Effect of weight loss on VLDL-triglyceride and apoB-100 kinetics in women with abdominal obesity

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The effects of obesity and weight loss on lipoprotein kinetics were evaluated in six lean women [body mass index (BMI): 21 ± 1 kg/m²] and seven women with abdominal obesity (BMI: 36 ± 1 kg/m²). Stable isotope tracer techniques, in conjunction with compartmental modeling, were used to determine VLDL-triglyceride (TG) and apolipoprotein B-100 (apoB-100) secretion rates in lean women and in obese women before and after 10% weight loss. VLDL-TG and VLDL-apoB-100 secretion rates were similar in lean and obese women. Weight loss decreased the rate of VLDL-TG secretion by ~40% (from 0.41 ± 0.05 to 0.23 ± 0.03 μmol·kg fat-free mass⁻¹·min⁻¹; P < 0.05). The relative decline in VLDL-TG produced from nonsystemic fatty acids, derived from intraperitoneal and intrahepatic TG, was greater (61 ± 7%) than the decline in VLDL-TG produced from systemic fatty acids, predominantly derived from subcutaneous TG (25 ± 8%; P < 0.05). Weight loss did not affect VLDL-apoB-100 secretion rate. We conclude that weight loss decreases the rate of VLDL-TG secretion in women with abdominal obesity, primarily by decreasing the availability of nonsystemic fatty acids. There is a dissociation in the effect of weight loss on VLDL-TG and apoB-100 metabolic pathways that may affect VLDL particle size.

Lipoprotein; fatty acids; lipolysis

Obese persons, particularly those with abdominal (upper-body) obesity, have an increased prevalence of dyslipidemia, manifested by increased fasting plasma triglyceride (TG) and decreased plasma HDL-cholesterol concentrations (12, 26). These alterations in the plasma lipids are associated with an increased risk of coronary heart disease (2, 8, 9, 12, 26). The increase in plasma TG concentration is presumably related to increased hepatic secretion of VLDL, which is the major carrier of TG in plasma during postabsorptive conditions. VLDL-TG secretion is largely regulated by the availability of fatty acids derived from lipolysis of subcutaneous, intraperitoneal, and intrahepatic TG (4, 28, 41). Therefore, the increase in endogenous TG stores and lipolytic rates that is associated with obesity may be responsible for increased VLDL-TG secretion.

Modest weight loss (5–10% of body wt) decreases plasma TG concentrations in obese persons (53). However, the mechanisms that are responsible for the alterations in plasma TG concentrations are not well understood. Moreover, results from several studies suggest that there may be sex differences in the response of lipoprotein kinetics to weight loss. We have recently found that both sex and obesity independently affect basal VLDL-TG metabolism (37). Studies conducted in hypertriglyceridemic (16) and obese (49) men found that weight loss decreased VLDL-TG (16) and VLDL-apolipoprotein B-100 (apoB-100) (16, 49) secretion rates. In contrast, a study conducted in obese women found that weight loss did not affect VLDL-TG secretion (20). However, the failure to show an effect of weight loss on VLDL-TG metabolism in obese women might have been confounded by negative energy balance and the methods used to assess VLDL kinetics, which did not account for tracer recycling or the conversion of tracer to other lipid components that can cause errors in calculating VLDL-TG secretion rate (44, 54). The effect of weight loss on VLDL-apoB-100 kinetics has not been studied in women.

The purpose of the present study was to evaluate the effect of modest weight loss (10% of initial body wt) on 1) VLDL-TG kinetics; 2) VLDL-, intermediate-density lipoprotein (IDL)-, and LDL-apoB-100 kinetics; 3) the relationship between VLDL-TG and VLDL-apoB-100 secretion rates; and 4) the contribution of systemic plasma fatty acids (derived from lipolysis of subcutaneous adipose tissue triglycerides) and nonsystemic fatty acids (derived from lipolysis of intraperitoneal and intrahepatic triglycerides) to VLDL-TG secretion in abdominally obese women. We hypothesized that weight loss will 1) decrease the rate of VLDL-TG secretion; 2) decrease the rate of VLDL-, IDL-, and LDL-apoB-100 secretion; 3) cause a greater decrease in VLDL-TG than in VLDL-apoB-100 secretion rate; and 4) decrease the relative contribution of nonsystemic plasma fatty acids to VLDL-TG. Lipoprotein kinetics and the contribution of fatty acids from different origins of the plasma fatty acids will also be explored.

