Responses of adipose tissue lipoprotein lipase to weight loss affect lipid levels and weight regain in women

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Nicklas, Barbara J., Ellen M. Rogus, Dora M. Berman, Karen E. Dennis, and Andrew P. Goldberg. Responses of adipose tissue lipoprotein lipase to weight loss affect lipid levels and weight regain in women. Am J Physiol Endocrinol Metab 279: E1012–E1019, 2000.—This study determines whether changes in abdominal (ABD) and gluteal (GLT) adipose tissue lipoprotein lipase (LPL) activity in response to a 6-mo weight loss intervention, comprised of a hypocaloric diet and low-intensity walking, affect changes in body composition, fat distribution, lipid metabolism, and the magnitude of weight regain in 36 obese postmenopausal women. Average adipose tissue LPL activity did not change with an average 5.6-kg weight loss, but changes in LPL activity were inversely related to baseline LPL activity (ABD: \( r = -0.60, \) GLT: \( r = -0.48; P < 0.01 \)). The loss of abdominal body fat and decreases in total and low-density lipoprotein cholesterol were greater in women whose adipose tissue LPL activity decreased with weight loss despite a similar loss of total body weight and fat mass. Moreover, weight regain after a 6-mo follow-up was less in women whose adipose tissue LPL activity decreased than in women whose LPL increased (ABD: \( 0.9 \pm 0.5 \) vs. \( 2.8 \pm 0.6 \) kg, \( P < 0.05 \); GLT: \( 0.2 \pm 0.5 \) vs. \( 2.8 \pm 0.5 \) kg, \( P < 0.01 \)). These results suggest that a reduction in adipose tissue LPL activity with weight loss is associated with improvements in lipid metabolic risk factors with weight loss and with diminished weight regain in postmenopausal women.

adipose tissue metabolism; obesity; lipoprotein lipids; weight gain; postmenopausal women

Lipoprotein Lipase (LPL), located on the luminal surface of the capillary endothelium near muscle and adipose tissue, is the rate-limiting enzyme for the hydrolysis and clearance of circulating triglyceride (TG) (9). Free fatty acids (FFA) derived from the hydrolyzed TG are readily available for transport into adjacent tissues for oxidation and/or storage. Because there is a direct relationship between FFA uptake and LPL activity (5, 39), the relative activity of the enzyme determines FFA availability in muscle and adipose tissue. Through its role in the regulation of circulating TG and FFA uptake, LPL may influence the efficiency of energy storage, composition and concentration of lipoprotein lipids, and relative rates of substrate oxidation.

Adipose tissue LPL activity in humans responds to acute and chronic changes in energy balance. During feeding in normal subjects, adipose tissue LPL activity increases to direct fuel toward storage in adipose tissue (8), whereas during fasting and periods of low energy intake, adipose tissue LPL activity decreases (8, 10), presumably to spare FFA for energy production. Obese individuals have a higher adipose tissue LPL activity than lean persons, even when expressed relative to fat cell size (6, 16, 25, 39). After weight loss and a period of weight maintenance at a reduced body weight, there are variable changes in adipose tissue LPL activity. Some studies show that fasting LPL activity is increased in abdominal (ABD) and gluteal (GLT) subcutaneous adipose tissue of weight-reduced subjects (18, 33, 34), but others show no change or a decrease in LPL activity in the weight-reduced state (10, 17, 27, 30, 37).

This discrepancy among studies in the response of adipose tissue LPL activity to weight reduction may be due to differences in the amount of weight lost (35), the initial degree of obesity, or the initial LPL activity (10, 18). Subjects who lose less weight or have a low initial LPL activity are more likely to increase their adipose tissue LPL activity with weight loss (10, 34, 35). An increase in LPL activity could subsequently affect changes in body fat storage and lipid metabolism. This study was designed to test the hypothesis that changes in ABD and GLT adipose tissue LPL activity in response to a 6-mo dietary weight-loss intervention affect changes in body composition, body fat distribution, lipid metabolism, and/or the magnitude of weight regain during a 6-mo follow-up in obese postmenopausal women.

