Activities of Lipoprotein Lipase and Hepatic Triglyceride Lipase in Postheparin Plasma of Patients with Low Concentrations of HDL Cholesterol

Barbara Blades, Gloria Lena Vega, and Scott M. Grundy

Previous investigations have shown that abnormalities in the postheparin plasma levels of the lipolytic enzymes, lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL), are correlated with variations in plasma high-density lipoprotein cholesterol (HDL-C) levels. The present study was performed to determine correlations between the postheparin plasma activities of these two enzymes and HDL levels in a sizable number of subjects with low HDL-C levels. Two types of low-HDL subjects were investigated: 159 male subjects with low HDL-C (<40 mg/dL) and normal triglyceride (<250 mg/dL) levels (the low-HDL group) and 80 male subjects with low HDL-C (<40 mg/dL) and elevated triglyceride (≥250 mg/dL) levels (the low-HDL/high-TG group). Postheparin plasma activities of LPL and HTGL were determined in these two groups, and these levels were compared with those obtained from 51 normolipidemic (normal-HDL) male subjects. Postheparin LPL activities were significantly lower in the low-HDL and low-HDL/high-TG groups (mean±SD, 9.9±2.9 and 10.4±3.0 mmol/h per liter, respectively; P<.001 for both) compared with the normal-HDL group (12.5±3.7 mmol/h per liter). Conversely, postheparin HTGL activities were significantly higher in the low-HDL and low-HDL/high-TG groups (39.3±16.2 and 44.4±16.7 mmol/h per liter, respectively; P<.001 for both) compared with the normal-HDL group (29.7±11.3 mmol/h per liter). Consequently, mean LPL/HTGL ratios were markedly lower in the two low-HDL groups compared with the normal-HDL group. Within each group, analysis revealed no specific relationships between the enzyme activities and potential modifying factors (cigarette smoking and β-adrenergic blocking agents). When subjects from each group who were neither smokers nor taking β-blockers were compared, HTGL activities, but not LPL activities, were significantly different for the low-HDL groups compared with the normal-HDL group. The results of this study suggest that high HTGL activity and low LPL activity are both important contributors to low HDL levels in both normotriglyceridemic and hypertriglyceridemic subjects. However, in the absence of potential modifying factors, high HTGL activity appears to be the major change in lipolytic enzymes associated with HDL levels. (Arteriosclerosis and Thrombosis 1993;13:1227-1235)

KEY WORDS • lipoprotein lipase • hepatic triglyceride lipase • hypoalphalipoproteinemia • HDL • hypertriglyceridemia

Low serum concentrations of high-density lipoprotein cholesterol (HDL-C) are a major risk factor for coronary heart disease (CHD). Therefore, the causes of low HDL-C levels may be determinants of coronary atherosclerosis and thus deserve elucidation. In many patients, secondary factors, eg, obesity, cigarette smoking, and lack of exercise, reduce HDL levels. In other patients, raised serum triglycerides (TGs) appear to underlie low HDL levels. In other patients, raised serum triglycerides (TGs) appear to underlie low HDL levels. Extensive studies on the relation of these lipolytic enzymes to HDL levels have been carried out by Nikkila and other investigators in Finland, and related, similar studies have been performed by other workers. Several reports indicate that HDL-C levels are directly correlated with postheparin plasma and adipose tissue activities of LPL, whereas an inverse correlation has been noted between postheparin HTGL activity and HDL concentrations. If the availability of these two
enzymes directly affects concentrations of HDL, then variability in enzyme activity could form a common mechanism whereby many other factors influence HDL levels.

Although previous studies provide convincing data that the activities of these endothelial lipolytic enzymes affect HDL concentrations, many of the studies were performed with a limited number of subjects or did not directly consider patients with low HDL levels. Furthermore, few direct comparisons of activities of these enzymes have been made between subjects with low HDL and normal TG levels and those with low HDL and elevated TG levels. The present study, therefore, was performed on a sizable number of subjects to compare postheparin plasma activities of LPL and HTGL in normotriglyceremic patients with low HDL, hypertriglyceremic patients with low HDL, and normotriglyceremic subjects with normal HDL levels. Three questions were directly addressed in this study: (1) Do hypertriglyceremic patients with low HDL levels have predominantly a reduced LPL activity? (2) Do normotriglyceremic patients with low HDL levels have predominantly an increased HTGL activity? and (3) Does the LPL/HTGL ratio correlate better with low HDL levels than with the activities of either enzyme alone?