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sources to VLDL-TG were determined by using stable isotope tracer techniques in conjunction with compartmental modeling (44).

RESEARCH DESIGN AND METHODS

Subjects

Six lean women (age 27 ± 3 yr) and seven women with class II abdominal obesity (age 40 ± 2 yr; waist circumference >90 cm) participated in this study (Table 1). Subjects were considered to be in good health, except for obesity, after completion of a comprehensive medical evaluation, which included a history and physical examination, an electrocardiogram, standard blood and urine tests, and a 2-h oral glucose tolerance test. Persons with increased fasting plasma glucose concentration (>110 mg/dl), impaired oral glucose tolerance, hypertriglyceridemia (>200 mg/dl), and those taking medications regularly or who smoked tobacco were excluded. All subjects had been weight stable for ≥2 mo and had been sedentary (regular exercise <1 h/wk) for ≥6 mo before the beginning of the study. All women were premenopausal and were studied during the follicular phase of their menstrual cycle.

Written informed consent was obtained from all subjects before their participation in the study, which was approved by the Human Studies Committee and the General Clinical Research Center (GCRC) Scientific Advisory Committee of Washington University School of Medicine in St. Louis, MO.

Experimental Protocol

**Body composition analyses.** Fat mass (FM) and fat-free mass (FFM) were determined by dual-energy X-ray absorptiometry (Hologic QDR 1,000/w, Waltham, MA). Abdominal fat mass was determined by magnetic resonance imaging (Siemens, Iselin, NJ); a five-slice image at the L3–L4 interspace was analyzed to determine average subcutaneous and intra-abdominal adipose tissue mass.

**Isotope infusion study.** Subjects were admitted to the inpatient unit of the GCRC at Washington University School of Medicine the day before the isotope infusion study. At 1900, subjects consumed a standard meal, containing 12 kcal/kg body weight for lean subjects and 12 kcal/kg adjusted body weight for obese subjects. Adjusted body weight was calculated as ideal body weight (the midpoint of the medium frame of the Metropolitan Life Insurance Table (35) + 0.25 × (actual body weight – ideal body weight). An adjusted body weight was used in obese subjects to help match relative energy intake with energy requirements in lean and obese groups. The meal consisted of 55% of total energy as carbohydrates, 30% as fat, and 15% as protein. At 2000, the subjects ingested a liquid formula (Ensure; Ross Laboratories, Columbus, OH) containing 250 kcal (40 g carbohydrates, 6.1 g fat, and 8.8 g protein) and then fasted until the completion of the isotope infusion and blood sampling protocol the next day.

On the following morning, an isotope infusion study was performed to measure VLDL-TG and VLDL-, IDL-, and LDL-apoB-100 kinetics. At 0530, one catheter was inserted into a forearm vein to administer stable isotope-labeled tracers, and a second catheter was inserted into a contralateral hand vein; this hand was heated to 55°C with a thermostatically controlled box to obtain arterialized blood samples. At 0600, 50 μmol/kg body wt of [1,2,3,3-H2]glycerol dissolved in 0.9% NaCl were injected as a bolus, and constant infusions of [2,2-2H2]palmitate (0.035 μmol·kg body wt⁻¹·min⁻¹), bound to human albumin (Centeon LLC, Kankakee, IL), and of [5,5,5-2H3]leucine (0.12 μmol·kg body wt⁻¹·min⁻¹; priming dose: 7.2 μmol/kg body wt), dissolved in 0.9% NaCl solution, were started and maintained for 8 h (leucine) and 12 h (palmitate). All stable isotope-labeled tracers were purchased from Cambridge Isotope Laboratories (Andover, MA).

