Role of Hepatic-Triglyceride Lipase Activity in the Association between Intra-abdominal Fat and Plasma HDL Cholesterol in Obese Women

Jean-Pierre Després, Mario Ferland, Sital Moorjani, André Nadeau, Angelo Tremblay, Paul J. Lupien, Germain Thériault, and Claude Bouchard

Intra-abdominal fat content is an important variable in the association between regional body fat distribution and plasma high density lipoprotein (HDL) cholesterol levels. In the present study, we report on the role of plasma postheparin lipases as well as abdominal and femoral adipose tissue lipoprotein lipase activities in the association between body fat distribution and plasma lipoprotein levels. Postheparin plasma lipoprotein lipase (LPL), hepatic-triglyceride lipase (H-TGL), abdominal and femoral adipose tissue (AT>LPL) activities and plasma lipoprotein levels were measured after an overnight fast in a sample of 16 obese women (ages 36.0±6.1 years [mean±SD], percent body fat 46±6%). Computed axial tomography was used to assess body fat distribution. Plasma postheparin LPL activity was neither correlated with total adiposity nor with the level of intra-abdominal fat. Intra-abdominal fat deposition was, however, positively correlated with H-TGL activity (r=0.66, p<0.005). Furthermore, covariance analysis showed that the association between intra-abdominal fat and H-TGL was independent from total adiposity. Plasma postheparin LPL and abdominal AT>LPL activities showed no significant correlation with plasma lipoprotein levels, whereas femoral AT>LPL activity was positively correlated with the HDL₃ cholesterol/HDL₄ cholesterol ratio (r=0.51, p<0.05). H-TGL activity was, however, negatively correlated with HDL₄ cholesterol (r=-0.60, p<0.05), but not with HDL₃ cholesterol (r=-0.28, NS). These results suggest that the high H-TGL activity in obese women with excess deep abdominal fat could be responsible for the reduction in plasma HDL₄ cholesterol levels. It should, however, be emphasized that these cross-sectional observations do not necessarily reflect a cause-effect relationship and that additional experimental studies are needed to substantiate the present findings.

(Arteriosclerosis 9:485-492, July/August 1989)

Numerous studies have demonstrated that variations in plasma lipid and lipoprotein levels that are observed in obesity are related to the regional distribution of body fat.¹⁻¹¹ These changes in plasma lipid and lipoprotein levels could be partly responsible for the independent relation of body fat distribution to the incidence of coronary heart disease (CHD).¹²⁻¹⁷ Indeed, studies that have used skinfolds and the waist-to-hip circumference ratio to assess regional body fat distribution have shown that individuals with a high proportion of abdominal fat display significant changes in their plasma lipid and lipoprotein levels, such as an increase in plasma triglyceride concentration¹⁻¹¹ and a reduction in plasma high density lipoprotein (HDL) cholesterol levels.⁵⁻¹¹ Individuals with a peripheral accumulation of body fat, however, display a normal lipoprotein profile and a low risk of CHD.¹⁻¹¹

Recent advances in the assessment of adipose tissue distribution have allowed the accurate measurement of both deep and subcutaneous fat content, and with the use of computed-assisted tomography,¹⁸⁻²³ it has been possible to determine the respective associations between deep and subcutaneous fat deposits and plasma lipoprotein levels. We have recently reported that, in a sample of obese women, deep abdominal fat was the critical variable in the association between body fat distribution and plasma HDL cholesterol levels.²⁴ Multiple regression analyses also indicated that intra-abdominal fat was the variable of body fat distribution that explained the largest amount of variance of lipoprotein ratios (HDL cholesterol/low density lipoprotein [LDL] cholesterol; HDL apoprotein [apo] A-I/LDL apo B; and HDL₃ cholesterol/HDL₄ cholesterol) that are often used in the estimation of the risk of CHD.²⁴ We have, therefore, suggested that a high intra-abdominal fat content should be considered as a risk factor for CHD.²⁴ The mechanisms for the association between intra-abdominal fat and HDL cholesterol levels have not, however, been elucidated.