Methods

Patients

A total of 290 male subjects were included in this study. They were recruited from the clinics of the Veterans Affairs Medical Centers (VAMCs) of Dallas and Bonham, Tex. They were all admitted to the metabolic ward of the VAMC Dallas for 3 days. During this period they were subjected to three measurements of fasting plasma lipids and lipoproteins and a single measurement of postheparin activities of LPL and HTGL. The patients were divided into three groups based on the average of three measurements of total lipids and lipoproteins: (1) a low-HDL group (HDL-C <40 mg/dL and total TGs <250 mg/dL); (2) a low-HDL/high-TG group (HDL-C <40 mg/dL and TGs ≥250 mg/dL); and (3) a normal-HDL group (HDL-C ≥40 mg/dL and TGs <250 mg/dL). In this study, low-HDL-C was defined as a concentration below 40 mg/dL; this value was chosen because of data from the Framingham Heart Study showing that a striking increase in risk for CHD occurs below this level. Hypertriglyceridemia was defined as fasting TG concentrations over 250 mg/dL, in accordance with recommended definitions. Patients were excluded from the study if they had diabetes, other endocrine disorders, or other serious illness. They were not excluded if they had CHD; however, none of the patients had congestive heart failure or unstable angina pectoris.

The demographic characteristics of the patients are presented in Table 1. One hundred fifty-nine patients fell into the low-HDL group, 80 were in the low-HDL/high-TG group, and 51 were in the normal-HDL group. Ages of patients in the three groups were similar. Body mass indexes were similar for low-HDL and normal-HDL groups, but they were significantly higher in the low-HDL/high-TG group. The low-HDL group had the highest percentage with established CHD; low-HDL/high-TG patients were intermediate, and the normal-HDL group had the lowest percentage with CHD. The percentages of subjects who had hypertension or who were taking β-adrenergic blocking agents were similar for the three groups. However, percentages of low-HDL and low-HDL/high-TG patients who were cigarette smokers were higher than in the normal group. Total cholesterol levels averaged somewhat lower in the low-HDL group than in the other two groups. The low-HDL group had somewhat higher total TG levels than the normal-HDL group, whereas average HDL-C levels were markedly and similarly reduced in the two low-HDL groups. The normal-HDL group had lipid and lipoprotein levels similar to those of the normal population of men of the same age range.

Laboratory Procedures

Each morning during admission, after a 12-hour fast, venous blood samples were collected into EDTA-containing tubes for determination of plasma total lipids and lipoprotein cholesterol. On the third day, after an overnight fast and after obtaining a baseline blood sample for lipids and lipoproteins, porcine heparin (Elkins-Sinn Inc, Cherry Hill, NJ) was injected intravenously (75 U/kg of body weight), and blood was drawn 15 minutes after injection. Blood was collected into iced tubes containing EDTA. Samples were spun immediately at 4°C to isolate plasma; once isolated, postheparin plasma (PHP) was stored at −70°C until assayed.

Table 1. Demographic Data and Lipoprotein Cholesterol and Triglyceride Levels for the Three Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal-HDL</th>
<th>Low-HDL</th>
<th>Low-HDL/high-TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51</td>
<td>159</td>
<td>80</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58±9</td>
<td>59±9</td>
<td>58±8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27±4</td>
<td>27±3</td>
<td>29±4</td>
</tr>
<tr>
<td>CHD</td>
<td>19 (37%)*</td>
<td>94 (59%)</td>
<td>35 (44%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (45%)</td>
<td>79 (50%)</td>
<td>42 (53%)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>12 (24%)</td>
<td>43 (27%)</td>
<td>23 (29%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>16 (31%)</td>
<td>73 (46%)</td>
<td>38 (48%)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>231±39</td>
<td>207±32†</td>
<td>236±48</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>139±53</td>
<td>163±44‡</td>
<td>429±255‡</td>
</tr>
<tr>
<td>TG (mg/dL)§</td>
<td>122</td>
<td>165</td>
<td>335</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>47±6</td>
<td>31±5‡</td>
<td>29±5†</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; TG, triglycerides; BMI, body mass index; CHD, established coronary heart disease; TC, total cholesterol; HDL-C, HDL cholesterol. See "Methods" for definitions of normal-HDL, low-HDL, and low-HDL/high-TG. Results are expressed as mean±SD. *Parenthetical percentages are percentages of total in the group. †Significantly different from normal values; P<.001. ‡Significantly different from normal values; P<.002. §Median value.
with heparin-manganese in the Lipid Research Clinics procedure.43,44

