Relationship of Phospholipid Transfer Protein Activity to HDL and Apolipoprotein B–Containing Lipoproteins in Subjects With and Without Type 1 Diabetes

Helen M. Colhoun, Marja-Riitta Taskinen, James D. Otvos, Paul van den Berg, John O’Connor, and Arie Van Tol

Patients with type 1 diabetes have greatly increased phospholipid transfer protein (PLTP) activity and have an altered HDL subclass distribution. In 195 patients with type 1 diabetes and in 194 men and women aged 30–55 years, we examined the relationship of PLTP activity to HDL and examined whether PLTP activity contributes to differences in HDL found in type 1 diabetes. PLTP activity was measured using an exogenous substrate assay. Average HDL particle size and HDL subclasses were measured using nuclear magnetic resonance spectroscopy. Apolipoprotein AI (apoAI) and apolipoprotein AII (apoAII) were measured by immunoturbidimetry, and the amount of apoAI in LpAII was inferred from the apoAI and LpAI data. Higher PLTP activity was associated with more large HDL (P < 0.001) and less small HDL (P < 0.01), more apoAI and apoAII (both at P < 0.001), and more apoAI in both LpAI and LpAII (P = 0.02 and P < 0.001, respectively). These associations were independent of other lipids and enzyme activities. Adjusting for PLTP activity halved the difference between subjects with and without diabetes in apoAI (from 10.1 mg/dl higher in subjects with diabetes to 4.6 mg/dl higher) and large HDL (2.4 μmol/l higher to 1.2 μmol/l higher) and reduced the difference in HDL size (from 0.31 nm higher to 0.26 nm higher). PLTP activity was also positively associated with apoB, total VLDL and LDL particle number, and IDL level in subjects with diabetes. These data support the idea that PLTP is a major factor in HDL conversion and remodeling in humans and that higher PLTP activity makes an important contribution to the higher apoAI levels and altered HDL subclass distribution in type 1 diabetes. They also support a role for PLTP in the metabolism of apoB-containing lipoproteins. Diabetes 51:3300–3305, 2002

HDL exists as several subpopulations that differ in size, density, and apolipoprotein (apo) content as well as capacity to accept cellular cholesterol. These subpopulations undergo remodeling and interconversion by the addition and removal of their neutral lipids, phospholipids, and apo components. Proteins known to be involved in HDL metabolism include lecithin:cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP), and the endothelial-bound enzymes hepatic and lipoprotein lipase. Phospholipid transfer protein (PLTP) enhances the transfer of phospholipids from VLDL to HDL particles. In vitro and animal studies also demonstrate a role for PLTP in the remodeling of HDL, including promotion of the generation of pre-β HDL particles and large HDL particles from HDL₃. However, in vivo data on the relationship of PLTP to HDL metabolism in humans are sparse and in parts conflicting (5–7).

We previously demonstrated that patients with type 1 diabetes have a significantly elevated PLTP activity (~1 SD higher than in the general population) and that PLTP activity correlates with HDL cholesterol (8). Many studies have demonstrated that, in the absence of renal failure, HDL cholesterol and apoAI are often higher in subjects with type 1 diabetes than in the background population (9). We recently demonstrated that patients with type 1 diabetes have more large and less small HDL with a consequently increased average HDL particle size (10). The role of PLTP activity in these diabetic–nondiabetic differences in HDL has not been examined.

To provide more detailed data on the relationship of PLTP and HDL metabolism in the general population and in patients with type 1 diabetes, we examined the association of PLTP activity with several aspects of HDL, namely, nuclear magnetic resonance (NMR) spectroscopy–defined HDL subclass levels and average particle size, the levels of apoAI and apoAII, and the amount of apoAI that resides in LpAI (HDL particles that contain only apoAI) and in LpAII (particles that contain apoAI and apoAII). We examined to what extent the elevated PLTP activity in type 1 diabetes we have recently reported (8) might account for differences in various aspects of HDL between subjects with and without diabetes. As recent studies have suggested a role for PLTP in apoB secretion...
VLDL and LDL size as previously described (10). HDL (H1) is robust to samples that have been frozen. NMR spectroscopy was also used to determine the concentration of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) subclasses: H5 (11.5 ± 1.5 nm), small HDL (H6; 8.0 ± 0.2 nm), and H1 (7.5 ± 0.2 nm). Average HDL particle sizes (nm diameter) were determined by weighting the relative mass percentage of each subclass by its diameter. For simplifying analyses, the HDL subclasses were grouped into three categories: large HDL (H4), intermediate HDL (H3), and small HDL (H1). The Spearman correlation coefficient and regression coefficients for the association of PLTP activity with various aspects of HDL were determined using the endogenous plasma substrates, as the plasma cholesterol esterification rate (EST) (19). \( ^{19} \)Hcholesterol complexed with albumin was added to plasma and plasma free cholesterol, and the labeled cholesterol was allowed to equilibrate overnight at 4°C. Serum apoAI and apoAII concentrations were measured by an immunoturbidimetric method with commercially available kits (Boehringer Mannheim) as previously described (18). The amount of apoAI residing in LpAI (hereafter termed LpAI-apoAI) was quantified using a differential electroimmunoassay with hydrated agarose gels containing monospecific antibodies against apoAI and apoAII (Sebia, Issy-Les-Moulineaux, France) as described (18). Serum apoAI in LpAII (termed LpAII-apoAI) was then estimated by subtracting the concentration of LpAI from the immunoturbidimetrically measured total level of apoAI. The between-assay CVs for these assays were 3.5%, 2.1%, and 7.3% for apoAI, apoAII, and LpAII-apoAI, respectively.