Blood samples were obtained before the administration of tracers to determine plasma lipid and insulin concentrations and background glycerol, palmitate, and leucine isotopic enrichment (tracer-to-tracee ratio; TTR) in plasma, and at 5, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 500, 520, 540, 570, 600, 720, and 960 min after the start of the isotope infusion to determine glycerol and palmitate TTR in plasma and VLDL-TG, and leucine TTR in plasma and VLDL-, IDL-, and LDL-apoB-100. We have previously shown that VLDL-TG concentration is at steady state during the 12-h study period (37); thus VLDL-TG and apoB-100 concentrations were measured at 2, 6, and 12 h to verify that concentrations remained constant. Subjects remained in bed for the entire duration of the isotope infusion. Dinner was served after the blood sample at 960 min (2200) was obtained. The following morning at 0600, after an overnight fast, a blood sample was obtained to determine leucine enrichment in VLDL-, IDL-, and LDL-apoB-100. After that, subjects received breakfast and were discharged from the GCRC. Each subject returned to the GCRC 36, 48, and 72 h after the start of the isotope infusion study for a blood sample to determine leucine enrichment in VLDL-, IDL-, and LDL-apoB-100. After completing the isotope infusion study, obese subjects enrolled in a weight loss program conducted by the Washington University Weight Management Center. This program involved instructions for a low-fat, 1,200–1,400 kcal/day, diet, with 1–2 meals/day provided as a liquid meal replacement (Nutrarecipes; Novartis Nutrition, Minneapolis, MN). Food records were obtained weekly, and subjects attended weekly group behavior modification sessions that were led by an experienced counselor. Body weight was measured weekly at each visit. After a 10% reduction in body weight was achieved (~6 mo after enrollment in the weight management program), dietary intake was adjusted to maintain body weight and prevent further weight loss. When subjects were weight stable for ≥4 wk (<1% change in body wt), the isotope infusion protocol described previously was repeated.

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**Table 1. Body composition of study subjects**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lean</th>
<th>Before weight loss</th>
<th>After weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>58 ± 2</td>
<td>103 ± 5*</td>
<td>93 ± 4†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21 ± 1</td>
<td>36 ± 1*</td>
<td>32 ± 1†</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>70 ± 3</td>
<td>106 ± 3*</td>
<td>ND</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>43 ± 2</td>
<td>53 ± 2*</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>15 ± 1</td>
<td>50 ± 3*</td>
<td>42 ± 3†</td>
</tr>
<tr>
<td>Fat mass, % body wt</td>
<td>26 ± 1</td>
<td>48 ± 1*</td>
<td>45 ± 1†</td>
</tr>
<tr>
<td>Intra-abdominal adipose tissue, cm²</td>
<td>49 ± 32</td>
<td>187 ± 17*</td>
<td>ND</td>
</tr>
<tr>
<td>Subcutaneous abdominal adipose tissue, cm²</td>
<td>115 ± 47</td>
<td>427 ± 28*</td>
<td>ND</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of women, except abdominal adipose tissue data are for 4 lean women. ND, no data. *Value significantly different from corresponding value in lean subjects, P < 0.05. †Value significantly different from corresponding value before weight loss, P < 0.05.

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**Sample Collection**

Blood samples were collected in chilled tubes containing EDTA to determine substrate concentrations and TTRs, and in chilled tubes containing EDTA and aprotinin (Trasylo) to determine insulin concentrations. Samples were placed in an ice bath, and plasma was separated by centrifugation within 30 min of collection. Aliquots of plasma (2 ml) were refrigerated at 4°C for subsequent isolation of lipoproteins. The remaining plasma samples were stored at −70°C until final analyses were performed.

**Isolation of Lipoproteins**

Lipoprotein fractions (VLDL, IDL, and LDL) were isolated by sequential ultracentrifugation (11) within 12 h of blood collection. Briefly, 2 ml of plasma were transferred into Opti Seal tubes (Beckman Instruments, Palo Alto, CA), overlaid with a NaCl-EDTA solution (1.006 kg/l), and centrifuged in a 50.4 Ti rotor (Beckman Instruments) at 100,000 g for 16 h at 8°C. The top layer, containing VLDL, was removed by tube slicing (Beckman Instruments). The density of the remaining sample was adjusted to 1.019 kg/l and centrifuged, and the top layer that contained LDL was collected. The exact amounts of the fractions containing VLDL, IDL, and LDL recovered by tube slicing (~1.3 ml) were recorded to calculate TG and apoB-100 concentrations. The isolated lipoprotein fractions of each sample were stored at −70°C until final analyses were performed.

