

Dissociation Between Cholesteryl Ester Transfer Protein Mass and Activity in Coronary Artery Disease Patients with Elevated High-Density Lipoprotein Cholesterol: Implications for High-Density Lipoprotein Function and Residual Cardiovascular Risk

ABSTRACT

Background: High-density lipoprotein cholesterol (HDL-C) is traditionally viewed as cardioprotective; however, some patients with coronary artery disease (CAD) may present with elevated HDL-C levels, challenging this assumption. This study aimed to investigate the roles of HDL subclasses, apolipoproteins, and cholesteryl ester transfer protein (CETP) activity and mass in patients with CAD with high HDL-C and low-density lipoprotein cholesterol (LDL-C) levels.

Methods: A total of 35 patients with CAD and 35 age- and lipid-matched control participants (HDL-C $\geq$ 60 mg/dL and LDL-C $\geq$ 130 mg/dL) were enrolled. Cholesteryl ester transfer protein mass and activity, apolipoprotein A-I (ApoA-I), ApoA-II, ApoB, and HDL subclasses (HDL2 and HDL3) were measured and compared between groups. Correlation analyses and multivariate logistic regression were performed to assess the relationship between CETP activity and CAD.

Results: The CETP activity was significantly higher in patients with CAD compared with control participants (1.08 vs. 0.98 nmol/ μ L/h, $P=.007$), whereas CETP mass, HDL2, and HDL3 levels were similar. The ApoA-I levels were paradoxically higher in patients with CAD ($P=.006$), with no differences in ApoA-II or ApoB. In multivariate analysis, CETP activity remained independently associated with CAD after adjusting for age and sex (OR 2.03; 95% CI 1.27-3.24; $P=.002$).

Conclusion: In patients with high HDL-C and LDL-C, increased CETP activity—but not mass—was associated with the presence of CAD, suggesting CETP function may contribute to residual cardiovascular risk. Elevated ApoA-I levels in patients with CAD may reflect dysfunctional HDL, emphasizing that HDL quality, rather than quantity, plays a more critical role in atheroprotection. These findings support a functional evaluation of lipoproteins in cardiovascular risk assessment.

Keywords: Cholesteryl ester transfer protein activity, coronary artery disease, high-density lipoprotein cholesterol, mass

INTRODUCTION

Atherosclerotic cardiovascular disease remains the leading cause of mortality worldwide despite significant advances in risk factor control and lipid-lowering therapies.^{1,2} High-density lipoprotein cholesterol (HDL-C) has traditionally been considered cardioprotective due to its roles in reverse cholesterol transport, antioxidant, and anti-inflammatory functions.^{3,4} However, recent evidence suggests that elevated HDL-C does not always equate to lower cardiovascular risk, challenging the classic "HDL hypothesis."^{5,6} Some patients with coronary artery disease (CAD) maintain high HDL-C concentrations yet still experience adverse cardiovascular events, suggesting that HDL function, rather than its concentration alone, may be impaired.⁷

ORIGINAL INVESTIGATION

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The HDL particles are heterogeneous, with subclasses such as HDL2 and HDL3 differing in size, density, and protein composition, potentially influencing their cardioprotective effects.⁸ In addition, apolipoproteins, particularly apolipoprotein A-I (ApoA-I) and ApoA-II, are critical for HDL structure and its capacity to promote cholesterol efflux.^{9,10} Alterations in these components may contribute to dysfunctional HDL in CAD.

Cholesteryl ester transfer protein (CETP) is another key regulator of HDL metabolism, mediating the transfer of cholesteryl esters from HDL to ApoB-containing lipoproteins, thereby affecting HDL levels and function.¹¹ Elevated CETP activity has been linked to impaired reverse cholesterol transport and a more atherogenic lipid profile.^{12,13} Importantly, CETP mass alone may not fully reflect its biological activity, underscoring the need to measure both CETP mass and activity to better characterize residual cardiovascular risk.¹⁴

Therefore, this study aimed to examine CETP mass and activity, HDL subclasses, and apolipoprotein levels in patients with CAD and elevated HDL-C, in order to clarify the paradox of high HDL-C levels coexisting with atherosclerosis. It was hypothesized that CETP activity, rather than CETP mass, would be higher in patients with CAD and elevated HDL-C.