Postheparin LPL and HTGL activities were determined independently by using a modification of the methods of Baginsky and Brown.45 For both assays, a gum arabic-stabilized [3H]triolein (0.5 μCi of glycerol tri[9,10-3H]oleate per tube; Amersham Corp, Arlington Heights, Ill) substrate was used, with a final triolein concentration of 15 mmol/L. LPL activity was determined after preincubation at 28°C of 25 μL PHP with 25 μL of 50 mmol/L sodium dodecyl sulfate for 45 minutes to inhibit HTGL activity.46 The LPL assay was carried out at 28°C in 0.2 mol/L tris(hydroxymethyl)aminomethane (Tris) buffer, pH 8.2, in the presence of apo C-II (100 μL of heat-inactivated human serum per tube). The substrate was preincubated with the activator serum for 45 minutes at 37°C. HTGL activity was determined in 25 μL PHP at 28°C in 0.2 mol/L Tris-chloride buffer, pH 8.8, in the presence of 0.75 mol/L NaCl to inhibit LPL activity. In both assays, the final concentration of fatty acid-free bovine serum albumin (fraction V) was 50 g/L, the final assay volume was 0.5 mL, and the reaction time was 60 minutes. The free [3H]oleic acid released from [3H]triolein by lipase activity was extracted by using the method of Belfrage and Vaughan46 using 3.9 mL of methanol/chloroform/heptane (1.41:1.25:1.0, vol/vol/vol) followed by 1.0 mL of 0.1 mol/L potassium carbonate buffer, pH 10.5. All solvents were high-performance liquid chromatography grade from Aldrich Chemical Company, Milwaukee, Wis.

Extraction efficiency was determined using 0.01 μCi of [1-14C]oleic acid (Amersham) added to each tube before extraction.3H and 14C activities were determined in 2 mL of extract (methanol/water as the upper phase) in a Tracor Analytic Mark II Liquid Scintillation System (TM Analytic, Elk Grove, Ill). Two quality control PHP samples were used in each assay. The values obtained for these controls were used to normalize the results to the mean of the control values obtained for all runs. Mean values for each quality control in the LPL assay were 7.67 and 10.41 mmol free fatty acid (FFA) released/h per liter. For the HTGL assay, average values for the quality controls were 22.03 and 58.20 mmol FFA released/h per liter. The between-assay (n=24) coefficient of variance (CV) for each control, respectively, in the LPL assay was 4.6% and 3.4%, and for the HTGL assay it was 3.2% and 1.2%. The mean (n=10 assays) within-assay CV was 3.5% for the LPL assay and 3.0% for the HTGL assay.

Statistical Methods

Assumptions of normality and homogeneity of variances were tested with the Anderson-Darling test and Levene’s test, respectively. Since these assumptions were not met for some variables (TGs, LPL, HTGL, and LPL/HTGL ratio), nonparametric tests were used. For lipids, enzyme activity, and LPL/HTGL ratio variables (Tables 1 and 2), the Kruskal-Wallis test was used to compare the three groups. Multiple comparisons were performed by using Bonferroni-adjusted (α=0.05/3=0.0167) Mann-Whitney U tests. Pearson’s χ² contingency table analysis was performed to compare the proportions of patients with risk factors (hypertension, smoking, and β-blockers) between groups. The distributions of LPL, HTGL, and LPL/HTGL ratios for the populations were determined as percentage frequencies and cumulative percentage frequencies.