**Sample Analyses**

Plasma insulin concentration was measured by radioimmunoassay (18). Total plasma TG and VLDL-TG concentrations were measured by using spectrophotometric analysis and a commercially available enzymatic kit (Sigma Chemical, St. Louis, MO). Plasma fatty acid concentrations were quantified by gas chromatography (Hewlett-Packard 5890-II, Palo Alto, CA) after addition of heptadecanoic acid to plasma as an internal standard (33, 45). Total plasma and VLDL-, IDL-, and LDL-apoB-100 concentrations were measured by using a commercially available immunoturbidimetric kit (Wako Chemicals, Richmond, VA) and spectrophotometric analysis. We used a model-predicted (54) relative mass distribution of plasma VLDL-, IDL-, and LDL-apoB-100, in conjunction with total plasma apoB-100 concentration measurements, to calculate plasma VLDL-apoB-100 concentration, to avoid the confounding effect of incomplete recovery of VLDL-, IDL-, and LDL-apoB-100 (15).

All isotopic enrichments were measured by electron impact ionization gas chromatography-mass spectrometry (GC-MS; MSD 5973 system with capillary column; Hewlett-Packard). Plasma glycerol, palmitate, and leucine TTRs were determined as previously described (19, 42, 43, 45). Plasma proteins were precipitated with ice-cold acetone, lipids were extracted with hexane, and the aqueous fraction was dried under vacuum (Savant Instruments); the t-butylmethyldimethylsilyl (t-BDMS) derivative was prepared for analysis, and ions at m/z 200 and 203 were monitored.

ApoB-100 was isolated from the lipoprotein fractions (24) and hydrolyzed with HCl (6 M). The N-Heptafluorobutyryl n-propyl ester of leucine was formed for analysis by GC-MS, and ions at m/z 282 and 285 were monitored to determine leucine TTR. VLDL-TGs were isolated by thin-layer chromatography, and the methyl ester and HFB derivative of palmitate and glycerol in VLDL-TG were prepared as previously described (44–46); ions at m/z 270 and 272 (methyl-palmitate) and 467 and 472 (HFB-glycerol) were monitored to determine palmitate and glycerol TTR in VLDL-TG.

**Calculations**

Basal palmitate rate of appearance (R_a) in plasma was calculated by using the Steele equation for steady-state kinetics (i.e., dividing the palmitate tracer infusion rate by the average plasma palmitate TTR value from 60 to 180 min) (52). FFA R_a was calculated by dividing the palmitate R_a by the proportional contribution of palmitate to total fatty acid concentration in plasma (19, 36).

The fractional catabolic rate (FCR) of VLDL-TG (in pools/ h), which represents the fraction of the VLDL-TG pool that leaves the pool per unit of time, was calculated by fitting the glycerol TTR in plasma and in VLDL-TG to a multicompart- mental model, as previously described (44). During steady-state conditions, the VLDL-TG FCR is equal to the VLDL-TG fractional secretion rate. The absolute rate of VLDL-TG secretion (equal to the absolute rate of VLDL-TG catabolism) was calculated as J total secretion rate, which represents the total amount of VLDL-TG produced by the liver, normalized to FFM; and 2) secretion per unit of plasma, which represents the rate of release of VLDL-TG from the liver into the bloodstream, as follows

\[
\text{VLDL-TG secretion rate (in } \mu\text{mol} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}) = \frac{\left[ (\text{VLDL-TG FCR/60} \times C_{VLDL-TG} \times PV/FFM) \right]}{C_{VLDL-TG}} \tag{1}
\]

\[
\text{VLDL-TG secretion into plasma (in } \mu\text{mol} \cdot \text{l plasma}^{-1} \cdot \text{min}^{-1}) \tag{2} = \frac{(\text{VLDL-TG FCR/60} \times C_{VLDL-TG})}{C_{VLDL-TG}}
\]

where \( C_{VLDL-TG} \) is the concentration of VLDL-TG in plasma, and PV is plasma volume, which was estimated on the basis of each subject’s FFM (PV = 0.055 liter × kg FFM) (7, 13). It was assumed that PV was equal to the VLDL-TG volume of distribution, because VLDL is restricted to the plasma compartment and does not enter the interstitial space or the lymphatic system (47).

