (0.30 × hematocrit) (34). Leg blood flow was determined using the plasma flow and hematocrit values for each individual. Leg glucose uptake was calculated by the Fick principle as the product of the arteriovenous difference for blood glucose and leg blood flow.

Statistics. All values are expressed as means ± SE except where indicated. Comparisons between UB and LB obese women used unpaired, two-sided Student's t test or nonparametric approaches if the variances were significantly different between groups. To compare plasma triglyceride concentrations, ln-transformed values were used. Within-group comparisons (splanchnic vs. leg, basal vs. meal ingestion) used paired, two-sided Student's t test.

RESULTS

Subject characteristics. UB and LB obese women were well matched for age, BMI, and body weight (Table 1). As expected, the visceral fat area was significantly greater in UB than in LB obese women. Leg fat mass tended to be greater in LB than in UB obese women. Percent body fat was slightly greater in LB than in UB obese women.

Plasma glucose, insulin, and catecholamine concentrations. The time course and changes in plasma glucose and insulin concentrations are shown in Fig. 1. The average basal plasma glucose concentrations in UB and LB obese women were 6.2 ± 0.9 and 5.1 ± 0.1 µmol/l, respectively (NS). As expected, plasma glucose concentrations were greater (P < 0.001) during the final hour of meal ingestion than during the basal time interval in both UB and LB obese women (7.8 ± 1.3 and 6.7 ± 0.1 mmol/l, respectively, NS). One of the UB obese women was diabetic, with basal and mealtime glucose concentrations of 12.3 and 17.0 mmol/l, respectively. Excluding this subject, the basal and meal plasma glucose concentrations of UB obese women were 5.4 ± 0.1 and 6.4 ± 0.2 mmol/l, respectively (also NS).

The average basal plasma insulin concentration in UB obese women was significantly greater than that in LB obese women (95 ± 9 vs. 44 ± 5 pmol/l, respectively, P < 0.001). During the final hour of meal ingestion, average plasma insulin concentrations in UB obese women (472 ± 63 pmol/l) remained significantly greater than those in LB obese women (266 ± 42 pmol/l, P = 0.02).

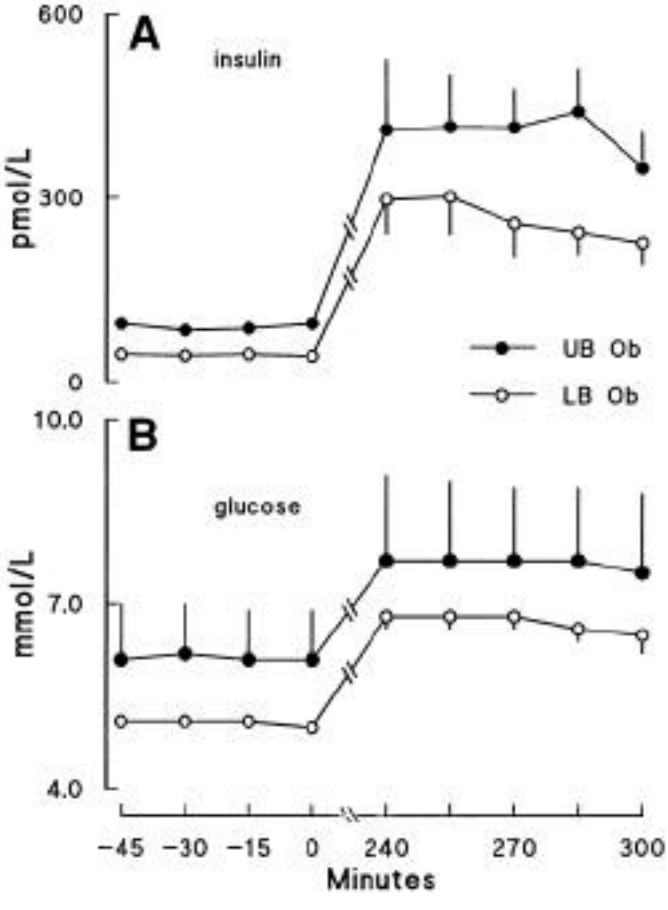

FIG. 1. Plasma insulin (*A*) and glucose (*B*) concentrations during the baseline (–45 to 0 min) and the end of the meal ingestion (240 to 300 min) intervals are shown. UB Ob, upper-body obese women (n = 8); LB Ob, lower-body obese women (n = 8). Differences in mean baseline and meal interval concentration values between groups are provided in RESULTS.