METHODS

Subject Selection

All subjects were healthy Caucasian postmenopausal (no menstruation for ≥1 yr, follicle-stimulating hormone >30

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IU/l), overweight and obese [body mass index (BMI) 27–40 kg/m²] women. None of the women were on estrogen replacement therapy or medications affecting lipid or glucose metabolism. The women were sedentary (<20 min of exercise, 2×/wk), weight stable (<2.0 kg weight change in past year) and had not smoked for ≥5 yr. All women provided informed consent to participate in the study according to the guidelines of the University of Maryland Institutional Review Board for Human Research.

Initial screening evaluations included a medical history, physical examination, fasting blood profile, and 12-lead resting electrocardiogram to exclude subjects with evidence of hypertension (blood pressure >160/90 mmHg), hyperlipidemia, cancer, liver, renal, or hematological disease, other medical disorders, or orthopedic limitations that would affect physical activity. Women were given a 2-h oral glucose tolerance test (OGTT) to exclude those with diabetes (fasting blood glucose >126 mg/dl; 2-h glucose >200 mg/dl). The second screening visit included a graded exercise test to exclude women with an abnormal cardiovascular response to exercise. Eligible subjects (n = 55) were enrolled in a dietary-induced weight-loss plus low-intensity walking intervention for 6 mo. We report findings on the 36 women who completed the intervention, the second fat biopsy, and all other metabolic studies. Women who did not complete the study had similar baseline characteristics to those who completed the study.

Study Design

Dietary control. Before beginning the weight-loss intervention, all women completed an initial 7-day food record to provide information about their dietary habits. To establish dietary control before metabolic testing and to eliminate changes in dietary composition as a confounder of metabolic changes with weight loss, all women met weekly with a registered dietitian for 6–8 wk for instruction in the principles of a hypocaloric diet that followed the AHA guidelines. The WL program focused on eating behavior, stress management, control of portion sizes, modification of binge eating, and other adverse habits and also encouraged low-intensity walking 3 days/wk for 30–45 min. The women walked 1 day/wk on a treadmill at our exercise facility, at 50–60% heart rate reserve, under the supervision of an exercise physiologist, and they were instructed to walk 2 days/wk on their own. This amount of exercise was maintained constant throughout the 6-mo intervention. After the intervention, the women were weight stabilized (<0.5 kg change) on a eucaloric diet that followed the AHA guidelines for a period of 2 wk before retesting. They had to be weight stable on this diet for ≥2 wk before they were allowed to be tested or else the period was extended. They maintained their 3 days/wk of walking during this period, and the fat biopsy was performed ≥36 h after a bout of walking.

Follow-up. During the 6-mo follow-up, the women were encouraged to maintain their 3-days/wk walking program, and they met every 2nd week with the dietitian for instruction in strategies useful for maintaining WL. We report the changes in body weight of 30 of the 36 women who continued in the program and returned for the 6-mo follow-up assessment of body weight.

Testing Procedures

Body composition. Waist-to-hip ratio (WHR) was measured in duplicate and calculated as the ratio of the minimal waist circumference to the circumference of the maximal gluteal protuberance. Percent body fat, fat-free (bone and muscle) mass, and adipose tissue mass were measured using dual-energy X-ray absorptiometry (model DPX-L, Lunar Radiation, Madison, WI). A single-slice computed tomography (CT) scan taken midway between L4 and L5 was performed using a GE Hi-Light CT scanner to measure intra-abdominal and subcutaneous fat areas as previously described (21).

Maximal aerobic capacity. VO\textsubscript{2max} was measured on a motor-driven treadmill (Quinton) during a progressive exercise test to voluntary exhaustion as previously described (19). A valid VO\textsubscript{2max} was obtained when at least two of these three criteria were met: 1) maximal heart rate >90% of age-predicted maximal heart rate (220 beats/min – age), 2) respiratory exchange ratio of ≥1.10, and 3) plateau in VO\textsubscript{2} (<200 ml/min change) with increasing work rate.