The relative contribution of systemic plasma FFA to VLDL-TG-bound fatty acids was calculated by fitting the palmitate TTR in plasma and VLDL-TG to a multicompart- mental model (44) to determine the fraction of VLDL-TG-bound palmitate that is derived from systemic plasma palmitate. The contributions of systemic plasma fatty acids (VLDL-TG_{FFA}) and nonsystemic plasma fatty acids (VLDL-TG_{FFA}) to VLDL-TG secretion were calculated as follows

\[
\text{VLDL-TG_{FFA} = VLDL-TG secretion \times fraction of VLDL-TG derived from systemic plasma palmitate} \tag{3}
\]

\[
\text{VLDL-TG_{FFA} = VLDL-TG secretion} - \text{VLDL-TG}_{\text{FFA}} \tag{4}
\]
Whole body fatty acid and VLDL-TG kinetics

The systemic plasma fatty acid pool includes fatty acids from the systemic circulation that are taken up by the liver and directly incorporated into VLDL-TG or temporarily incorporated into rapidly turning over intrahepatic and intraperitoneal TG stores before incorporation into VLDL-TG. The non-systemic fatty acid pool includes fatty acids derived from 1) preexisting lipid stores in the liver and intraperitoneal fat depots, 2) hepatic uptake and lipolysis of plasma lipoproteins, and 3) hepatic de novo lipogenesis.

The fractional turnover rates (in pools/h) of apoB-100 in the VLDL, IDL, and LDL fractions were assessed as previously described (14, 27) by using a compartment model developed by Zech et al. (54) and the TTR of plasma free leucine and leucine bound to VLDL and IDL (from 0 to 48 h) and the TTR of leucine bound to LDL (from 0 to 72 h). The total rate of VLDL-apoB-100 secretion (in mg·dl·plasma−1·h−1) was calculated by multiplying plasma VLDL-apoB-100 concentration, determined by the fraction of total plasma apoB-100 in VLDL, and the VLDL-apoB-100 fractional turnover rate.

VLDL-TG clearance from plasma (ml/min) was calculated by dividing the rate of VLDL-TG disappearance from plasma (VLDL-TG catabolic rate in μmol/min) by the plasma VLDL-TG concentration (in μmol/ml).

Statistical Analyses

A Student’s t-test for independent samples was used to test for significant differences in lipoprotein kinetics between lean and obese subjects before weight loss. A Student’s t-test for paired samples was used to evaluate the significance of the effect of weight loss on lipoprotein kinetics in obese subjects. A P value ≤0.05 was considered to be statistically significant. On the basis of previous data (37), we estimated that six subjects in each group would be sufficient to detect a 25% change in the rate of VLDL-TG secretion or VLDL-apoB-100 secretion induced by weight loss in obese subjects with a power ≥0.80 and an α-value of ≤0.05. All data are expressed as means ± SE.

RESULTS

Body Composition

Body composition of lean and obese subjects is shown in Table 1. Total body, intra-abdominal, and abdominal subcutaneous fat masses were much greater in obese than in lean women. Obese subjects lost 10 ± 1% of their body weight after completing the weight loss program. Most of the weight loss was due to a decrease in body fat (17 ± 2% of initial fat mass), with only a small decrease in FFM (3 ± 1% of initial FFM).

Table 2. Plasma insulin and lipoprotein concentrations

<table>
<thead>
<tr>
<th></th>
<th>Lean Before weight loss</th>
<th>After weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, μU/ml</td>
<td>6 ± 1</td>
<td>14 ± 1*</td>
</tr>
<tr>
<td>Total TG, mg/dl</td>
<td>81 ± 14</td>
<td>164 ± 9*</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>167 ± 7</td>
<td>197 ± 14</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>83 ± 5</td>
<td>120 ± 13*</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>67 ± 3</td>
<td>44 ± 3*</td>
</tr>
<tr>
<td>Total apoB-100, mg/dl</td>
<td>54 ± 5</td>
<td>84 ± 6*</td>
</tr>
</tbody>
</table>

Values are means ± SE. TG, triglycerides; apoB, apolipoprotein B.