RESEARCH DESIGN AND METHODS

Subjects. The methods have been described in detail previously (10). A random sample of men and women with type 1 diabetes aged 30–55 years was taken from the diabetes registers of five London hospitals. Type 1 diabetes was defined by age of onset ≤25 years and onset of permanent insulin therapy within 1 year of diagnosis. A random sample of the general population, stratified to have a similar age and sex distribution to the patients, was drawn from the lists of two London general practices. Patients on renal replacement therapy were excluded. Ethics Committee approval was obtained from our Institution and the Local Research Ethics Committees covering the practices involved. Written informed consent was obtained from all subjects. In all, 198 subjects with and 198 subjects without diabetes were recruited and had PLTP activity measured. Three subjects who had diabetes and were on lipid-lowering therapy and four subjects who did not have diabetes but had hypertriglyceridemia (>6 mmol/l) were excluded from these analyses.

Laboratory methods. After an overnight fast, blood samples were taken and total cholesterol, HDL cholesterol, and triglyceride levels were measured using enzymatic colorimetric methods (12,13). HDL cholesterol was measured directly after stabilization of other lipoproteins. (14) LDL cholesterol was calculated as described by Friedewald et al. (Friedewald WT, Levy RI, Frederickson DS). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502, 1972). HbA1c was measured using a latex enhanced immunoassay (between-assay coefficient of variation [CV] 1.7%). ApoB was measured by using an immunochemical assay (Orion Diagnostica).

Fasting citrated samples were centrifuged at 4°C within 1 h of sampling and then stored at −70°C. On average, samples had been stored for 8 months before analysis. Plasma PLTP activity was measured with labeled liposome vesicles as phospholipid donor and excess pooled human HDL as phospholipid acceptors, as described. (15). The between-assay CV (i.e., running a reference sample on different days) was 4.8%, and the within-assay CV was 3.0% (i.e., running a reference assay several times within the assay run). Plasma PLTP activity levels were related to the activity in a human reference plasma pool analyzed in each run and are expressed in arbitrary units (AU), corresponding to the percentage of the activity in the reference plasma. CETP activity and the actual mass of cholesterol esters transferred (plasma CET) were measured as previously described (8) (between-assay CV 4.5% and 7.2%, respectively) and modified as described (16). The rate of CET is expressed in absolute units of nanomoles of cholesteryl ester transferred per milliliter of plasma per hour and is constant during 3 h of incubation.

HDL size and subclass concentration were measured using a 400-MHz proton NMR analyzer at Liposcience, Inc., as described (8,17). Subclass particle levels in units of micromoles per liter were measured for five HDL subclasses: H5 (11.5 ± 1.5 nm), H4 (9.4 ± 0.6 nm), H3 (8.5 ± 0.3 nm), H2 (8.0 ± 0.2 nm), and H1 (7.5 ± 0.2 nm). Average HDL particle sizes (nm diameter) were determined by weighting the relative mass percentage of each subclass by its diameter. For simplifying analyses, the HDL subclasses were grouped into three categories: large HDL (H4–H5), intermediate HDL (H3), and small HDL (H1-H2). In-house experiments have shown that the measures are robust to samples that have been frozen. NMR spectroscopy was also used to quantify large VLDL (~90–200 nm ± chylomicrons), intermediate VLDL (35–60 nm), and small VLDL (27–35 nm), intermediate-density lipoprotein (IDL; 35–27 nm), large LDL (19.8–33 nm), and small LDL (18.3–19.7 nm) as well as average VLDL and LDL size as previously described (10).