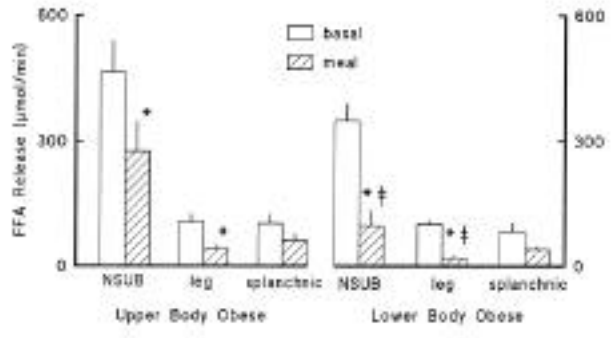

FIG. 2. Regional FFA release rates from nonsplanchnic upper body (NSUB), leg, and splanchnic beds under basal and meal ingestion conditions are depicted for UB (n = 8) and LB (n = 8) obese women. *P < 0.05 vs. basal values; ‡P < 0.05 vs. UB obese.

There were no significant differences in the basal (115 ± 16 vs. 150 ± 27 pmol/l) or meal (160 ± 27 vs. 213 ± 71 pmol/l) plasma epinephrine concentrations between UB and LB obese women, respectively, and no differences between the basal and meal concentrations within groups. Likewise, basal (0.82 ± 0.08 vs. 0.90 ± 0.14 nmol/l) and meal (1.06 ± 0.15 vs. 1.06 ± 0.17 nmol/l) plasma norepinephrine concentrations were not different between UB and LB obese women or between time intervals within groups.

Leg and splanchnic plasma flow. Leg and splanchnic plasma flow under baseline and meal conditions were not different between UB and LB obese women. For all women, leg plasma flow during the meal interval (355 ± 25 ml/min) was greater than basal leg plasma flow (324 ± 27 ml/min, P < 0.05). The hepatic vein catheter became dislodged in two of the LB obese women after the basal collection time interval; therefore, during-meal values for the splanchnic bed are available for only six LB obese women. When all women are considered together, splanchnic plasma flow during the meal (1,112 ± 82 ml/min) was greater than basal splanchnic plasma flow (952 ± 94 ml/min, P = 0.053).

Systemic FFA kinetics. Steady-state FFA kinetics was observed during both sampling periods. Average basal FFA concentration was somewhat greater in UB than in LB obese women (726 ± 42 vs. 617 ± 33 μmol/l, respectively, P = 0.05), whereas systemic FFA flux was not significantly different (653 ± 55 vs. 635 ± 30 μmol/min, respectively); the same was true when FFA flux was expressed relative to FFM (15.0 ± 1.2 vs. 14.5 ± 0.5 μmol · kg^{-1} FFM · min^{-1}, respectively). During the meal, plasma FFA concentrations and flux decreased (P < 0.001) in both groups. The average FFA concentrations during the meal interval (279 ± 55 vs. 80 ± 13 μmol/l, P < 0.0001) and flux (8.5 ± 1.2 vs. 3.9 ± 0.8 μmol · kg^{-1} FFM · min^{-1}, P < 0.0001) were both greater in UB than in LB obese women. The differences in FFA kinetics between groups were not affected if the data from the volunteer with type 2 diabetes was excluded.

Regional FFA kinetics. To determine the adipose depot source of the excess FFA release, regional FFA release rates were examined during meal ingestion in UB compared with LB obese women (Fig. 2). Relative to basal values, leg FFA release during meal ingestion was less in both UB (106 ± 19 vs. 41 ± 10 μmol/min, P < 0.01) and LB (101 ± 11 vs. 20 ± 5 μmol/min, P < 0.001) obese women; meal interval leg FFA release was greater in UB than in LB obese women (P < 0.05). Splanchnic FFA release was less during the meal ingestion interval in both groups; however, the difference from the basal interval was not statistically significant in either UB or LB obese women (Fig. 2). Differences in nonsplanchnic UB FFA release between UB and LB obese women accounted for the majority of the difference in systemic FFA release between the two groups (Fig. 2). Although FFA release from this site was significantly suppressed during the meal interval in UB (464 ± 76 vs. 276 ± 71 μmol/min, P < 0.01) and LB (349 ± 41 vs. 97 ± 37 μmol/min, P < 0.001) obese women, the nonsplanchnic UB FFA release was greater (P < 0.01) in UB obese women.