*Value significantly different from corresponding value in lean subjects, P < 0.05. †Value significantly different from corresponding value before weight loss, P < 0.05.

Plasma Insulin and Lipid Concentrations

Baseline plasma insulin concentration was twice as high in obese as in lean women, and it decreased by 25 ± 6% after weight loss (Table 2). Baseline plasma TG and LDL-cholesterol concentrations were higher in obese than in lean subjects, and they decreased by 18 ± 7 and 10 ± 6%, respectively, after weight loss (Table 2). Baseline plasma apoB-100 concentrations were higher in obese than in lean women (P < 0.05) and did not change with weight loss. The proportional contribution of apoB-100 concentration of each lipoprotein subfraction was similar in lean (6 ± 1% VLDL, 6 ± 1% IDL, 88 ± 2% LDL) and obese (7 ± 1% VLDL, 5 ± 1% IDL, 88 ± 1% LDL) subjects and was not affected by weight loss.

Fatty Acid and VLDL-TG Kinetics

Total FFA Ra was significantly higher in obese than in lean women. Weight loss reduced FFA Ra by ~10% (Table 3).

The FCR of VLDL-TG was higher in lean than in obese women before weight loss. Weight loss reduced the FCR of VLDL-TG in obese women by ~30%. The rates of total VLDL-TG secretion and VLDL-TG secre-
tion into plasma were not different between lean and obese women before weight loss. Weight loss caused a 40% decrease in the rate of VLDL-TG secretion (Table 3 and Fig. 1).

The relative contributions of systemic plasma fatty acids (derived from lipolysis of subcutaneous adipose tissue TGs) and nonsystemic fatty acids (derived from lipolysis of intraperitoneal adipose tissue and intrahepatic TGs) to VLDL-TG were not different between lean women and obese women before weight loss (Table 3). Weight loss reduced the secretion rate of VLDL-TG derived from both systemic and nonsystemic fatty acids. However, the relative decrease in VLDL-TG secretion from nonsystemic fatty acids was greater than that from systemic plasma fatty acids (Fig. 2), so the proportional contribution of systemic plasma fatty acids that were incorporated into VLDL-TG decreased by 20%, and the relative contribution of nonsystemic fatty acids decreased by 40% (Table 3).

The clearance rate of VLDL-TG from plasma was greater in lean women than in obese women before weight loss. Weight loss tended to decrease the clearance rate of VLDL-TG, but the differences between the clearance rate before and after weight loss were not statistically significant (P < 0.05) (Table 3).

ApoB-100 Kinetics

The FCR of apoB-100 in the VLDL, IDL, and LDL fractions was greater in lean than in obese women. However, the absolute rate of VLDL-apoB-100 secretion was similar in lean and obese women (Fig. 3). Weight loss did not affect apoB-100 FCR in the lipoprotein fractions (Table 4) or the absolute rate of VLDL-apoB-100 secretion (Fig. 3).

Relationship Between VLDL-TG and VLDL-apoB-100 Secretion

The ratio between the rate of secretion of VLDL-TG to VLDL-apoB-100 tended to be higher in obese than in lean women, but the differences between groups were not statistically significant. Weight loss reduced the rate of VLDL-TG secretion relative to the rate of VLDL-apoB-100 secretion (Fig. 4).

DISCUSSION

In the present study, we investigated the effect of modest, diet-induced weight loss on lipoprotein kinetics in women with abdominal obesity. Our data demonstrate that a 10% loss in body weight causes a 40%
decrease in the basal rate of VLDL-TG secretion by decreasing the contribution of both systemic fatty acids (predominantly derived from lipolysis of subcutaneous adipose tissue TGs) and nonsystemic fatty acids (presumably derived predominantly from lipolysis of intraperitoneal and intrahepatic TGs) to hepatic VLDL-TG formation. Two-thirds of the decrease in VLDL-TG secretion was caused by a decrease in the supply of nonsystemic fatty acids, suggesting that altering lipolytic activity within intraperitoneal and intraperitoneal TGs can have considerable metabolic implications. Weight loss did not affect VLDL-apoB-100 secretion, demonstrating a dissociation in the regulation of VLDL-TG and apoB-100 metabolic pathways.