It is well known that the activity of triglyceride lipases, namely lipoprotein lipase (LPL) and hepatic triglyceride...
The sample of 16 obese women studied in the present paper was part of a larger group of 52 premenopausal obese women who participated in a study designed to investigate the associations between body fat distribution measured by computed tomography and metabolic variables, such as glucose tolerance and plasma insulin levels, and plasma lipoprotein concentrations. The physical and metabolic characteristics of the original sample of 52 obese women have, therefore, been described in detail. At the time of the study, the subjects were solicited for further tests that required adipose tissue biopsies and collection of postheparin plasma for the measurement of adipose tissue and plasma lipase activities. Among the 52 women originally studied, 16 subjects volunteered to participate in the additional tests. The physical and metabolic characteristics of this subsample of 16 women, presented in Table 1, were not significantly different from those of the original sample. All subjects signed an informed consent document as required by the Laval University Medical Ethics Committee. A physician gave each subject a complete physical examination that included a medical history, and subjects with cardiovascular disease or endocrine disorders (such as hirsutism) or those on medication were excluded. Diabetic subjects were excluded from the study, but two women had plasma glucose values >140 but <200 mg/dl at 2 hours after an oral glucose tolerance test and were diagnosed by the classification of the National Diabetes Data Group as having impaired glucose tolerance. All participants were tested during the early follicular phase of their menstrual cycles and in weight-stable periods.

**Computed Tomography**

Computed tomography was performed on a Siemens Somatom DRH scanner (Erlangen, FRG) by using the procedures of Sjöström et al. as previously described. Briefly, we performed an abdominal scan using a radiograph of the skeleton as a reference to establish the position of the scan (between L4 and L5) to the nearest millimeter. The total and deep fat areas were calculated by delineating these areas with a graph pen and then computing the adipose tissue surfaces; an attenuation range of -30 to -190 HU was used. The intra-abdominal fat area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The subcutaneous fat was calculated by subtracting the amount of intra-abdominal fat from the total fat area.

**Measurement of Total Body Fat**

The total body fat was obtained from the body density measured by hydrostatic weighing as previously described and the percent body fat was derived from body density using the equation of Siri. The fat mass was obtained by multiplying percent body fat by body weight. Pulmonary residual volume was measured by using the helium dilution technique of Meeneely and Kaltreider. Waist and hip circumferences were also measured by following the procedures of the Airlie Conference.

**Oral Glucose Tolerance Test**

A 75 g oral glucose tolerance test (OGTT) was performed in the morning after an overnight fast. Blood samples were collected through a venous catheter from an antecubital vein at -15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 minutes for the determination of plasma glucose and insulin concentrations. Plasma glucose was enzymatically measured, whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation. The postglucose plasma glucose and insulin areas under the curve were determined by using the trapezoid method.

**Adipose T issue Biopsies and Measurement of Adipose Tissue Lipoprotein Lipase Activity**

Adipose tissue was surgically removed under local anesthesia from the abdominal (lateral to the umbilicus) and the femoral (anterior midthigh) fat deposits. Approximately 500 mg of adipose tissue was obtained from each site. Samples of adipose tissue were immediately frozen for the measurement of heparin releasable LPL activity as previously described. Fat cells were also isolated by collagenase digestion, and the mean fat cell size was measured by using a microscope equipped with a graduated ocular as previously described. The density of triolein was used to transform adipose cell volume into fat cell weight. Adipose tissue (AT)-LPL activity was expressed in µmol free fatty acid (FFA)/h/10^6 cells. Due to the