Splanchnic and hepatic FFA delivery. Basal splanchnic FFA delivery was not different in UB and LB obese women (677 ± 124 vs. 662 ± 104 μmol/min); however, splanchnic FFA delivery during meal ingestion was greater in UB than in LB obese women (275 ± 45 vs. 88 ± 24 μmol/min, respectively, P < 0.005). The maximum estimates of hepatic FFA delivery during meal ingestion in UB and LB obese women were 9.3 ± 1.9 vs. 4.3 ± 0.8 μmol · kg^{-1} FFM · min^{-1}, respectively (P < 0.01 UB vs. LB obese), and the minimum estimates were 5.2 ± 1.1 vs. 2.0 ± 0.4 μmol · kg^{-1} FFM · min^{-1} (P < 0.01). Note that the minimum estimate of meal interval hepatic FFA delivery in UB obese women is numerically (although not significantly) greater than the maximum estimate in LB obese women.

Regional FFA uptake. Basal leg (66 ± 10 vs. 66 ± 11 μmol/min) and splanchnic (322 ± 56 vs. 294 ± 41 μmol/min) FFA uptake was not significantly different in UB and LB obese women, respectively. During the meal ingestion, leg FFA uptake decreased (P < 0.05) in both groups but was greater in UB than in LB obese women (39 ± 5 vs. 18 ± 4 μmol/min, respectively, P < 0.05). Postprandial splanchnic FFA uptake was less (P < 0.05) than basal values in both groups and was greater in UB than LB obese women (133 ± 26 vs. 39 ± 8 μmol/min, respectively, P < 0.05).

Leg glucose uptake. Basal leg glucose uptake was similar in UB and LB obese women, in terms both absolute (37 ± 17 vs. 27 ± 13 μmol/min, respectively, NS) and relative (4.5 ± 2.1 vs. 3.4 ± 1.7 μmol · kg^{-1} leg FFM · min^{-1}, respectively, NS). In contrast, during the meal ingestion, leg glucose uptake was greater in LB than in UB obese women (22.9 ± 2.6 vs. 8.4 ± 5.1 μmol · kg^{-1} leg FFM · min^{-1}, respectively, P < 0.05).

Chylomicron-triglyceride kinetics. Figure 3*B* depicts the triglyceride concentrations in the chylomicron fraction during the basal and meal ingestion intervals. The plasma chylomicron triglyceride concentrations in UB obese women were greater than those in LB obese women during both the basal (125 ± 62 vs. 20 ± 7 μmol/l, respectively, P = 0.05) and meal ingestion (407 ± 178 vs. 154 ± 32 μmol/l, P < 0.05) intervals. The meal triglyceride ingestion rates in UB and LB obese women were 113 ± 3 and 109 ± 2 μmol/min, respectively (NS), equivalent to a caloric intake from meal triglycerides of 0.04 kJ · kg^{-1} · min^{-1} (0.01 kcal · kg^{-1} · min^{-1}) for both groups.

The calculated uptake rates of chylomicron triglycerides across the splanchnic bed during the final hour of meal ingestion are provided in Table 2. Chylomicron triglyceride uptake in the splanchnic bed accounted for 34 ± 8 and 24 ± 5% of the concomitant meal triglyceride ingestion rate in UB and LB obese women, respectively (NS). Leg chylomicron triglyceride uptake was not significantly different in UB and LB obese women during the meal interval (Table 2).

Nonchylomicron triglyceride kinetics. Plasma nonchylomicron triglyceride concentrations are shown in Fig. 3*A*. The average basal concentrations were 1,701 ± 395 and 707 ± 71 µmol/l, respectively, in UB and LB obese women ($P < 0.005$) and did not change significantly during meal ingestion.

Basal nonchylomicron triglyceride release from the splanchnic region was not significantly different between UB and LB obese women (Table 2). Release rates observed during the meal were not significantly different from basal values in either group. Leg nonchylomicron triglyceride uptake was not significantly changed by meal ingestion in either group, and there were no significant differences in leg uptake of nonchylomicron triglycerides between the two groups during either experimental interval.

DISCUSSION

These studies were undertaken to determine whether splanchnic/hepatic FFA delivery is increased in UB obese women compared with LB obese women during meal ingestion, and if so, whether visceral fat is the primary source of the excess FFA. The strong association between visceral fat and glucose intolerance/dyslipidemia (3,35) has prompted speculation that visceral adipose tissue lipolysis contributes directly and in a major fashion to excess hepatic FFA delivery in UB obesity (18). By combining measures of leg and splanchnic blood flow, substrate balance, and FFA kinetics before and during meal ingestion, we confirmed that postprandial hepatic FFA delivery is greater in UB than in LB obese women. To our surprise, we found that the primary source of the excess FFAs is nonsplanchnic UB fat rather than visceral fat.