Resting metabolic rate and substrate oxidation. RMR and rates of substrate oxidation were measured by indirect calorimetry in the early morning after a 12-h fast using the ventilated hood technique (Deltatrac Metabolic Monitor, SensorMedics, Yorba Linda, CA) as previously described (19). OGGT. After an overnight fast, a 20-gauge polyethylene catheter was placed in an antecubital vein to facilitate blood sampling. Samples were drawn at 10 and 5 min before oral ingestion of 75 g of glucose. Subsequent samples were drawn at 30, 60, 90, 120, 150, and 180 min after ingestion of the glucose. The plasma was separated by centrifugation, and glucose and insulin concentrations were measured in duplicate by the glucose oxidase method (Beckman glucose analyzer, Fullerton, CA) and RIA with an insulin-specific antibody (cross-reactivity with proinsulin <0.2%) (Linco, St. Louis, MO), respectively. Total glucose and insulin areas under the curve were calculated by the trapezoidal method (38).

Lipoprotein lipids and FFA. Venous blood samples for the measurement of lipoprotein lipids were collected in chilled tubes containing 1 mg EDTA/ml of blood. Plasma was sepa-
rated by centrifugation at 4°C, and lipoprotein lipids were measured as previously described (20). Fasting FFA concentrations were measured using the nonesterified fatty acid colorimetric (NEFA C) test kit (Wako Chemicals, Richmond, VA).

Adipocyte size and LPL activity. After a 12-h overnight fast, 4–6 g of subcutaneous adipose tissue were obtained under local anesthesia (1% xylocaine) from both the ABD (3–4 cm distal to the umbilicus) and GLT (upper distal quadrant) region by aspiration with a 16-gauge needle. Adipocytes were isolated, and adipocyte size was measured as previously described (21).

LPL was eluted from 30- to 50-mg fragments of adipose tissue into 2.5 ml Krebs-Ringer-Phosphate buffer containing 5 U heparin during a 45-min incubation at 37°C. Triplicate 0.5-ml aliquots of the eluate were incubated with 0.1 ml of substrate. The substrate was prepared by sonication of 4 μCi \([1-14C]\)glycerol triolein, 5 mg unlabeled triolein, and 240 μg lecithin in 4 ml of 0.5 M Tris buffer, pH 8.2, containing 2% FFA-free albumin and 0.25 ml fasting serum, which provides the cofactor needed for LPL activity, ApoC2. The enzyme reaction was stopped after 45 min at 37°C by addition of Belfrage’s extraction mixture (4) to separate the product, \([1-14C]\)-labeled FFA, from unreacted substrate. The labeled FFA was quantitated by liquid scintillation counting, and, after correction for recovery during the extraction, LPL activity was expressed as nanomoles fatty acid produced per minute by 10⁶ cells.

Statistics

Statistical analyses were performed with a Macintosh Statview program (Abacus Concepts, Berkeley, CA). Distribution of the data was first tested for departures from normality using the Shapiro-Wilk test. LPL, insulin, and triglyceride data were not normally distributed, so the logarithm of each was used for parametric statistical analyses. Differences between variables before and after weight loss were determined with a paired \(t\)-test. Regression analyses were used to determine statistically significant relationships between variables. All data are presented as means ± SE, and the level of significance was set at \(P < 0.05\) for all analyses.

RESULTS

Changes in Physical Characteristics with WL

The ages of the 36 women ranged from 51 to 67 yr with a mean of 59.2 ± 4 yr. On average, body weight decreased 6.5% during the 6-mo WL intervention (\(P < 0.0001\)), with a 13.3% decrease in fat mass (\(P < 0.0001\)) but no change in lean mass. Because both waist and hip circumference decreased with WL (\(P < 0.0001\)), there was no change in WHR. There were comparable 14% decreases in intra-abdominal fat (IAF) and subcutaneous abdominal fat (SAF) areas (\(P < 0.0001\)). On average, \(\text{VO}_{2\text{max}}\) increased 5.7% (\(P < 0.01\)) with 6 mo of hypocaloric diet therapy and walking (Table 1).