---

**Table 1. Characteristics of Sample of 16 Premenopausal Obese Women**

<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Means±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.0±6.1</td>
<td>25.1-49.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89.7±14.4</td>
<td>67.2-120.6</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>35.0±4.7</td>
<td>20.0-44.8</td>
</tr>
<tr>
<td>% body fat</td>
<td>46.4±6.2</td>
<td>34.8-55.1</td>
</tr>
<tr>
<td>WHR</td>
<td>0.81±0.05</td>
<td>0.75-0.93</td>
</tr>
<tr>
<td>Fat cell weight (µg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>0.79±0.22</td>
<td>0.52-1.23</td>
</tr>
<tr>
<td>Femoral</td>
<td>0.88±0.19</td>
<td>0.53-1.11</td>
</tr>
<tr>
<td>Plasma lipid and HDL cholesterol levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>145±42</td>
<td>88-222</td>
</tr>
<tr>
<td>CHOL (mg/dl)</td>
<td>213±34</td>
<td>153-293</td>
</tr>
<tr>
<td>HDL-CHOL (mg/dl)</td>
<td>43±9</td>
<td>32-61</td>
</tr>
</tbody>
</table>

BMI = body mass index, WHR = waist-to-hip circumference ratio, TG = triglyceride, CHOL = cholesterol, HDL = high density lipoprotein.
well-known association between fat cell size and AT-LPL activity,43 we also expressed AT-LPL activity per unit of cell surface (nmol FFA/h/μm²/10⁶ cells). We previously reported that the intraclass reliability of our LPL assay reached 0.81 under standardized conditions.43

**Plasma Postheparin Triglyceride Lipase Activities**

LPL and H-TGL activities were measured in plasma obtained from subjects who had fasted for 12 hours at 10 and 20 minutes after an i.v. injection of heparin (10 IU/kg body weight). Selective assays for enzyme activities of LPL and H-TGL were performed by a modification of the method of Nilsson-Ehle and Ekman.44 These assays are in agreement with the results obtained by the selective inhibition of H-TGL with antithropic lipase antibodies.47 Plasma was separated by low-speed centrifugation at 4°C, and a 0.5-ml aliquot was frozen and lyophilized overnight. Acetone-ether powders were then prepared from these lyophilized samples, dried under nitrogen, and were stored at −20°C until assayed. The acetone-ether powders were dissolved in 2 ml of 0.9% NaCl and used as an enzyme source for the measurements of both LPL and H-TGL activities. Two different substrates and selective assay conditions were used to measure the LPL and H-TGL activities.

The H-TGL activity was measured using as the substrate an artificial emulsion containing 0.2 M Tris-HCl buffer (pH 9.0), 4 mg/ml of FFA-free albumin, 0.17 mg/ml of egg lecithin, and 2.5 mg/ml of glycerol tri-14C-oleate (0.15 μCi/mg). The substrate was sonicated for 30 seconds three times at 1-minute intervals in an ice bath to avoid overheating; a Polytron (Brinkman Instruments Incorporated, Westbury, NY) was used. Two aliquots (0.2 ml each) of the enzyme extract were preincubated for 5 minutes at 37°C in a shaking water bath with an equal volume of 2.0 M NaCl to inhibit LPL activity; this was followed by a 20-minute incubation in the presence of 0.4 ml substrate. Incubations were terminated by addition of 2 ml mixture of isopropanol:3 N H₂SO₄ (40:1). Lipids were extracted by the addition of 1 ml H₂O and 2.5 ml hexane. The hexane phase was removed, and the aqueous phase was re-extracted with 2.5 ml hexane. One milliliter of 0.1 N NaOH in ethylene glycol was added to the combined hexane phases; this was shaken and centrifuged. One milliliter of the ethylene glycol phase containing the FFA was removed and counted for 14C in 14 ml of Aquasol (New England Nuclear, Lachine, Quebec).