(11), we also report on the association of PLTP activity with apoB and apoB-containing lipoproteins.

TABLE 1
Spearman correlation coefficients (r) for the association between PLTP activity and HDL-related variables

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic men (p)</th>
<th>Nondiabetic women (p)</th>
<th>Diabetic men (p)</th>
<th>Diabetic women (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.13</td>
<td>−0.08</td>
<td>0.03</td>
<td>0.36‡</td>
</tr>
<tr>
<td>HDL size (nm)</td>
<td>0.10</td>
<td>−0.06</td>
<td>0.10</td>
<td>0.21†</td>
</tr>
<tr>
<td>Small HDL (µmol/l)</td>
<td>−0.10</td>
<td>−0.15</td>
<td>−0.10</td>
<td>−0.28‡</td>
</tr>
<tr>
<td>Intermediate HDL (µmol/l)</td>
<td>0.1</td>
<td>−0.03</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Large HDL (µmol/l)</td>
<td>0.21*</td>
<td>0.15</td>
<td>0.22†</td>
<td>0.40†</td>
</tr>
<tr>
<td>ApoAII (mg/dl)</td>
<td>0.27*</td>
<td>0.0</td>
<td>0.11†</td>
<td>0.40†</td>
</tr>
<tr>
<td>LpAII (mg/dl)</td>
<td>0.24†</td>
<td>0.27†</td>
<td>0.13</td>
<td>0.34†</td>
</tr>
<tr>
<td>LpAII-apoAI (mg/dl)</td>
<td>0.11</td>
<td>0.16</td>
<td>0.12</td>
<td>0.21</td>
</tr>
</tbody>
</table>

‡P < 0.001; †P < 0.05; §P < 0.01.

RESULTS

Diabetic subjects had higher HDL cholesterol, apoAI, and LpAII-apoAI but not LpAII-apoAI levels (Table 3). Diabetes was associated with higher PLTP activity (mean $81 \pm 15$ AU in subjects without diabetes, $96 \pm 19$ AU in subjects with diabetes; $P < 0.001$), as reported previously (8).

The association of PLTP activity with aspects of HDL.

The Spearman correlation coefficients and regression coefficients for the association of PLTP activity with various aspects of HDL for each of the diabetes sex groups are shown in Tables 1 and 2, respectively. The most consistent findings across all four groups were that a higher PLTP activity was associated with lower levels of small HDL and higher levels of large HDL, apoAI, and apoAII.

As shown in Tables 1 and 2, not all of these associations were statistically significant within each of the four groups. In general, the difference in the HDL parameters...
Role of elevated PLTP activity in differences in HDL between subjects with and without diabetes. We examined whether the elevated PLTP activity in diabetes could explain differences in HDL in subjects with diabetes compared with subjects without diabetes. Adjusting for PLTP activity using multiple regression decreased the difference between subjects with and without diabetes in HDL size from 0.31 nm (9.41 nm vs. 9.1 nm, SD = 0.45) in subjects with diabetes to 0.26 nm, from 2.4 to 1.2 μmol/l for large HDL particle number, and from −3.2 to −2.2 μmol/l for small HDL particle number. The diabetic difference in apoA1 was halved from 10.1 to 4.6 mg/dl. The diabetic difference in HDL cholesterol was reduced from 0.14 to 0.09 mmol/l.

PLTP activity and apoB. PLTP activity was positively associated with apoB levels in subjects with diabetes (Spearman’s ρ = 0.28, P = 0.005 in men with diabetes; ρ = 0.22, P = 0.04 in women with diabetes) but was not associated with apoB in subjects without diabetes (ρ = 0.03, P = 0.8 in men; ρ = 0.1, P = 0.25 in women). Subjects with diabetes had a lower apoB than subjects without diabetes (9 mg/dl lower; P < 0.001). On adjustment for for a 10-unit difference in PLTP activity was greatest in women with diabetes and lowest in women without diabetes. In subjects with diabetes, PLTP activity was also positively correlated with average HDL particle size. In women with diabetes, there was a positive association with HDL cholesterol.