For subgroup analyses (Tables 3 through 6), comparisons were made using the .01 level of significance to adjust for multiplicity of testing. Data are expressed as mean±SD and in some cases as medians. CLINFO and BMDP software were used for data management and statistical analysis.

Results

Mean values for postheparin LPL and HTGL and LPL/HTGL ratios for the three groups are given in Table 2. For each, percentage frequencies and cumulative percentage frequencies are presented in Figs 1, 2, and 3, respectively. Postheparin LPL activities were significantly lower in the low-HDL and low-HDL/high-TG groups than in the normal-HDL group, but no differences in enzyme activities were noted between the former two groups. The trend toward lower values for LPL activities in the two low-HDL groups is clearly seen in Fig 1. In contrast, postheparin HTGL activities were significantly higher in the low-HDL and low-HDL/high-TG groups compared with the normal-HDL group; again, there were no differences in enzyme activities between the former two groups. HTGL results are shown graphically in Fig 2. Finally, because of the trends for LPL and HTGL activities, LPL/HTGL activity ratios were markedly lower, on the average, in the two low-HDL groups compared with the normal-HDL patients (Table 2). As shown in Fig 3, the pattern of this ratio was practically identical for the two low-HDL groups.

Since cigarette smoking and β-blockers can lower HDL levels, a subgroup analysis was performed in the attempt to determine whether these two factors appreciably influenced the overall results. Table 3 shows subgroup comparisons for normal-HDL patients. No significant differences in any of the parameters were found between smokers and nonsmokers or between those with or without β-blockers. The same compari-

### Table 2. Postheparin Activities of Lipoprotein Lipase and Hepatic Triglyceride Lipase in Three Patient Groups

<table>
<thead>
<tr>
<th>Postheparin lipase activity</th>
<th>Normal-HDL</th>
<th>Low-HDL</th>
<th>Low-HDL/high-TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL</td>
<td>Mean±SD</td>
<td>Median</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>12.5±3.7</td>
<td>12.5</td>
<td>10.4±3.0*</td>
</tr>
<tr>
<td></td>
<td>9.9±2.9*</td>
<td>9.5</td>
<td>44.4±16.2†</td>
</tr>
<tr>
<td>HTGL</td>
<td>Mean±SD</td>
<td>Median</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>28.7±11.3</td>
<td>38.3±16.7*</td>
<td>0.47±0.18</td>
</tr>
<tr>
<td></td>
<td>39.3±16.2*</td>
<td>35.9</td>
<td>0.31±0.20*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.28±0.16†</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; TG, triglycerides; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase. See "Methods" for definitions of normal-HDL, low-HDL, and low-HDL/high-TG. All postheparin lipase activities are given in millimoles per hour per liter.

*Significantly different from the normal-HDL group; P<.001.
†Not significantly different from the low-HDL group.
FIG 1. Line graphs showing distribution of postheparin activities of lipoprotein lipase (LPL) in low-HDL, low-HDL/high-TG, and normal-HDL patients. (See “Methods” for definitions of patient groups.) Percentage frequencies and cumulative percentage frequencies are shown. Percentage frequencies are given in increments of 2 mmol/h per liter.

FIG 2. Line graphs showing distributions of postheparin activities of hepatic triglyceride lipase (HTGL) in low-HDL, low-HDL/high-TG, and normal-HDL patients. (See “Methods” for definitions of patient groups.) Percentage frequencies and cumulative percentage frequencies are shown. Percentage frequencies are given in increments of 10 mmol/h per liter.

Discussion

Previous investigations have revealed a direct correlation between the activity of LPL and HDL levels\(^{15,21,26,31-35}\) and an inverse correlation between HTGL activity and HDL levels.\(^{19,22,30,31,35}\) The present study was designed to examine these relationships with expanded groups of patients and specifically to include patients with low HDL levels. Several questions were addressed. First, we asked whether hypertriglyceridemic patients with low HDL levels mainly have a reduced LPL activity with a relatively normal HTGL activity. Second, we conjectured that normotriglyceridemic patients with low HDL concentrations have primarily an increased activity of HTGL rather than a reduced activity of LPL. Third, we questioned whether the ratio of LPL to HTGL is more highly correlated with HDL levels than the activity of either enzyme alone. Finally, a subgroup analysis was carried out to determine whether there are differences in expression of lipolytic enzyme activities between smokers and nonsmokers and between patients taking β-blockers and those not taking β-blockers. Regardless of the latter results, the primary issue under consideration was whether abnormalities in the activities of LPL and HTGL are a common and unifying mechanism underlying low HDL levels.