Changes in Adipocyte Size and LPL Activity with WL

GLT adipocytes were larger than ABD adipocytes both before and after WL (\(P < 0.05\)); however, there was a comparable 11–13% decrease in both ABD and GLT adipocyte size with WL (\(P < 0.0001\); Table 2). Gluteal LPL activity was higher than ABD LPL activity both before (\(P < 0.05\)) and after WL (\(P < 0.01\); Table 2). Adipose tissue LPL activity was not related to body weight, BMI, fat mass, percent body fat, or \(\text{VO}_{2\text{max}}\) before or after WL. In addition, LPL activity (expressed per gram of tissue) was not related to adipocyte size before or after WL [ABD: \(r = 0.20\), GLT: \(r = 0.10\), \(P\) not significant (NS)]. However, because of individual changes in cell size with WL, LPL activity is expressed per cell number in all subsequent analyses.

On average, adipose tissue LPL activity, expressed per gram of tissue or per cell, did not change with WL at either site. However, the absolute changes in adipose tissue LPL activity were inversely related to baseline LPL activity at both ABD (\(r = -0.60\), \(P < 0.0001\)) and GLT (\(r = -0.48\), \(P < 0.01\)) sites (Fig. 1).

Changes in Metabolic Variables with WL

Fasting FFA levels were 16% lower after WL (\(P < 0.01\)). Fasting glucose as well as the glucose area during the OGTT decreased significantly with WL (\(P < 0.05\); Table 3). On average, fasting insulin decreased 5% and the insulin area decreased 10.5%, but these changes did not reach statistical significance. Total cholesterol and triglyceride levels decreased with WL (\(P < 0.05\) and \(P < 0.0001\)) and there was a tendency for a decrease in LDL cholesterol (\(P = 0.07\)). The average HDL cholesterol level tended to increase by 5% with WL (\(P = 0.07\)), whereas HDL₃ cholesterol increased 51% (\(P < 0.01\)).

Relationship of Changes in LPL Activity with WL and Changes in Body Weight and Fat Distribution with WL

Relative changes in LPL activity with WL did not correlate with relative changes in body weight, total fat mass, or \(\text{VO}_{2\text{max}}\). However, changes in LPL activity did correlate with regional changes in body fat. Relative changes in ABD LPL activity with WL correlated directly with relative changes in waist circumference (\(r = 0.43\), \(P < 0.05\)), hip circumference (\(r = 0.49\), \(P < 0.01\)), and IAF and SAF areas (\(r = 0.36\) and 0.45, \(P < 0.05\)), whereas relative changes in GLT LPL activity were related only to relative changes in hip circumfer-
and seven women decreased ABD but increased GLT changed in the same direction in both sites; three
site (P < 0.05).

To further examine the effects of changes in adipose tissue LPL activity on regional body composition, we
compared findings in women who increased their ABD and GLT LPL activity (n = 13 and 17, respectively)
with women who decreased their ABD and GLT LPL activity (n = 23 and 19, respectively). The average
relative changes in LPL activity with WL in these two groups were 156 ± 49% vs. —55 ± 5% for the ABD site
(P < 0.0001) and 121 ± 31% vs. —47 ± 6% for the GLT site (P < 0.0001). LPL activity in 26 of the 36 women
changed in the same direction in both sites; three women increased AB and decreased GLT LPL activity,
and seven women decreased ABD but increased GLT LPL activity.