METHODS

Patient Population

Thirty-five patients with CAD ($\geq 20\%$ stenosis in at least 1 coronary artery) with HDL-C ≥ 60 mg/dL and low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL were enrolled, along with 35 lipid-matched control participants. Control participants were confirmed to be free of CAD by coronary angiography or coronary CT angiography, excluding those with $\geq 20\%$ stenosis. The LDL-C values corresponded to measurements at diagnosis, before initiation of any lipid-lowering therapy. Patients were either newly diagnosed or had temporarily discontinued therapy; statin treatment was started after sample collection. The LDL-C was calculated using the Friedewald formula, and patients with triglyceride (TG) ≥ 400 mg/dL were excluded. Exclusion criteria included:

HIGHLIGHTS

- Cholesteryl ester transfer protein (CETP) activity, but not CETP mass, was significantly increased in patients with coronary artery disease (CAD) with high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol.
- The CETP activity was associated with the presence of CAD after adjustment for age and sex.
- The HDL2 and HDL3 subclass distributions did not differ between patients with CAD and control participants.
- Apolipoprotein A-I levels were paradoxically higher in patients with CAD, suggesting potential HDL dysfunction.
- The HDL function rather than HDL-C concentration alone may be critical for cardiovascular risk assessment.

current use of lipid-lowering drugs or steroids, unwillingness to participate, alcoholism, familial hyperlipidemia, thyroid dysfunction, chronic inflammatory diseases, malignancy, and marathon runners.

Baseline information, anthropometric measurements, medication usage, major atherosclerosis risk factors, and laboratory values (complete blood count, serum creatinine, lipid profile, thyroid function tests, and fasting blood glucose) were recorded before coronary angiography. Coronary angiography reports were used to document the number of obstructed vessels, localization of vascular obstruction, and degree of stenosis.

Blood Samples

Venous blood samples were drawn after a 12-hour overnight fast. Samples for plasma CETP activity and CETP mass were collected in EDTA-containing tubes, while serum samples for ApoA-I, ApoA-II, ApoB, HDL subclass 2 (HDL2), and HDL subclass 3 (HDL3) were collected in standard biochemical tubes. Following centrifugation at 4000 rpm for 15 minutes, plasma and serum aliquots were stored at -80°C until analysis.

Analytical Procedures

Plasma CETP activity was determined using the K601-100 coded CETP Activity Assay Kit (BioVision Research Products), and CETP mass was measured with the E90814Hu coded ELISA kit (Uscnk Life Science Inc.). Serum ApoA-I and ApoA-II concentrations were analyzed with the E90519Hu and E90604Hu kits, respectively, and ApoB was measured by the BNProspec[®] nephelometry system (Siemens). Serum HDL2 and HDL3 subfractions were separated by non-denaturing polyacrylamide gradient gel electrophoresis (3%-30% gradient). After electrophoresis, lipoprotein bands were visualized by lipid staining and quantified by densitometry. The HDL2 and HDL3 fractions were identified according to their established particle size ranges, and cholesterol content in each fraction was expressed as mg/dL. Intra-assay and inter-assay coefficients of variation for all assays were within acceptable ranges according to the manufacturers' instructions. All laboratory analyses were performed at the Biochemistry Central Laboratory of Gazi University Faculty of Medicine and all measurements were conducted by technicians blinded to the participants' clinical data.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive data are expressed as frequencies and percentages for categorical variables and as means $\pm$ standard deviations for continuous variables. Group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and the independent samples t-test for continuous variables, as appropriate.

Binary logistic regression analysis was conducted to evaluate the association between CETP activity and the presence of CAD, adjusting for age and sex. Given the relatively small sample size, the number of variables included in the multivariate logistic regression model was deliberately

limited to avoid model overfitting. Age and sex were selected as the most clinically relevant covariates, while other potential confounders (such as smoking status, diabetes, and serum creatinine) were not included due to limited statistical power.