LPL activity was measured by using as substrate an artificial emulsion containing 0.2 M Tris-HCl buffer (pH 8.0), 1.7 mg/ml of FFA-free albumin, 5 mg/ml of glycerol tri-14C-oleate (0.15 μCi/mg), and aceton-ether extract corresponding to 1.2 ml of pooled normal human serum as a source of apo C-II. The substrate was emulsified as described above with 1% Triton X-100 (0.07% final concentration). Aliquots in duplicate (0.2 ml) of the enzyme extract were preincubated for 5 minutes at 30°C in a shaking water bath with an equal volume of 0.2 M Tris-HCl (pH 8.0) with or without 3% protamin. The assay mixture was further incubated for 20 minutes in the presence of 0.4 ml substrate. After the termination of the incubation, the radioactivity was counted as described above. LPL activity was calculated as the lipase activity sensitive to 3% protamin from the total lipase activity (without protamin). LPL and H-TGL activities represent the means of the two samples obtained 10 and 20 minutes after heparin injection and are expressed as nmols of oleic acid released per millilitre of plasma per minute. The linearity of both assays was standardized using acetone powders prepared from human milk (unpublished data).

**Plasma Lipoprotein Analyses**

Blood samples were obtained in the morning after an overnight 12-hour fast from an antecubital vein into Vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA). Samples were collected while subjects were in the early follicular phase of their menstrual cycles. Cholesterol and triglyceride (TG) levels were determined in plasma and in lipoprotein fractions using an Auto-Analyzer II (Technicon Instruments Corporation, Tarrytown, NY) as previously described.44 Very low density lipoproteins (VLDL, d<1.006 g/ml) were isolated by ultracentrifugation,49 and the HDL fraction was obtained after precipitation of LDL in the infranatant (d>1.063 g/ml) with heparin and MnCl₂.50 The cholesterol content of LDL₂ and HDL₃ was also determined after further precipitation of HDL₂.51

**Results**

The characteristics of premenopausal women are summarized in Table 1. All subjects were younger than 50 years of age. The body fatness variables indicated that adiposity varied from moderate to massive obesity with large adipocytes as reflected by high abdominal and femoral fat cell weight values.

Table 2 presents the associations between the waist-to-hip circumference ratio (WHR), abdominal adipose tissue areas measured by computed tomography, and plasma lipoprotein levels. The WHR was positively correlated with plasma VLDL cholesterol levels and negatively correlated with plasma HDL cholesterol, HDL₃ cholesterol, and HDL₄ cholesterol levels. Table 2 also shows that plasma VLDL concentration was not significantly correlated with the abdominal adipose tissue areas. The HDL₂ cholesterol level was, however, negatively correlated with the deep abdominal fat area. Trends for associations between deep abdominal fat and HDL₃ cholesterol, as well as HDL₂ cholesterol/HDL₃ cholesterol ratio, were also noted, but they did not reach statistical significance in this subsample (n=16) as compared to our recently reported data on a larger sample of obese women.24

Table 3 shows the correlations between adiposity, indices of body fat distribution and of carbohydrate metabolism, and postheparin plasma and adipose tissue AT lipolytic enzyme activities. The plasma postheparin LPL and AT-LPL activities showed no significant correlation with total adiposity, with regional body fat distribution, nor with indices of carbohydrate metabolism. Plasma postheparin H-TGL activity was, however, positively correlated with the degree of adiposity as reflected by the significant positive correlations with percent body fat as well as with abdominal and femoral fat cell weights. Trends for positive correlations between abdominal and
Table 2. Correlation Coefficients between Waist-to-Hip Ratio, Adipose Tissue Areas at Abdominal (L4–L5) Region Determined by Computed Tomography, and Plasma Lipoprotein Levels in Obese Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>WHR</th>
<th>Total</th>
<th>Deep</th>
<th>Subc</th>
<th>Deep/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-CHOL (Log 10)</td>
<td>0.59*</td>
<td>0.08</td>
<td>0.20</td>
<td>0.02</td>
<td>0.24</td>
</tr>
<tr>
<td>LDL-CHOL</td>
<td>-0.39</td>
<td>-0.20</td>
<td>-0.27</td>
<td>-0.16</td>
<td>-0.14</td>
</tr>
<tr>
<td>HDL-CHOL</td>
<td>-0.66‡</td>
<td>-0.42</td>
<td>-0.44</td>
<td>-0.37</td>
<td>-0.03</td>
</tr>
<tr>
<td>HDL₂-CHOL</td>
<td>-0.61*</td>
<td>-0.48†</td>
<td>-0.50*</td>
<td>-0.43</td>
<td>-0.06</td>
</tr>
<tr>
<td>HDL₃-CHOL</td>
<td>-0.64‡</td>
<td>-0.30</td>
<td>-0.32</td>
<td>-0.27</td>
<td>-0.01</td>
</tr>
<tr>
<td>HDL-CHOL/LDL-CHOL</td>
<td>-0.25</td>
<td>-0.22</td>
<td>-0.19</td>
<td>-0.20</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL₂-CHOL/LDL₃-CHOL</td>
<td>0.29</td>
<td>-0.42</td>
<td>-0.43</td>
<td>-0.38</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