There were no differences in the changes in \( \dot{V}O_2_{max} \) or body weight in women who increased LPL activity
compared with those who decreased LPL activity (data not shown). Likewise, the decrease in adipocyte size
was similar in women whose LPL activity increased compared with women whose LPL activity decreased.
However, women whose ABD LPL activity decreased with WL lost more IAF (—18 ± 3% vs. —7 ± 4%, P <
0.05) and tended to lose more SAF (—15 ± 2% vs. —8 ± 3%, P = 0.08) than women whose ABD LPL activity
increased, whereas women whose GLT LPL activity decreased lost more SAF (—16 ± 2% vs. —8 ± 2%, P <
0.05) but not more IAF (—16 ± 3% vs. —11 ± 4%, P = NS) than women whose GLT LPL activity increased.

Effects of Changes in LPL Activity with WL on Lipid Metabolism

With WL, relative changes in total and LDL cholesterol were directly related to relative changes in ABD
(r = 0.44 and 0.39 respectively, P < 0.05) and GLT adipose tissue LPL activity (r = 0.60 and 0.44, respectiv-
ly, P < 0.01). On the other hand, relative changes in FFA concentrations correlated negatively with rela-
tive changes in adipose tissue LPL activity (ABD: r = —0.42; GLT: r = —0.49, P < 0.05), such that FFA
concentrations decreased more in women whose LPL activity increased with WL.

The lipoprotein lipid responses to WL in women who increased and decreased adipose tissue LPL activity
with WL are shown in Fig. 2. Total and LDL cholesterol decreased in women whose ABD and GLT adipose
adipose tissue LPL activity decreased with WL (P < 0.05) but did not change in women whose LPL activity
increased. The changes in total and LDL cholesterol between groups were significant (P < 0.05). There were no
differences in the triglyceride, HDL cholesterol, or HDL_2 subfraction responses to WL between groups,

![Fig. 1. Relationship of absolute changes in log transformed adipose tissue lipoprotein lipase (LPL) activity to baseline log transformed adipose tissue LPL activity in abdominal (A; r = —0.60, P < 0.01) and gluteal (B; r = —0.48, P < 0.01) sites. LPL activity is expressed as nmol free fatty acids 10^6 cells^-1 min^-1.](http://ajpendo.physiology.org/)

Table 2. Adipocyte size and LPL activity before and after weight loss

<table>
<thead>
<tr>
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<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>ABD cell size, µg TG</td>
<td>0.85 ± 0.02</td>
<td>0.74 ± 0.02*</td>
</tr>
<tr>
<td>GLT cell size, µg TG</td>
<td>0.90 ± 0.02</td>
<td>0.79 ± 0.02*</td>
</tr>
<tr>
<td>ABD LPL, nmol FFA g^-1·min^-1</td>
<td>3.9 ± 0.6</td>
<td>3.4 ± 0.6</td>
</tr>
<tr>
<td>GLT LPL, nmol FFA g^-1·min^-1</td>
<td>4.6 ± 0.5</td>
<td>5.4 ± 0.9</td>
</tr>
<tr>
<td>ABD LPL, nmol FFA 10^8 cells^-1·min^-1</td>
<td>3.2 ± 0.5</td>
<td>2.5 ± 0.5</td>
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<tr>
<td>GLT LPL, nmol FFA 10^8 cells^-1·min^-1</td>
<td>4.1 ± 0.5</td>
<td>4.2 ± 0.7</td>
</tr>
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</table>

Values are means ± SE; n = 36 women. TG, triglyceride; ABD, abdominal; GLT, gluteal; LPL, lipoprotein lipase activity; FFA, free fatty acids. *P < 0.0001 vs. before weight loss.

Table 3. FFA, glucose, and lipid metabolic risk factors before and after weight loss