The normality of data distribution was assessed prior to analysis. Correlations between CETP mass or activity and other clinical parameters were evaluated using Pearson or Spearman correlation analyses, as appropriate. A *P* value <.05 was considered statistically significant.

A post hoc power analysis (G*Power 3.1), based on the observed difference in CETP activity between CAD-positive and CAD-negative groups (*P* = .007), indicated a statistical power of 0.80 (α = 0.05, two-tailed).

Ethical Considerations and Approval

The study protocol was approved by the Ethics Committee of Gazi University (Approval number/date: 301/January 27, 2012). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Consent for Participation

All participants were informed about the study procedures, and written informed consent was obtained from each patient prior to study inclusion.

RESULTS

Baseline characteristics, lipid and lipoprotein parameters, and CETP measures are presented in Table 1 by CAD status. The patients with CAD had a significantly higher mean age and creatinine level, as well as a higher proportion of female participants, compared to the control participants. No significant differences were noted between groups for hypertension, diabetes, smoking status, family history, or body mass index (BMI). Although mean LDL-C levels tended to be higher in the patients with CAD, this difference was not statistically significant. Other lipid parameters were similar between groups.

Comparisons of HDL2 and HDL3 levels showed no significant differences between patients with CAD and control participants. The ApoA-I levels were significantly higher in patients with CAD (mean 588.6 ± 413 μ g/mL vs. 414 ± 80 μ g/mL, *P* = .006), a result that remained robust after excluding outliers. The ApoA-II and ApoB levels did not differ significantly between the 2 groups. Cholesteryl ester transfer protein mass was also similar (mean 27.7 ± 14.1 μ g/mL vs. 24.2 ± 12.4 μ g/mL, *P* = .27); however, CETP activity was significantly elevated in patients with CAD (mean 1.08 ± 0.14 nmol/ μ L plasma/hour vs. 0.98 ± 0.13 nmol/ μ L plasma/hour, *P* = .007) (Figure 1).

In the overall study population, CETP activity showed a positive correlation with total cholesterol (*r* = 0.298, *P* = .01), LDL-C (*r* = 0.263, *P* = .03), TGs (*r* = 0.403, *P* = .001), and ApoB (*r* = 0.300, *P* = .012). The CETP mass was positively correlated with total cholesterol (*r* = 0.264) and ApoB (*r* = 0.306), though these correlations did not reach statistical significance except for ApoB. No significant correlations were observed

Table 1. Baseline Characteristics, Lipid Profile, HDL Subclasses, Apolipoproteins, and CETP Parameters in Patients with CAD and Control Participants

Variables	Patients with CAD (n = 35)	Control Participants (n = 35)	P
Age (years)	66.71 $\pm$ 9.7	61.77 $\pm$ 8.7	.03
Sex			.002
Female	21 (60%)	32 (91.4%)	
Male	14 (40%)	3 (8.6%)	
Hypertension	20 (57.1%)	24 (68.6%)	.23
Diabetes	10 (28.6%)	5 (14.3%)	.14
Smoking status			.11
Nonsmokers	16 (45.7%)	24 (68.6%)	
Ex-smokers	9 (25.7%)	7 (20%)	
Smokers	10 (28.6%)	4 (11.4%)	
Family history	10 (28.6%)	14 (40%)	.23
BMI (kg/m ²)	28.07 $\pm$ 5.7	28.41 $\pm$ 4.5	.77
Creatinine (mg/dL)	0.94 $\pm$ 0.43	0.75 $\pm$ 0.12	.016
Total cholesterol (mg/dL)	239.7 $\pm$ 48.5	236.1 $\pm$ 29.3	.71
Triglycerides (mg/dL)	121.3 $\pm$ 88.5	98.9 $\pm$ 37.5	.18
LDL-C (mg/dL)	165.1 $\pm$ 31.3	156 $\pm$ 21	.17
HDL-C (mg/dL)	67.3 $\pm$ 7.5	67.6 $\pm$ 7.8	.85
HDL2 (mg/dL)	97.9 $\pm$ 46.1	95.8 $\pm$ 31.1	.82
HDL3 (mg/dL)	2742 $\pm$ 815	2995 $\pm$ 703	.17
ApoA-I (μ g/mL)	588.6 $\pm$ 413	414.2 $\pm$ 80	.006
ApoA-II (μ g/mL)	44.2 $\pm$ 4.9	43.9 $\pm$ 2.7	.75
ApoB (mg/dL)	76.98 $\pm$ 25.79	77.22 $\pm$ 19.86	.96
CETP mass (μ g/mL)	27.7 $\pm$ 14.1	24.2 $\pm$ 12.4	.27
CETP activity (nmol/ μ L plasma/hour)	1.08 $\pm$ 0.14	0.98 $\pm$ 0.13	.007