Patients in the three groups of this study were fairly well matched (Table 1). Their mean ages were similar. Hypertriglyceridemic patients were somewhat heavier than the two groups of normotriglyceridemic subjects; this is a common finding. Also, as might be expected, the low-HDL groups had higher percentages of patients with CHD than did the normal-HDL group; since β-blockers are widely used in CHD patients, a higher percentage of low-HDL patients took these agents. It is not surprising that more patients with low HDL were smokers, because cigarette smoking is associated with lower HDL levels.\(^6,7\) Since smoking or β-blockers might affect enzyme activities, subgroup analyses were performed to determine whether any changes observed in enzyme activities could be attributed to either smoking or β-blockers. As indicated above, however, the primary purpose of the study was to examine the direct correla-
Blades et al  Enzyme Activity in Postheparin Plasma of Low HDL-C Patients

• LowHDL—©—LowHDL/HighTG

FIG 3. Line graphs showing distributions of ratios of postheparin activities of lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) in low-HDL, low-HDL/high-TG, and normal-HDL patients. (See “Methods” for definitions of patient groups.) Percentage frequencies and cumulative percentage frequencies are shown. Percentage frequencies are given in increments of 0.1 unit of ratio.

ation between lipolytic enzymes and HDL concentrations; whether smoking and β-blockers might exert their HDL-lowering action through a modification of these enzymes was a secondary question.

In the group with low HDL and normal TG levels (the low-HDL group), the mean activity of postheparin LPL was significantly lower than in the normal-HDL group, whereas mean HTGL activity was significantly increased; compared with the normal-HDL group, activities of both enzymes were highly significantly different in the low-HDL group (Table 2). For LPL activities, there was overlap between the normal-HDL and low-HDL groups (Fig 1), but for many patients in the low-HDL group, LPL activities were clearly displaced toward lower values. Of particular interest is the observation that LPL levels were similarly reduced in both low-HDL groups, ie, in those with and without elevated TGs. Since the changes in activities of the two lipolytic enzymes were in opposite directions in both low-HDL groups, the depression of LPL/HTGL ratios was accentuated in both groups (Fig 3). Thus, if the activities of the two enzymes are determinants of HDL levels, the ratio of their activities should correlate strongly with HDL concentrations. The current results suggest that abnormalities in the two enzymes commonly act to lower HDL levels.

The mechanisms whereby activities of LPL and HTGL affect HDL concentrations are not fully understood. It has been postulated that a high activity of LPL enhances release of components of TG-rich lipoproteins (TGRLPs), eg, cholesterol and phospholipids, which can then be transferred to HDL to raise HDL levels; conversely, a deficiency of LPL might retard movement of these components to HDL. Alternatively, higher plasma levels of TGRLPs, resulting from a reduced activity of LPL, could promote depletion of cholesterol ester in HDL by exchange for TGs in TGRLPs.47 TGs entering HDL through this exchange process apparently are hydrolyzed rapidly, most likely by HTGL; the resulting HDL particle is smaller and has a reduced cholesterol content. Several reports suggest that HTGL can directly degrade HDL particles, particularly the larger HDL₂ particles. Part of this degradation may occur through the hydrolysis of HDL TGs; in addition, HTGL has a phospholipase activity that may hydrolyze surface coat phospholipids of HDL particles.

One hypothesis of this study was that patients having low HDL but normal TG levels (the low-HDL group) should have a predominant increase in HTGL activity, whereas LPL activity was not expected to be decreased.