Hepatic fatty acid availability is a major regulator of VLDL-TG secretion (28). Therefore, it is likely that a decrease in fatty acid release from subcutaneous adipose tissue, intraperitoneal adipose tissue, and intraperitoneal TGs was, at least in part, responsible for the decrease in VLDL-TG secretion in our obese subjects after weight loss. We found that weight loss in our obese women resulted in a decrease in whole body FFA Ra, which would reduce the delivery of systemic fatty acids to the liver. In fact, there was a direct relationship between the decrease in FFA Ra and the decrease in VLDL-TG secretion derived from systemic plasma fatty acids (R² = 0.39; P < 0.05). These results suggest that alterations in subcutaneous adipose tissue lipolytic activity and FFA release may be involved in the weight loss-induced decrease in VLDL-TG secretion. In addition, a weight loss-induced decrease in lipolysis is likely to contribute to the normalization of hepatic glucose production (5, 38) and muscle glucose uptake (6, 21–23) that was observed in other studies. The decrease in the contribution of nonsystemic fatty acids to VLDL-TG secretion suggests that weight loss also decreased lipolysis of intraperitoneal and/or intrahepatic TGs. Several factors that occur with weight loss may be responsible for the decrease in lipolytic rates, including a decrease in adipocyte hormone-sensitive lipase activity (25, 48), a decrease in adipocyte size (32), a decrease in intrahepatic (51), subcutaneous (17, 39, 50), and visceral (17, 39, 50) fat masses, and increased insulin sensitivity (17, 21). Although alterations in the rate of de novo lipogenesis could also have contributed to the reduction of VLDL-TG secretion from nonsystemic fatty acid sources in response to weight loss, it is unlikely to have had a major effect, because fatty acids synthesized de novo contribute <5% to total hepatic VLDL-TG secretion in the basal postabsorptive state in lean and overweight subjects (1, 31).

We are aware of three previous studies, conducted in overweight or obese subjects, that investigated the effect of weight loss on VLDL-TG secretion rate (16, 20, 40). The results from these studies suggest that there may be gender-specific differences in the effect of weight loss on VLDL-TG kinetics. In two studies conducted primarily in men, 5–11% weight loss decreased the rate of VLDL-TG secretion (16, 40), whereas in one study that was conducted in women (20), a 6–10% weight loss did not affect VLDL-TG secretion. However, conclusions regarding gender effects on VLDL-TG kinetics from these studies are confounded because the men had greater dyslipidemia than women, and men were studied when they were weight stable, whereas women were studied when they were actively losing weight. In addition, the methods used to measure VLDL-TG kinetics in these studies were not able to fully account for tracer recycling, which can have a considerable effect on VLDL-TG turnover and secretion rate measurements (44, 54). In the present study, we measured VLDL-TG kinetics by a combination of stable isotope tracer and compartmental modeling techniques that account for tracer recycling (44).

In addition, we studied each subject before and after a predetermined 10% weight loss and after ≥4 wk of weight stability, to eliminate the confounding effects of differences in individual weight loss and negative energy balance on VLDL-TG metabolism. Our results demonstrate that modest weight loss in women who have abdominal obesity and plasma TG concentrations within the upper range of normal causes a considerable decrease in VLDL-TG secretion rate and plasma TG concentrations, similar to what has been observed in men with hypertriglyceridemia.