WHR=waist-to-hip ratio, Subc= subcutaneous, VLDL=very low density lipoprotein, LDL=low density lipoprotein, HDL=high density lipoprotein, CHOL=cholesterol.

* p<0.05, †0.05<p<0.06, ‡p<0.01.

Table 3. Correlation Coefficients between Total Adiposity, Indices of Body Fat Distribution and of Carbohydrate Metabolism, and Triglyceride Lipases in Obese Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Postheparin plasma LPL</th>
<th>H-TGL (10⁶ cells)</th>
<th>(μm²)</th>
<th>Abdominal</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.25</td>
<td>0.47</td>
<td>0.22</td>
<td>0.20</td>
<td>0.04</td>
</tr>
<tr>
<td>% body fat</td>
<td>-0.33</td>
<td>0.55*</td>
<td>0.29</td>
<td>0.23</td>
<td>0.18</td>
</tr>
<tr>
<td>Fat cell weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>-0.14</td>
<td>0.51*</td>
<td>0.43</td>
<td>0.21</td>
<td>0.24</td>
</tr>
<tr>
<td>Femoral</td>
<td>-0.20</td>
<td>0.53*</td>
<td>0.32</td>
<td>0.21</td>
<td>0.44</td>
</tr>
<tr>
<td>WHR</td>
<td>-0.20</td>
<td>0.49†</td>
<td>0.13</td>
<td>0.19</td>
<td>-0.12</td>
</tr>
<tr>
<td>OGTT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin area</td>
<td>-0.16</td>
<td>0.32</td>
<td>0.62‡</td>
<td>0.49†</td>
<td>0.19</td>
</tr>
<tr>
<td>Glucose area</td>
<td>-0.13</td>
<td>0.05</td>
<td>-0.40</td>
<td>-0.39</td>
<td>-0.48†</td>
</tr>
<tr>
<td>Ins/glu areas</td>
<td>-0.10</td>
<td>0.26</td>
<td>0.74‡</td>
<td>0.63‡</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Adipose tissue LPL: 10⁶ cells=μmole FFA/hr/10⁸ cells; μm²=nmole FFA/hr/μm²/10⁸ cells.

†p<0.05, *p<0.01, †p<0.001.

LPL=lipoprotein lipase, H-TGL=hepatic triglyceride lipase, BMI=body mass index, WHR=waist-to-hip circumference ratio, OGTT=oral glucose tolerance test, Ins/glu areas=ratio of insulin area/glucose area, FFA=fatty acid.

femoral fat cell weights, on one hand, and abdominal and femoral AT-LPL activities expressed per 10⁶ cells, on the other hand, were observed but they did not reach statistical significance. The plasma insulin area under the curve measured during the OGTT was, however, positively correlated with abdominal AT-LPL activity, and the correlation remained significant after control for fat cell surface. The insulinogenic index (ratio of insulin area/glucose area) displayed an even closer relationship with abdominal AT-LPL activity. These relationships were not observed, however, for femoral AT-LPL activity. In the femoral deposit, a trend for a negative correlation was observed between the glucose area and AT-LPL activity expressed on a per cell basis, suggesting that women with impaired glucose tolerance had a reduced femoral AT-LPL activity.