ApoA-I/A-II/B, apolipoprotein A-I/A-II/B; BMI, body mass index; CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; HDL2/HDL3: HDL Subclasses 2 and 3; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

between CETP activity or mass and HDL2, HDL3, ApoA-I, or ApoA-II in the total group.

In patients with CAD, CETP activity correlated significantly with total cholesterol (*r* = 0.379, *P* = .03), TGs (*r* = 0.439, *P* = .008), and ApoB (*r* = 0.486, *P* = .003). The CETP mass did not show significant correlations with most lipid parameters in this group.

In the control group, CETP mass showed a significant positive correlation with total cholesterol (*r* = 0.430, *P* = .01), LDL-C (*r* = 0.372, *P* = .03), and ApoB (*r* = 0.437, *P* = .009). The CETP activity did not demonstrate statistically significant correlations in the control group.

To further evaluate the relationship between CETP activity and the presence of CAD, a multivariate binary logistic regression analysis adjusted for age and sex was performed. CETP activity remained significantly associated with CAD (β = 0.708, SE = 0.233, *P* = .002). When expressed per 0.1 nmol/ μ L/h increment, the adjusted odds ratio was 2.03 (95% CI: 1.27-3.24). Age showed a borderline association (β = 0.062,

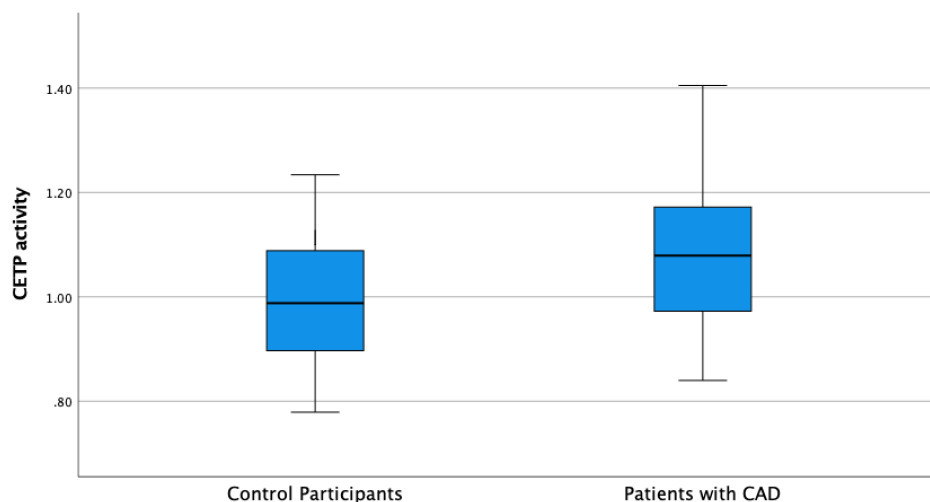


Figure 1. CETP activity in patients with CAD and control participants. Box plot showing plasma CETP activity (nmol/μL plasma/hour) in patients with CAD (n = 35) and controls (n = 35). Mean values are indicated; CETP activity was higher in patients with CAD ($P = .007$).