Adjusting for other factors. We examined whether the association between PLTP activity and HDL parameters might be attributable to any factors associated with PLTP activity other than PLTP activity itself. CET was positively correlated with PLTP activity (r = 0.16 in subjects without diabetes and r = 0.27 in subjects with diabetes; both P < 0.001). LCAT activity as measured by EST was also positively associated with PLTP activity in subjects both with and without diabetes (a difference of 4 units in EST with every 10-unit difference in PLTP activity in both groups; both P < 0.01). Other correlates of PLTP activity include CETP activity and LDL cholesterol levels (8). Adjusting for these variables, whether singly or simultaneously, increased rather than decreased the strength of the observed associations between PLTP activity and HDL parameters. For example, adjusting simultaneously for triglycerides, LDL cholesterol, CETP, CET, and EST increased the association between PLTP activity and large HDL (regression coefficient β = 0.86, P < 0.001 in subjects without diabetes; β = 1.4, P < 0.001 in subjects with diabetes on adjustment), reflecting that most of these positive correlates of PLTP activity are inversely correlated with HDL.

Adjustment for BMI and waist:hip ratio did not affect the associations observed either (data not shown). The strength of the relationship between PLTP activity and HDL parameters did not differ by triglyceride level (test for interaction between triglycerides and PLTP was >0.05 for all parameters). The conclusions were also unchanged when women who were on the pill or hormone replacement therapy were excluded from the analysis (data not shown) and when four subjects who were on β-blockers were excluded. Adjusting for alcohol consumption did not affect any of the associations between PLTP activity and HDL-related variables.
PLTP activity, the difference became more pronounced (12 mg/dl lower). We examined the relationship of PLTP activity to VLDL and LDL subclasses, total particle level, IDL level, and average VLDL and LDL particle size. The main findings were as follows: in subjects with diabetes, adjusted for sex, PLTP activity was positively associated with total VLDL particle number ($P = 0.001$), small VLDL ($P = 0.001$), IDL ($P = 0.004$), and total LDL particle number ($P = 0.02$) but not average VLDL or LDL particle size; in subjects without diabetes, PLTP activity was positively associated with small VLDL ($P = 0.03$).

**DISCUSSION**

In this large cross-sectional study, we demonstrated that higher PLTP activity is associated with having more large HDL and less small HDL and having more apoAI and apoAII. These associations were similar in direction in subjects with and without diabetes but were generally stronger in subjects with diabetes in whom PLTP activity was substantially elevated as previously reported (8). The observed associations were independent of other lipid and enzyme activities with which PLTP activity is correlated. The higher PLTP activity in patients with diabetes was sufficient to explain half of the diabetic–nondiabetic differences in apoAI and large HDL and less of the difference in HDL cholesterol, HDL size, and other aspects of HDL. Higher PLTP activity was also associated with higher apoB in subjects with diabetes.

The data are consistent with in vitro and in vivo studies that have demonstrated that PLTP has an effect on HDL metabolism. In humans, the role of PLTP in HDL metabolism is sufficiently critical to be detectable at the population level in a cross-sectional study. The large HDL that we measured by the NMR spectroscopy method is equivalent in size to the gradient gel electrophoresis subclasses 2b and 2a, and the small HDL that we defined is equivalent to 3b and 3c. PLTP co-elutes with large HDL in human serum (15), but there are few previous data on the association of PLTP activity with size-defined HDL subclasses in vivo. In a study of the effect of dietary change in 32 subjects, PLTP activity was positively associated with HDL$_{2b}$ and HDL$_{2a}$ subfractions and inversely correlated with HDL$_{3a}$ and HDL$_{3b}$, consistent with our data on large and small HDL despite using different laboratory methods (23). In another study, HDL$_{2b}$ and HDL$_{2a}$ subfractions increased with increasing PLTP activity in 32 alcoholic patients in a cessation program (5).

Previous data on the relationship between PLTP activity and apoAI and apoAII are conflicting with PLTP activity being positively associated with apoAI but not apoAII in one study (24). In nonfasting samples in another study, PLTP activity was unrelated to apoAI but was positively correlated with apoAII (7). In our large fasting sample, we found a consistent pattern across all four diabetes sex groups of higher apoAI and apoAII with higher PLTP activity.