As shown in Figure 1, the plasma postheparin LPL activity was not significantly associated with the absolute amount of deep abdominal fat measured by computed tomography nor with the subcutaneous adipose tissue area measured in the same region. As illustrated in Figure 2, H-TGL activity was positively correlated with the absolute amount of deep abdominal fat, but it showed no significant relationship with subcutaneous abdominal fat.

Since both total adiposity and deep abdominal fat were significantly correlated with H-TGL activity, partial correlation coefficients were calculated to measure the independent contribution of deep abdominal fat and total adiposity to H-TGL activity. The results indicate that when we controlled for the effect of total adiposity on the H-TGL activity, deep abdominal fat remained significantly correlated with activity of H-TGL (r=0.48, p<0.05). On the contrary, when we adjusted percent body fat for the effect of deep abdominal fat, there was no significant residual correlation between total adiposity and H-TGL activity (r=0.22, NS). These results demonstrate that the association between deep abdominal fat content and H-TGL activity is entirely independent of the variation in total body fatness.

Table 4 shows data on the relationships between postheparin plasma triglyceride lipase activities, abdominal and femoral AT-LPL activities, and plasma lipoprotein levels. In this sample of obese women, both plasma and abdominal AT-LPL activities were not significantly corre-
INTRA-ABDOMINAL FAT AND HEPATIC LIPASE ACTIVITY

Correlations between plasma postheparin lipoprotein lipase (LPL) activity and abdominal (L4-L5) subcutaneous fat (A) and deep fat (B).

Discussion

Intra-abdominal Fat, Hepatic Triglyceride Lipase Activity, and HDL2 Cholesterol

Our results clearly demonstrate that there is a significant association between intra-abdominal fat accumulation and the activity of postheparin plasma H-TGL, and that this association is independent from the effect of obesity per se. A positive relationship between the level of obesity and plasma H-TGL activity was reported previously, and our results are concordant with these observations. However, in the covariance analysis with the inclusion of intra-abdominal fat as a covariate, no significant residual correlation could be found between obesity and plasma H-TGL activity, thereby suggesting that intra-abdominal fat accumulation is the best fatness correlate of H-TGL activity. The negative association that we found between postheparin plasma H-TGL activity and plasma HDL2 cholesterol levels is concordant with the results of numerous studies that have suggested that H-TGL plays a role in the catabolism of HDL2, or in the conversion of HDL2 to HDL3. In the present study, however, H-TGL activity was negatively correlated with the ratio of HDL2 cholesterol/HDL3 cholesterol, and this association was due to a reduction in HDL2 cholesterol.
rather than to an increase in HDL₃ cholesterol levels. This finding is concordant with the observation of Applebaum-Bowden et al.²² who reported that an increase in H-TGL activity induced by administration of an anabolic steroid was associated with a reduction in plasma HDL₂ cholesterol but not with an increase in HDL₃ cholesterol.