The contribution of systemic plasma fatty acids to total VLDL-TG secretion tended to be higher, and the

### Table 4. Apolipoprotein B-100 fractional catabolic rates of different lipoprotein subfractions

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Lean</th>
<th>Before weight loss</th>
<th>After weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-apoB-100</td>
<td>0.60 ± 0.07</td>
<td>0.30 ± 0.04*</td>
<td>0.31 ± 0.02</td>
</tr>
<tr>
<td>IDL-apoB-100</td>
<td>0.74 ± 0.15</td>
<td>0.43 ± 0.07†</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>LDL-apoB-100</td>
<td>0.038 ± 0.003</td>
<td>0.024 ± 0.003*</td>
<td>0.028 ± 0.004</td>
</tr>
</tbody>
</table>

Values are means ± SE expressed in pools/h; apoB, apolipoprotein B; IDL, intermediate-density lipoprotein. Value different from corresponding value in lean women: *P < 0.05, †P < 0.09.
contribution of nonsystemic fatty acids tended to be lower, in our obese than in our lean women, but the differences between groups were not statistically significant \((P = 0.11)\). It is possible that our inability to detect a difference in the sources of fatty acids used for VLDL-TG secretion was caused by a type II statistical error because of the small number of subjects in our study. However, we believe that a type II error is unlikely, because we failed to find a relationship between body mass index (BMI) and the relative contribution of systemic and nonsystemic fatty acids to total VLDL-TG secretion in a study of 26 lean, overweight, and obese women (Mittendorfer B and Klein S, unpublished observation). Therefore, the results of the present study and our unpublished observations suggest that, in women, intrahepatic trafficking of systemic and nonsystemic fatty acids into VLDL-TG is not determined by total adiposity. In contrast, Barter and Nestel (4) found that the relative contribution of systemic plasma fatty acids to total VLDL-TG secretion was less in obese than in lean subjects. However, their results may have been confounded by the inclusion of both men and women, and of subjects with hypertriglyceridemia, because gender independently affects basal VLDL-TG kinetics (37), and hypertriglyceridemia is associated with a decrease in the relative contribution of plasma fatty acids to VLDL-TG secretion (41).

Weight loss in our obese women did not affect total VLDL-apoB-100 secretion rate or VLDL-, IDL-, and LDL-apoB-100 FCR. Our findings differ from data reported in two previous studies that were conducted in men, which found that weight loss decreased the rate of VLDL-apoB-100 secretion (16, 49). Initial BMI and percent weight loss in these men (16, 49) were similar to those of the women in our study. Therefore, these results suggest the presence of sexual dimorphism in the response of apoB-100 kinetics to weight loss. We have also found gender differences in baseline VLDL-apoB-100 secretion. The VLDL-apoB-100 secretion rate is similar in lean and obese women, which is consistent with a previous study conducted in women (29) but different from observations made in men, in which VLDL-apoB-100 secretion rates were greater in obese than in lean men (10).

Our data demonstrate that weight loss in obese women has different effects on VLDL-TG and VLDL-apoB-100 metabolism. The dissociation between VLDL-TG and VLDL-apoB-100 responses is consistent with the results of several previous studies that evaluated VLDL metabolism during other physiological interventions. Lewis et al. (30) found that increasing plasma fatty acid availability, by infusing Intralipid and heparin, caused a much greater increase in VLDL-TG than in VLDL-apoB-100 secretion rate, and that artificially maintaining normal plasma fatty acid concentration during an insulin infusion increased VLDL-TG, but not VLDL-apoB-100, secretion. In addition, Melish et al. (34) found that a high-carbohydrate diet increased VLDL-TG, but not VLDL-apoB-100, secretion rate. The composite of these data suggests that VLDL-TG metabolism and apoB-100 metabolism are regulated differently and that alterations in the factors that affect VLDL-TG secretion do not necessarily cause a concomitant change in VLDL-apoB-100 metabolism.

In summary, the results of the present study demonstrate that modest weight loss decreases VLDL-TG secretion in obese women, primarily by decreasing the rate of VLDL-TG secretion from nonsystemic fatty acids derived from lipolysis of intrahepatic and/or intra-peritoneal TG. In contrast, weight loss did not affect the rate of VLDL-apoB-100 secretion. Changes in the rate of VLDL-TG secretion without concomitant changes in VLDL-apoB-100 kinetics suggest that weight loss in women does not change the number of VLDL particles produced by the liver but alters the average TG content of VLDL or increases the secretion of small VLDL particles. More studies are needed to evaluate the clinical implications of these findings.

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