SE = 0.033, $P = .057$), whereas female sex was inversely associated with CAD ($\beta = -2.259$, SE = 0.797, $P = .005$) (Table 2).

DISCUSSION

This study demonstrates that patients with CAD who have elevated HDL-C and LDL-C levels exhibit significantly increased CETP activity, despite no significant difference in CETP mass compared to control participants. These findings suggest that CETP functional activity, rather than CETP protein concentration alone, may be a more critical determinant of atherogenic processes in this high-risk group. To the best of knowledge, this is among the few clinical studies to highlight a dissociation between CETP mass and activity in patients with CAD and high HDL-C, contributing novel insight into the complex regulation of CETP and its impact on cardiovascular risk. Recent genetic studies have supported this notion, showing that CETP gene polymorphisms and haplotypes significantly influence CETP activity and thereby modify cardiovascular risk profiles.^{15,16}

In the multivariate analysis, CETP activity demonstrated an association with the presence of CAD after adjustment for age and sex. This finding supports the potential role of CETP activity as a functional determinant of atherosclerotic risk, beyond conventional lipid parameters. However, given the

modest sample size, this association should be interpreted cautiously.

Elevated CETP activity promotes the transfer of cholesteryl esters from HDL to ApoB-containing lipoproteins, potentially impairing reverse cholesterol transport and facilitating atherogenesis.^{11,12} Thus, the observed increase in CETP activity may represent a potential residual risk factor in patients with seemingly favorable HDL-C levels. Importantly, data from the IMPROVE study have shown that the association between HDL-C and subclinical atherosclerosis is modulated by plasma CETP concentration, highlighting the interplay between CETP and HDL functionality in atheroprotection.¹⁷

Interestingly, HDL subclass distribution (HDL2 and HDL3) was similar between groups, suggesting that traditional measures of HDL quantity and subclass composition are insufficient proxies for HDL function. This supports the emerging evidence that HDL cholesterol concentration alone poorly reflects HDL's anti-atherogenic roles, such as cholesterol efflux capacity, antioxidative activity, and anti-inflammatory effects.^{5,6,18} The results reinforce the paradigm shift in cardiovascular research focusing on HDL quality and function rather than quantity.

Notably, ApoA-I levels were higher in patients with CAD compared with controls, which appears paradoxical given the pro-atherogenic phenotype of this group. This increase may reflect a compensatory upregulation of ApoA-I synthesis in response to oxidative or inflammatory stress, potentially aimed at preserving reverse cholesterol transport. However, HDL functional capacity was not directly assessed; therefore, impaired HDL functionality should be considered a plausible hypothesis rather than a definitive conclusion. Previous studies indicate that post-translational modifications of ApoA-I, such as oxidation or glycation, can reduce interaction with ABCA1 transporters, decrease cholesterol efflux capacity, and impair antioxidant properties

Table 2. Binary Logistic Regression Analysis for Predictors of Coronary Artery Disease

Variables	β	SE	OR	95% CI	P
Age (Years)	0.062	0.033	1.06	0.99-1.13	.057
Sex (Female vs. male)	-2.259	0.797	0.10	0.02-0.50	.005
CETP activity (per 0.1 nmol/μL/h increase)	0.708	0.233	2.03	1.27-3.24	.002

β indicates regression coefficients. OR indicates odds ratio. Odds ratios for CETP activity are expressed per 0.1 nmol/μL/h increase. The model was adjusted for age and sex. CETP, cholesteryl ester transfer protein.

even when circulating ApoA-I levels are normal or elevated.¹⁹⁻²² Therefore, the higher ApoA-I levels observed in the study may represent an adaptive yet insufficient response to oxidative or inflammatory stress rather than a truly protective phenotype. Further mechanistic studies, including ApoA-I oxidation and glycation assays, are warranted to confirm this interpretation.