To the best of our knowledge, it is the first time that significant associations between deep abdominal fat, plasma H-TGL activity, and plasma HDL₂ cholesterol levels have been reported. Although the association between plasma H-TGL activity and HDL₂ cholesterol levels appears to reflect a cause-effect relationship, the mechanism by which intra-abdominal fat accumulation is correlated with plasma H-TGL activity is not known. This association is perhaps not causal, and it may represent the influence of sex steroids that are significantly associated with the regional distribution of body fat (for a review, see reference 8), H-TGL activity, and plasma HDL₃ levels.²⁹ Evans et al.⁵ have shown that obese women with a high proportion of abdominal fat had higher plasma free testosterone levels (percent of total) and lower sex hormone binding globulin levels than did obese women with peripheral fat accumulation, suggesting that obese women with high androgenic activity could be at risk for the development of the metabolic disturbances associated with high abdominal fat content. In a recent review, Tikkanen and Nikkila²⁸ have reported that sex steroids affect plasma HDL₂ cholesterol levels by up- or down-regulating the H-TGL activity. Steroids with androgenic activity increase H-TGL activity and reduce plasma HDL₂ cholesterol levels.²⁹ Applebaum-Bowden et al.²² also recently reported that administration of stanozolol, an androgenic anabolic steroid, is associated with an increase in plasma H-TGL activity that precedes the decrease in plasma HDL₂ cholesterol levels, suggesting a clear causal relationship between H-TGL and plasma HDL₂ cholesterol. These data indicate that variations in sex steroids, which influence both plasma H-TGL and HDL₂ cholesterol levels, may also represent an important factor for the association between intra-abdominal fat and H-TGL activity; however, further work is required to substantiate this hypothesis.

**Intra-abdominal Fat and Plasma Lipoprotein Lipase Activity**

In the present study, no significant association was found between the amount of intra-abdominal fat, plasma postheparin LPL activity, and plasma lipoprotein levels. Such a lack of association must not be taken as an evidence against the role for LPL activity in regulating plasma lipoprotein levels. It may be argued that because we used low doses of heparin, a maximum release of the enzyme was not achieved. However, there is recent evidence indicating that although both LPL and H-TGL activities increased with increasing doses of heparin, subjects maintained their rank order despite the dose effects.⁵³ Furthermore, obese women in this study were rather homogeneous, and different results could have been obtained by using subjects with wider ranges of body fatness. Indeed, it has been shown that LPL plays an important role in the regulation of plasma HDL levels. A low LPL activity results in low plasma HDL levels²⁵-²⁶ and, conversely, a high plasma LPL activity is generally associated with high levels of HDL.²⁶-²⁸ The results of the present study indicate, however, that variations in plasma LPL activity are not, in obese premenopausal women, an important factor for the independent association between the level of intra-abdominal fat and plasma HDL cholesterol levels.

**Adipose Tissue Lipoprotein Lipase Activity**

Variation in abdominal AT-LPL activity was not associated with changes in plasma HDL-cholesterol levels. Femoral AT-LPL activity, when expressed by unit of cell surface, displayed a significant positive correlation with the ratio of HDL₂ cholesterol/HDL₃ cholesterol, and trends for associations with plasma VLDL cholesterol and HDL₂ cholesterol levels were noted. These results suggest that variations in abdominal and femoral AT-LPL activities will not necessarily have the same impact on the regulation of plasma HDL cholesterol levels. Furthermore, it also appears that abdominal and femoral AT-LPL activities could display different responses to variation in plasma insulin levels. Whereas we observed a strong positive association between the insulin area under the curve measured during an OGTT and abdominal AT-LPL activity, such a relationship was not observed for femoral AT-LPL activity. The association between plasma insulin levels and AT-LPL activity has been well documented,⁵⁴,⁵⁵ and it is known that the enzyme is insulin-sensitive.⁵⁶,⁵⁷ The results of the present study further indicate, however, that regional variation is observed in the response of AT-LPL to changes in systemic insulin levels.