<table>
<thead>
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<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>FFA, meq/l</td>
<td>0.81 ± 0.28</td>
<td>0.68 ± 0.22*</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.27 ± 0.11</td>
<td>5.05 ± 0.06*</td>
</tr>
<tr>
<td>Glucose area, mmol·min^-1·l^-1</td>
<td>1,290 ± 46</td>
<td>1,116 ± 34†</td>
</tr>
<tr>
<td>Fasting insulin, pmol/l</td>
<td>76 ± 6</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>Insulin area, pmol·min^-1·l^-1</td>
<td>75,109 ± 6,657</td>
<td>66,054 ± 6,473</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.55 ± 0.08</td>
<td>1.39 ± 0.07‡</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.02 ± 0.13</td>
<td>4.81 ± 0.16*</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.19 ± 0.03</td>
<td>1.24 ± 0.03</td>
</tr>
<tr>
<td>HDL_2 cholesterol</td>
<td>0.10 ± 0.01</td>
<td>0.14 ± 0.02†</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.26 ± 0.13</td>
<td>3.13 ± 0.10</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 36 women, except FFA, n = 27. *P < 0.05, †P < 0.01, ‡P < 0.0001 vs. before weight loss.
although there was a trend for an increase in HDL cholesterol in women who increased, compared with those who decreased, their GLT LPL activity ($P = 0.06$).

Effects of Changes in LPL Activity with WL on Weight Regain

The 30 women who completed the 6-mo follow-up lost $6.8 \pm 0.6\%$ of their body weight during WL (pre: $85.5 \pm 1.8$, post: $79.7 \pm 1.8$ kg, $P < 0.0001$). Their results did not differ from the entire group of women in terms of amount of weight lost or ABD or GLT LPL response to WL (data not shown). The average body weight increased $1.5 \pm 0.4$ kg (or $1.8 \pm 0.5\%$) to $81.4 \pm 2.0$ kg during the 6-mo follow-up, which remained, on average, $5.2 \pm 0.9\%$ or $4.4 \pm 0.7$ kg below the average baseline body weight.

Weight regain during the 6-mo follow-up was less in women whose ABD and GLT adipose tissue LPL activity decreased (Table 4; $P < 0.01$). Furthermore, the total amount of weight lost from baseline to follow-up was greater in women whose ABD and GLT LPL activity decreased than in those whose LPL activity increased (Table 4; $P < 0.05$). These changes in body weight during the follow-up correlated positively with changes in GLT adipose tissue LPL activity ($r = 0.52$, $P < 0.01$) and tended to correlate with changes in ABD adipose tissue LPL activity ($r = 0.30$, $P = 0.10$). In addition, changes in body weight from baseline to follow-up correlated positively with relative changes in both GLT ($r = 0.53$, $P < 0.01$) and ABD ($r = 0.42$, $P < 0.01$) adipose tissue LPL activity, suggesting that a greater increase in adipose tissue LPL with WL is associated with a greater tendency for body weight to return to baseline.

**DISCUSSION**

Previous studies in obese subjects show that weight loss induces variable changes in adipose tissue LPL activity. In the present study, we show that body weight outcomes and lipid metabolic responses to weight loss in overweight and moderately obese postmenopausal women are affected by changes in adipose tissue LPL activity with weight loss. The differential changes in ABD and GLT adipose tissue LPL activity with weight loss correlated with the baseline LPL activity, which in turn affected reductions in abdominal obesity and total and LDL cholesterol levels. The loss of abdominal body fat and decreases in total and LDL cholesterol were greater in women whose ABD and GLT LPL activity decreased with weight loss, despite a similar loss of total body weight and fat mass after 6 mo of caloric restriction. Moreover, women whose ABD and GLT adipose tissue LPL activity decreased with weight loss regained less weight during the follow-up than women whose LPL activity increased.

The effects of dietary-induced weight loss on adipose tissue LPL activity may depend on the timing of the LPL measurement. During, or within days of, a hypocaloric diet, all studies show that adipose tissue LPL activity is reduced (6, 8, 16, 37, 39). However, when measured after a period of weight maintenance, fasting adipose tissue LPL activity is either increased (18, 33, 34), decreased (10, 17, 27, 30), or unchanged (17, 37) in

Table 4. Body weight changes after weight loss and follow-up in women who increased or decreased adipose tissue LPL activity