Nonsplanchnic UB fat contributed the majority of FFAs under postabsorptive conditions in these groups of subjects, consistent with previous observations in lean (36) and obese (12) humans. The ~72% meal-related suppression of FFA release from this adipose tissue depot in LB obese women is virtually identical to the suppression observed in nonobese women under comparable conditions (14). In contrast, meal ingestion suppressed nonsplanchnic UB FFA release by only ~40% in UB obese women, resulting in significantly greater plasma FFA concentrations and thus excess delivery of FFAs to the splanchnic bed from the systemic circulation. Even if the relative amounts of extrahepatic and hepatic FFA uptake changed in the opposite directions in UB and LB obese women, we would still be forced to conclude that visceral adipose tissue FFA release is not the major source of postprandial hepatic FFA delivery in UB obesity. Thus, increased visceral fat may predict abnormal postprandial FFA kinetics but does not appear to be the primary source of excess FFAs.

In our previous studies of FFA metabolism in obese women, all LB obese volunteers had WHRs <0.76 because this value is associated with a very low risk of insulin resistance, hypertriglyceridemia, and other associated conditions (37). For example, the mean WHR of LB obese women in our first study was 0.72 (10). A decision was made to recruit LB obese volunteers with a WHR up to 0.80 in the present study, which resulted in the mean WHR of the women in this LB obese group being 0.76. The inclusion of obese women with slightly greater WHR than the traditional LB obese definition did not limit the discrimination from UB obese women in terms of visceral fat area, postabsorptive or postprandial plasma insulin concentrations or lipid profiles, leg glucose uptake, or postprandial FFA kinetics. We note, however, that postabsorptive

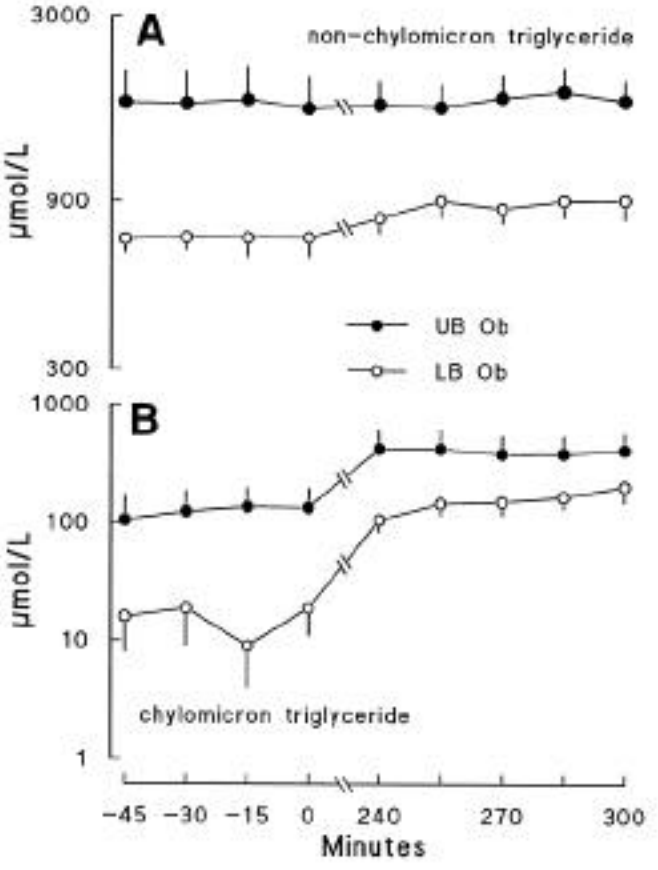

FIG. 3. Plasma nonchylomicron (*A*) and chylomicron (*B*) triglyceride concentrations during the baseline (–45 to 0 min) and the end of the meal ingestion (240 to 300 min) intervals are shown. UB Ob, upper-body obese women (n = 8); LB Ob, lower-body obese women (n = 8). Differences in mean baseline and meal interval concentration values between groups are provided in RESULTS.