**Table 4. Correlation Coefficients between Lipolytic Activities and Plasma Lipoprotein Levels In Obese Women**

<table>
<thead>
<tr>
<th></th>
<th>Postheparin plasma LPL</th>
<th>H-TGL</th>
<th>Abdominal Adipose tissue LPL</th>
<th>Femoral Adipose tissue LPL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10⁶ cells)</td>
<td>(µm²)</td>
<td>(10⁶ cells)</td>
<td>(µm²)</td>
</tr>
<tr>
<td>VLDL-CHOL (Log 10)</td>
<td>-0.40</td>
<td>0.34</td>
<td>-0.15</td>
<td>-0.18</td>
</tr>
<tr>
<td>LDL-CHOL</td>
<td>0.00</td>
<td>-0.20</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL₂-CHOL</td>
<td>0.37</td>
<td>-0.47†</td>
<td>-0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>HDL₃-CHOL</td>
<td>0.29</td>
<td>-0.60*</td>
<td>-0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL₄-CHOL</td>
<td>0.40</td>
<td>-0.28</td>
<td>-0.06</td>
<td>-0.09</td>
</tr>
<tr>
<td>HDL₅-CHOL/LDL-CHOL</td>
<td>0.39</td>
<td>-0.25</td>
<td>-0.08</td>
<td>-0.08</td>
</tr>
<tr>
<td>HDL₆-CHOL/HDL₇-CHOL</td>
<td>-0.02</td>
<td>-0.62*</td>
<td>0.13</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Abbreviations are explained in the legends for Tables 2 and 3.

*p<0.05, †0.05<p<0.06.
levels. The lack of association between plasma insulin levels and femoral AT-LPL could be explained by two observations. First, women with a gluteal-femoral accumulation of body fat display a higher insulin sensitivity and lower plasma insulin levels, but they have a higher femoral AT-LPL activity than women with a high relative accumulation of abdominal fat. Second, regional variation in insulin responsiveness has been documented, and the antilipolytic effect of insulin has reportedly been higher in abdominal, than in femoral, adipocytes. It, therefore, appears reasonable to suggest that the response of AT-LPL to hyperinsulinemia displays regional variation and that further studies will be required to elucidate the mechanisms underlying these observations.

In conclusion, this study demonstrates that, in a sample of obese premenopausal women for which the level of intra-abdominal fat appears to be the critical variable in the association between regional body fat distribution and plasma HDL cholesterol levels, a high plasma H-TGL is associated with high levels of intra-abdominal fat and with low HDL cholesterol levels. This association between the amount of intra-abdominal fat and H-TGL activity was independent from the level of obesity. The mechanisms responsible for these relations will require further studies, but from present knowledge, it is suggested that variations in sex steroid levels are involved in this association. Since low HDL cholesterol levels are considered as a risk factor for CHD, a variation in H-TGL activity might play an important role in the disturbance in plasma lipoprotein transport observed in obese women with high levels of deep abdominal fat.

Acknowledgments

The authors express their gratitude to Judith Maheux, Martine Marcotte, Claude Leblanc, Henri Beissette, and Marie-Christine Pouliot of the Physical Activity Sciences Laboratory for their excellent collaboration. We also thank Nicole Roy, Yolande Montrouil, Marie Martin, Rachel Duchesne, Suzanne Brellotte, and Jean-Guy Bertrand for their assistance in the data collection. The excellent assistance of the Lipid Research Center staff is also acknowledged.

References


30. Patsch JR, Prasad S, Gotto AM Jr, Patsch W. High density lipoproteins. Relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia, and to the activities of lipoprotein lipase and hepatic lipase. J Clin Invest 1987;80:341–347


32. Applebaum-Bowden D, Haffner SM, Hazzard WR. The dyslipoproteinemia of anabolic steroid therapy: Increase in hepatic triglyceride lipase precedes the decrease in high density lipoprotein cholesterol. Metabolism 1987;36:949–952


52. Harno K, Nikkila EA, Kuusel T. Plasma HDL-cholesterol and postheparin plasma hepatic endothelial lipase (HL) activity: Relationship to obesity and non-insulin dependent diabetes (NIDDM) [abstr]. Diabetologia 1980;19:281A


Role of hepatic-triglyceride lipase activity in the association between intra-abdominal fat and plasma HDL cholesterol in obese women.
J P Després, M Ferland, S Moorjani, A Nadeau, A Tremblay, P J Lupien, G Thériault and C Bouchard

doi: 10.1161/01.ATV.9.4.485

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/9/4/485

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/