From a therapeutic perspective, these findings may have implications for CETP inhibition. Although CETP inhibitors effectively raise HDL-C levels, clinical trials have yielded mixed results in reducing cardiovascular events, possibly because they did not sufficiently inhibit CETP activity or address HDL dysfunction.^{23,24} Moreover, recent Mendelian randomization studies suggest that combined genetic inhibition of CETP and PCSK9 may offer additive cardiovascular benefits, pointing toward promising combination strategies.²⁵ The results, demonstrating increased CETP activity independent of mass, highlight the importance of developing biomarkers that directly measure CETP function and HDL quality to better guide treatment decisions.

Study Limitations

The study has several limitations. First, the relatively small sample size and cross-sectional design preclude causal inferences and limit the interpretation of potential therapeutic implications derived from the observed associations. Second, direct functional assays of HDL, such as cholesterol efflux capacity or antioxidative and anti-inflammatory activity, were not performed, which would have provided more detailed mechanistic insight into HDL functionality. This limitation is particularly relevant, as the elevated CETP activity and higher ApoA-I levels observed in patients with CAD may indirectly suggest impaired HDL function. Direct functional HDL assays would help clarify whether these biochemical alterations truly reflect reduced cholesterol efflux or antioxidant capacity.

Although the multivariate logistic regression analysis demonstrated an association between CETP activity and CAD, the strength of this finding is limited by the modest sample size and single-center design. Moreover, the regression model was adjusted only for age and sex to minimize overfitting. Other potential confounders, including smoking status, diabetes, and renal function, which may influence cardiovascular risk, were therefore not included.

An imbalance in sex distribution between patients with CAD and control participants is also acknowledged, with a higher proportion of females in the control group. Although sex was adjusted for in the regression analysis, residual effects related to sex-specific differences in lipoprotein metabolism and cardiovascular risk cannot be excluded. In addition, dietary habits and physical activity were not systematically assessed, which may have influenced lipid profiles and cardiovascular risk.

Finally, control participants were selected from individuals undergoing coronary angiography or coronary CT

angiography, which may represent a relatively higher-risk or symptomatic population. This selection could have attenuated the differences observed between patients with CAD and controls, potentially biasing the results toward the null. Future studies in larger and more diverse cohorts, incorporating direct HDL functional assays and longitudinal follow-up, are needed to confirm and extend these findings.

CONCLUSION

In conclusion, the study suggests that altered CETP activity, rather than CETP mass, may play a more significant role in the development of atherosclerosis in patients with CAD and elevated HDL-C. The unexpectedly higher ApoA-I levels in patients with CAD, combined with the lack of significant changes in HDL subclass distribution, indicate that HDL functionality, rather than its quantity alone, may be a crucial factor in the pathogenesis of CAD. Further research is needed to fully understand the complex interactions among lipid metabolism, lipoprotein functionality, and the progression of atherosclerosis in patients with CAD. However, as this study is cross-sectional, these findings demonstrate associations rather than causation, and the therapeutic implications should therefore be interpreted with caution. This study adds to the growing body of evidence suggesting that targeting HDL function and CETP activity may be important for improving cardiovascular risk assessment, while the clinical implications should be interpreted with caution given the cross-sectional design.

Clinical Trial Registration: This study was not registered in the ClinicalTrials.gov database.

Ethics Committee Approval: The Ethics Committee of Gazi University, Türkiye, approved the study (Approval number/date: 301/January 27, 2012). The study was conducted in compliance with the good clinical practices protocol and Declaration of Helsinki principles.

Informed Consent: All patients were informed about the study procedure and provided written consent to participate.

Peer-review: Externally peer-reviewed.

Author Contributions: All authors of this manuscript meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors (ICMJE), and all authors have seen and approved the manuscript being submitted and published. T.K.; contributed to the study conception, design, data collection, statistical analysis, and drafted the manuscript. A.Ü.K.; contributed to patient recruitment, clinical data acquisition, and manuscript editing. A.A.; supervised the overall study design, provided intellectual input, and critically revised the final manuscript for important intellectual content.

Declaration of Interests: The authors have no conflicts of interest to declare.

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