Previous data on the relationship of PLTP activity with HDL cholesterol and with LpAI and LpAII are also conflicting (7,24). We found PLTP activity to be positively

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**TABLE 3**

<table>
<thead>
<tr>
<th>Men</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
<th>Mean Value</th>
<th>P Value</th>
<th>Nondiabetic</th>
<th>Diabetic</th>
<th>Mean Value</th>
<th>P Value</th>
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<tr>
<td>Men</td>
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<td>Nondiabetic</td>
<td>Mean Value</td>
<td>P Value</td>
<td>Nondiabetic</td>
<td>Diabetic</td>
<td>Mean Value</td>
<td>P Value</td>
</tr>
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<td>24.9 (4.4)</td>
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<td>21 (6)</td>
<td>21 (6)</td>
<td>0.004</td>
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<td>23.6 (4.6)</td>
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<td>21 (6)</td>
<td>0.004</td>
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<td>22.3 (4.8)</td>
<td>0.001</td>
<td>21 (6)</td>
<td>21 (6)</td>
<td>0.004</td>
<td>21 (6)</td>
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<tr>
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<td>21.1 (5.0)</td>
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<td>21 (6)</td>
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<td>0.004</td>
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<tr>
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<td>19.9 (5.2)</td>
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<td>21 (6)</td>
<td>21 (6)</td>
<td>0.004</td>
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**TABLE 4**

<table>
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<tr>
<th>Women</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
<th>Mean Value</th>
<th>P Value</th>
<th>Nondiabetic</th>
<th>Diabetic</th>
<th>Mean Value</th>
<th>P Value</th>
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correlated with LpAIAII-apoAI in subjects with diabetes also with LpAI-apoAI. The ratio of apoAI in LpAI to LpAIAII was unrelated to PLTP activity (data not shown). We found that PLTP activity was associated with HDL cholesterol in women with diabetes only. HDL cholesterol was positively associated with PLTP activity in fasting samples in some studies (5,6,24), but there was an inverse association between PLTP activity and HDL cholesterol in nonfasting samples in another (7). No association was found in two other studies (25,26). These inconsistent findings may reflect different assay methods, sample sizes, prevailing lipid levels, or the difference in fasting versus nonfasting assessment. In a sample of premenopausal women, PLTP activity was positively correlated with HDL2 and HDL3 cholesterol more strongly so in nonobese subjects (6).

Because our assay measures phospholipid transfer, our data are consistent with recent in vitro data demonstrating that the ability of PLTP to catalyze HDL conversion involves phospholipid transfer (27). HDL remodeling is a dynamic process, whereas we are assessing the relationship between PLTP activity and HDL cholesterol in a single snapshot in time in the fasted state. Our study was cross-sectional and as such can only describe associations between PLTP activity and HDL. Demonstrating the role of PLTP in HDL remodeling definitively requires intervention studies. Other dynamic studies have supported the potential role for PLTP in HDL remodeling in humans by using infusions of insulin to reduce PLTP activity and observing a decrease in HDL cholesterol and apoAI (28,29). Our study design complements these intervention studies in that it reflects the prevailing levels of PLTP activity usually seen in the fasted state. However, as it is a cross-sectional study, it is of course possible that some other correlate of PLTP activity, rather than PLTP activity itself, is responsible for the associations observed. If so, then these correlates do not seem to be lipids, CETP activity, or LCAT activity. A possible correlate is hepatic lipase activity. However, PLTP activity and hepatic lipase activity have been reported to be unrelated, at least in subjects without diabetes, so this seems an unlikely explanation for our results (6). Lipoprotein lipase activity was found to be positively associated with PLTP activity in one study (6). In that study, PLTP activity was associated with HDL2 cholesterol when obese subjects were excluded and the association was not independent of lipoprotein lipase activity. We did not measure lipoprotein lipase activity as it is logistically difficult to do this on the large numbers of subjects as studied here, and so it cannot be excluded that it may be a partial explanation of the relationship of PLTP activity with HDL.

It is also the case that the relationship of lipoprotein composition to PLTP activity observed in this cross-sectional study may reflect a bidirectional association. For example, in pigs, the apoAI/apoAII molar ratio in HDL is unknown. Although increased generation of pre-β HDL would be expected to be antiatherogenic, it remains to be seen whether the composition of large HDL associated with elevated PLTP activity is such that it retains its antiatherogenic potential compared with large HDL at more usual levels of PLTP activity.

More recently, it has been suggested that increased PLTP might have atherogenic properties as there was reduced secretion of apoB-containing lipoproteins and atherosclerosis in PLTP-deficient mice (11). PLTP is probably involved in the lipiddation of nascent apoB-containing particles within the secretory pathway. Our finding of a positive association between PLTP activity and apoB, total VLDL particle number, small VLDL, and IDL and LDL particle number is consistent with an important role for PLTP in apoB-containing lipoprotein secretion.

In conclusion, these data are consistent with an important role for PLTP in remodeling of HDL in the usual conditions pertaining in both the general population and subjects with diabetes. Elevated PLTP activity likely contributes to but is not the sole explanation for differences in HDL subclasses and apoAI in type 1 diabetes.

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