### Table 3. Subgroup Analysis of Normolipoproteinemic Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonsmokers</th>
<th>Smokers*</th>
<th>Without β-blockers</th>
<th>With β-blockers†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>35</td>
<td>16</td>
<td>39</td>
<td>12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58±10</td>
<td>59±9</td>
<td>57±10</td>
<td>62±7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8±3.7</td>
<td>27.4±3.7</td>
<td>26.6±3.7</td>
<td>28.2±3.3</td>
</tr>
<tr>
<td>CHD</td>
<td>13</td>
<td>6</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>231±29</td>
<td>232±57</td>
<td>238±41</td>
<td>207±22</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>138±58</td>
<td>140±44</td>
<td>141±54</td>
<td>130±52</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>47±5</td>
<td>47±6</td>
<td>46±6</td>
<td>46±4</td>
</tr>
<tr>
<td>LPL (mmol/h per liter)</td>
<td>12.4±3.5</td>
<td>12.7±4.4</td>
<td>12.5±3.8</td>
<td>12.8±3.5</td>
</tr>
<tr>
<td>HTGL (mmol/h per liter)</td>
<td>28.6±10.5</td>
<td>32.2±12.9</td>
<td>30.4±11.8</td>
<td>27.6±9.8</td>
</tr>
<tr>
<td>LPL/HTGL ratio</td>
<td>0.48±0.18</td>
<td>0.44±0.19</td>
<td>0.46±0.19</td>
<td>0.50±0.17</td>
</tr>
</tbody>
</table>

BMI, body mass index; CHD, established coronary heart disease; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase. Results are expressed as mean±SD.

*None of the values for smokers were significantly different from those for nonsmokers.
†None of the values for patients with β-blockers were significantly different from those without β-blockers.
In accordance with this concept, the results for this group indeed suggested that HTGL activity was increased somewhat more than LPL activity was reduced. On average, however, the activity of LPL was significantly reduced as well. This average decrease in LPL activity might account for the significantly higher, albeit not abnormally high, mean level of TGs compared with the control (normal-HDL) group. Thus, it appeared that an increased activity of HTGL, often combined with a reduced activity of LPL, resulted in lower HDL levels in many patients with isolated low HDL levels.

For the low-HDL/high-TG group, we expected the predominant defect to be a reduced activity of LPL, with a lesser increase in HTGL. In fact, the pattern of enzyme activities was virtually identical to that of the low-HDL group. In the low-HDL/high-TG group, the HTGL activity was just as raised and the LPL activity no more reduced than in the low-HDL group. A pertinent question is why there was not a difference in LPL activities in view of the marked difference in TG levels between the two groups. The explanation may reside partly in differences in body weight. The low-HDL/high-TG group on the average had a higher body weight; this undoubtedly led to higher production rates for very-low-density lipoprotein (VLDL) TGs, which, when combined with a mildly reduced activity of LPL, caused higher TG levels.

Two findings with respect to LPL activities are worth noting. First, the results leave little doubt that many patients with endogenous hypertriglyceridemia have a relatively low activity of LPL. Whether patients with endogenous hypertriglyceridemia commonly have a reduced activity of LPL has been a disputed point in the literature, as reviewed by Nikkila and Babirak et al. Certainly a moderate reduction of LPL can cause hypertriglyceridemia, because patients who are heterozygous for hereditary LPL deficiency may have moderate hypertriglyceridemia. The causes of lowered LPL activity in hypertriglyceridemic patients of the present study are unclear, but presumably most patients

### Table 4. Subgroup Analysis of Patients with Low HDL and Normal Triglyceride Levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonsmokers</th>
<th>Smokers*</th>
<th>Without β-blockers</th>
<th>With β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>86</td>
<td>73</td>
<td>116</td>
<td>43</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.5±7.7</td>
<td>56.0±8.7</td>
<td>57.7±8.6</td>
<td>58.2±7.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8±3.8</td>
<td>28.2±4.3</td>
<td>28.5±4.4</td>
<td>28.6±3.3</td>
</tr>
<tr>
<td>CHD</td>
<td>21</td>
<td>14</td>
<td>19</td>
<td>16†</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>236±38</td>
<td>237±58</td>
<td>239±43</td>
<td>230±59</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>427±221</td>
<td>431±292</td>
<td>430±263</td>
<td>427±240</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>29±5</td>
<td>29±5</td>
<td>30±5</td>
<td>27±6</td>
</tr>
<tr>
<td>LPL (mmol/h per liter)</td>
<td>11.0±3.1</td>
<td>9.8±2.7</td>
<td>10.9±3.1</td>
<td>9.30±2.4</td>
</tr>
<tr>
<td>HTGL (mmol/h per liter)</td>
<td>43.6±15.9</td>
<td>45.2±16.8</td>
<td>43.0±17.2</td>
<td>47.8±13.2</td>
</tr>
<tr>
<td>LPL/HTGL ratio</td>
<td>0.30±0.17</td>
<td>0.25±0.14</td>
<td>0.30±0.17</td>
<td>0.21±0.09</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; BMI, body mass index; CHD, established coronary heart disease; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase. Results are expressed as mean±SD.