<table>
<thead>
<tr>
<th></th>
<th>↑ ABD LPL (n = 10)</th>
<th>↓ ABD LPL (n = 20)</th>
<th>↑ GLT LPL (n = 15)</th>
<th>↓ GLT LPL (n = 15)</th>
</tr>
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<tbody>
<tr>
<td>Body weight, kg during 6-mo WL</td>
<td>$-5.2 \pm 0.9$</td>
<td>$-6.2 \pm 0.7$</td>
<td>$-4.8 \pm 0.7$</td>
<td>$-6.9 \pm 0.8$</td>
</tr>
<tr>
<td>Body weight, kg during 6-mo follow-up</td>
<td>$2.8 \pm 0.6$</td>
<td>$0.9 \pm 0.5^*$</td>
<td>$2.8 \pm 0.5$</td>
<td>$0.2 \pm 0.5^*$</td>
</tr>
<tr>
<td>Body weight, kg during WL &amp; follow-up</td>
<td>$-2.4 \pm 1.0$</td>
<td>$-5.4 \pm 0.9^*$</td>
<td>$-2.0 \pm 0.8$</td>
<td>$-6.8 \pm 0.8^*$</td>
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Values are means ± SE. WL, weight loss. $^* P \leq 0.05$; $^\dagger P < 0.01$. 

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**Fig. 2.** Relative changes in lipoprotein lipid levels in women who increased and those who decreased abdominal (A) and gluteal (B) adipose tissue LPL activity with weight loss.
the weight-reduced state. Taken together, our results are consistent with all of these findings, because, although on average LPL activity did not change with weight loss in these women, there was a wide range in the response of LPL activity in both ABD and GLT sites. Indeed, GLT LPL activity increased in about one-half of subjects and decreased in the other one-half, whereas ABD LPL activity increased in about one-third of subjects and decreased in the other two-thirds.

Changes in LPL activity were not related to the initial degree of obesity or to the total amount of body weight or adipose tissue lost; rather, changes in regional fat mass were related to regional changes in adipose tissue LPL activity. Specifically, changes in waist and hip circumferences and in abdominal visceral and subcutaneous fat areas were directly related to changes in ABD LPL activity, whereas changes in hip circumference and abdominal subcutaneous fat area were related to changes in GLT LPL activity. This suggests that changes in body fat distribution are, in part, related to changes in regional adipose tissue LPL activity and supports previous findings that regional differences in fat deposition correlate with regional differences in LPL activity (11, 26, 28).

The theory that adipose tissue LPL plays an important role in the regulation of body weight is derived from the enzyme's known function in the hydrolysis of circulating TG into FFA for uptake and storage by adipose tissue. Although it is postulated that a high adipose tissue LPL activity, leading to increased efficiency of energy storage, is an underlying mechanism for the commonly observed weight regain after weight loss (10, 14, 18, 34), to our knowledge, this is the first study to show such a relationship in humans. Our finding of a greater weight regain in women whose adipose tissue LPL increased with weight loss is consistent with a previous finding that a high initial fasting adipose tissue LPL activity predicts a greater weight gain in women who stop smoking (7). In addition, supporting data from experiments involving animal models of obesity show that an increased adipose tissue LPL activity in the preobese state of genetically obese Zucker rats (fa/fa) precedes their development of obesity (15). Conversely, ob/ob mice deficient in adipose tissue LPL gain less weight and fat mass than control ob/ob mice (40).

Our finding that women whose ABD and GLT LPL activity increased with weight loss regained more weight during follow-up suggests that there was an increased efficiency of energy storage in the weight-reduced state of these women. However, the mechanism by which a higher adipose tissue LPL activity influences energy intake or energy expenditure to cause weight regain requires further study. Presumably, an elevated adipose tissue LPL activity would predispose one to increased triglyceride storage, because uptake of FFA by adipose tissue correlates with LPL activity in adipose tissue (39). Our finding of an indirect correlation between changes in FFA concentrations and adipose tissue LPL activity may indicate that FFA are more readily taken up by adipose tissue in women who increase their ABD and GLT adipose tissue LPL activity. A preferential shunting of lipid substrate into adipose tissue rather than to muscle could reduce fat oxidation, which is a predictor of weight gain (32, 41). Moreover, LPL may act as a peripheral signal, through insulin, leptin, or some other circulating factor, to the central nervous system to stimulate food intake or reduce energy expenditure (13). This suggests that women who increase their ABD and GLT adipose tissue LPL activity with weight loss and have a faster rate of weight regain are more likely to reduce their fat oxidation or energy expenditure and/or increase their food intake more than women who decrease their adipose tissue LPL activity with weight loss.