FFA flux was approximately equal in our LB and UB obese groups, in contrast with previous publications (10,12,38). This set of findings suggests that *1*) overnight postabsorptive FFA kinetics are "normal" in LB obese women only if they are

TABLE 2
Regional triglyceride kinetics

	Basal		Meal	
	LB	UB	LB	UB
Chylomicron triglycerides				
Splanchnic uptake (µmol/min)	–2 ± 2	10 ± 5	26 ± 6	38 ± 9
Leg uptake (µmol/min)	0 ± 1	5 ± 2	14 ± 4	15 ± 3
Nonchylomicron triglycerides				
Net splanchnic release (µmol/min)	54 ± 11	71 ± 25	28 ± 9	47 ± 3
Leg uptake (µmol/min)	10 ± 4	2 ± 5	5 ± 3	15 ± 7

Data are means ± SE. For leg values, n = 7 UB and 8 LB obese women; for splanchnic values, n = 6 for both LB and UB obese women.

in the lower WHR range of this phenotype, and *2*) to the extent that excess FFA availability contributes to the insulin resistance and hypertriglyceridemia seen in obesity, the postprandial resistance to antilipolysis may be more important than overnight postabsorptive FFA levels.

Splanchnic chylomicron triglyceride uptake rates in UB and LB obese women in this study (34 and 24% of meal triglyceride ingestion rates, respectively) are not substantially different from the 20% we observed in nonobese women using the same experimental paradigm (14). These values are substantially less than the 71% splanchnic meal triglyceride uptake noted in lean men (14). The visceral fat area of lean men in that study (14) was considerably less (58 ± 16 cm^2) than the visceral fat area of either group of obese women in the present study, suggesting that fat mass alone cannot account for the differences in regional chylomicron clearance. We caution that it is technically difficult to accurately measure splanchnic triglyceride balance and that we cannot guarantee entirely constant delivery of chylomicrons to the circulation because of gastric emptying variability. These factors would be expected to make it quite difficult to provide precise estimates of regional chylomicron clearance. Nevertheless, it seems unlikely that differences in meal triglyceride fatty acid uptake by visceral fat are the sole determinant of the increased intra-abdominal fat in UB obese women. We cannot exclude the possibility that increased visceral adipose tissue uptake of VLDL triglyceride fatty acids may occur in UB obesity, however. Net splanchnic nonchylomicron triglyceride release reflects the balance between uptake of triglyceride fatty acids from VLDL particles by omental and mesenteric adipose tissue and the release of newly formed VLDL by the liver. It is possible that hepatic VLDL output in UB obese women is substantially greater than the net splanchnic release we observed if visceral adipose tissue in this group takes up more VLDL triglycerides. This pathway could essentially result in the transfer of nonsplanchnic UB fat to visceral fat or vice versa, depending on the relative sources of hepatic fatty acids and the relative avidity of the different depots for VLDL triglycerides.

Despite much greater plasma insulin concentrations in UB than in LB obese women, postprandial leg glucose uptake was significantly less in UB obese women. This is consistent with the peripheral insulin resistance reported in this group (10) and could relate to their greater postprandial leg FFA uptake; increased FFAs inhibit leg glucose uptake (39). Another potential effect of the failure to adequately suppress FFA release during meal ingestion is greater hepatic VLDL triglyceride production (40), which could have resulted in the greater nonchylomicron triglyceride concentrations in UB than in LB obese women. These triglyceride-rich lipoproteins are thought to compete with chylomicrons for clearance, which could account for the greater chylomicron triglyceride concentrations we observed in UB obese women during meal ingestion (Fig. 3). This lipid pattern is consistent with recent reports of exaggerated postprandial triglyceridemia in viscerally obese men (41).

In summary, the greater postprandial FFA availability in UB obese women compared with LB obese women was found to originate from nonsplanchnic UB fat rather than visceral fat. This failure to adequately suppress lipolysis during meal ingestion results in greater plasma FFA concentrations, and thus greater splanchnic and leg FFA delivery in UB obesity. Metabolic abnormalities associated with, and perhaps attributable to, the excess FFA included hypertriglyceridemia and decreased meal-stimulated leg glucose uptake in UB obesity. Our findings imply that increased visceral fat is predictive of, but not the source of, excess FFAs in the postprandial state. We suggest that more attention should be given to the interactions and associations between the metabolic properties of nonsplanchnic UB fat and visceral fat, rather than focusing solely on the metabolic properties of visceral fat.

ACKNOWLEDGMENTS

Supported by grants DK45343, DK50456 (Minnesota Obesity Center), and RR-0585 from the U.S. Public Health Service and by the Mayo Foundation.

We acknowledge the technical assistance of Carol Siverling, Rita Nelson, Joan Aikens, the staff of the Mayo Clinic General Clinical Research Center and the Mayo Clinic Vascular Radiology Department, and Susan Leachman for editorial assistance.

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