*None of the values for smokers were significantly different from those for nonsmokers.
†Percentage of patients taking β-blockers who had CHD (81%) was significantly higher than those who had CHD but who were not taking β-blockers.
did not have a structural defect in the gene encoding for LPL; the homozygous state for such defects is too rare for heterozygotes to be common in the general population. More likely, abnormalities in the regulation of LPL expression were responsible for most instances of reduced activity of LPL; such regulatory abnormalities could be either genetic or secondary in origin.

A second interesting point is that many patients with low HDL levels have a reduced activity of LPL without distinct hypertriglyceridemia (Fig 3). Perhaps this should not be surprising because individuals who are obligate heterozygotes for LPL deficiency and hence have only half-normal LPL activities often do not have elevated plasma TG levels; on the other hand, Wilson et al recently reported that most normotriglyceridemic heterozygotes for LPL deficiency do have low HDL levels. Presumably, in the presence of a moderate reduction of LPL activity, whether structural or functional in origin, other factors, i.e., overproduction of VLDL triglycerides or defective VLDL particles, must be present before a patient develops definite hypertriglyceridemia. Nonetheless, even without elevated TGs, reduced activity of LPL still leads to low HDL levels. In support of this concept, a recent report from our laboratory indicated that weight reduction in many hypertriglyceridemic patients fails to raise HDL levels or to correct defects in apoA-I metabolism in spite of lowering triglyceride levels. Other workers likewise have found that TG lowering often fails to appreciably raise HDL levels. The failure of plasma TG reduction to increase HDL levels suggests that the low HDL concentrations accompanying elevated TGs are due to mechanisms other than the exchange of VLDL TGs for HDL-C esters. In some way, mechanisms underlying hypertriglyceridemia, such as reduced LPL activity, may directly affect the metabolism of HDL.

At least some of the decrease in LPL activity in many of our low-HDL patients probably was the result of secondary factors, i.e., cigarette smoking and β-blockers. Both of the latter are known to raise TG levels and to reduce HDL concentrations; how they increase TG levels is not known, but the effect could be mediated through a reduction in LPL. On the other hand, according to Babirak et al, evidence that β-blockers in particular reduce LPL activity is relatively weak. Little is known about the effect of smoking on LPL. In the three groups of the present study, when patients who were nonsmokers and who were not taking β-blockers were compared, no differences in LPL activities were detected among any of the groups. Thus it is possible, although not necessarily proven, that low LPL levels found in the groups as a whole were related to smoking and β-blockers.

The current data suggest that an increase in HTGL activity is a more consistent abnormality in patients with low HDL levels than is a decrease in LPL activity. Mechanisms for elevated HTGL levels are not well understood. Androgens, progestins, and related steroids have been reported to raise the activity of HTGL. One study in twins found that the activity of HTGL is under strong genetic control; if so, an inherited increase in HTGL activity could be a common cause of low HDL levels. Whether cigarette smoking or other drugs increase expression of HTGL is unknown. Whatever the reasons for high HTGL activities in patients with low HDL levels, the strong association noted in the current and previous research implicates an overactivity of HTGL as a major factor in causing low HDL levels. The HDL-lowering action of elevated HTGL activity appears to be accentuated when LPL activity is concomitantly reduced. Further investigation of factors regulating expression of HTGL may prove fruitful for understanding the common occurrence of low HDL levels. Because of the high correlation between low HDL and the risk of CHD, an increased activity of HTGL could prove to be one of the more atherogenic changes in lipoprotein metabolism.

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