LPL plays an important role in lipoprotein metabolism by catalyzing circulating triglyceride-rich lipoproteins (chylomicrons and VLDL), leading to the formation of HDL and LDL cholesterol (2, 12, 24, 29). In addition, LPL serves as a ligand for lipoprotein receptors, thereby facilitating cellular uptake of lipoprotein particles (3, 31). An increase in LPL activity with weight loss could lead to an increase in triglyceride clearance, resulting in lower plasma levels of triglycerides and increases in HDL and LDL cholesterol. Our results show that, despite a similar amount of weight loss and a similar reduction in fat cell size, women whose ABD and GLT LPL activity increases with weight loss have smaller reductions in total and LDL cholesterol than women whose LPL activity decreases. In a similar study, Imbeault et al. (17) showed an indirect relationship between changes in LDL cholesterol and abdominal adipose tissue LPL activity with weight loss in men but not such relationship in women. In addition, they showed that women whose femoral LPL activity decreased had greater reductions in HDL cholesterol. Although not statistically significant, our data showed a similar trend for an increase in HDL cholesterol in women with an increase in GLT LPL activity compared with those with a decrease. There was no association between changes in triglyceride levels and changes in adipose tissue LPL activity, as might be expected due to the role of LPL in the hydrolysis of triglyceride-rich lipoproteins in our study or that of Imbeault. However, results of studies investigating the effects of exercise or lipid-lowering drugs on triglyceride concentration indicate that reductions in triglycerides are associated with fasting skeletal muscle LPL, rather than with adipose tissue LPL activity (22, 23, 36). Thus skeletal muscle LPL may play a more important role in the regulation of fasting plasma triglyceride levels with diet-induced weight loss.

The findings of this study significantly advance our understanding of the role of adipose tissue LPL in the regulation of body weight and lipid metabolism. Postmenopausal women who decrease their adipose tissue LPL activity with weight loss selectively reduce abdominal subcutaneous and visceral fat, regain body weight at a slower rate, and have greater improve-
ments in lipid metabolic disease risk factors than women whose adipose tissue LPL activity increases after weight reduction. Although these findings are novel with regard to their demonstration of the metabolic consequences of a weight loss-induced increase in adipose tissue LPL, there are several questions remaining to be addressed in future research. First, the weight loss intervention in this study was a lifestyle intervention designed for moderate weight loss, and the women remained considerably overweight at the time of the posttesting. It would be of interest to study the effects of changes in LPL activity after a more severe weight loss that reduces women to a normal body weight. Second, determination of fasting LPL activity alone may not be representative of the overall efficiency of adipose tissue to store energy in the fed state. Eckel and Yost (10) showed no change in fasting adipose tissue LPL activity after weight reduction despite marked increases in LPL responsiveness to insulin infusion and food ingestion. Moreover, just as there are variable results with LPL activity, other weight loss studies show that LPL mRNA expression may be increased (18) or unchanged with weight loss (17). Thus measurement of LPL mRNA levels would permit examination of whether weight loss-induced differences in LPL expression are also predictive of body weight and metabolic responses to hypocaloric diets. In the same regard, weight-loss studies in which simultaneous measurements of adipose tissue and skeletal muscle LPL activity and mRNA levels are made would address the question of tissue-specific regulation of LPL and its effects on body weight, body composition, and lipid metabolism. These future studies would complement the findings of the current study to advance our understanding of the mechanisms regulating fat metabolism in the obese and weight-reduced states.

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