Association of lecithin-cholesterol acyltransferase activity and low-density lipoprotein heterogeneity with atherosclerotic cardiovascular disease risk: a longitudinal pilot study

Katsuaki Yokoyama, Shigemasa Tani*, Rei Matsuo and Naoya Matsumoto

Abstract

Background: Lecithin-cholesterol acyltransferase (LCAT) is believed to be involved in reverse cholesterol transport, which is known to play a key role in suppression of atherosclerosis. However, recent investigations have demonstrated that higher LCAT activity, measured in terms of the serum cholesterol esterification rate by an endogenous substrate method, is associated with increased formation of triglyceride (TG)-rich lipoproteins (TRLs), leading to a decrease in the low-density lipoprotein (LDL) particle size. The purpose of this hospital-based longitudinal study was to clarify the causal relationship between changes in the LCAT activity and changes in the LDL-particle size.

Methods: The subjects were a total of 335 patients, derived from our previous study cohort, with one or more risk factors for atherosclerotic cardiovascular disease (ASCVD). For this study, we measured the LDL-particle size (relative LDL migration [LDL-Rm value]) by polyacrylamide gel electrophoresis in the subjects, along with the changes in the LCAT activity, at the end of a follow-up period of at least 1 year.

Results: The results revealed that the absolute change ($\Delta$) in the LDL-particle size increased significantly as the quartile of $\Delta$ LCAT activity increased ($p = 0.01$). A multi-logistic regression adjusted-analysis revealed that $\Delta$ LCAT activity in the fourth quartile as compared to that in the first quartile was independently predictive of an increased LDL-particle size (odds ratio [95% confidence interval]: 2.03 [1.02/4.04], $p = 0.04$). Moreover, the $\Delta$ LCAT activity was also positively correlated with $\Delta$ TRL-related markers (i.e., TG, remnant particle-like cholesterol [RLP-C], apolipoprotein B, apolipoprotein C-2, and apolipoprotein C-3).

Conclusions: The results lend support to the hypothesis that increased LCAT activity may be associated with increased formation of TRLs, leading to a reduction in the LDL-particle size in patients at a high risk for ASCVD. To reduce the risk of ASCVD, it may be important to focus not only on the quantitative changes in the serum LDL-cholesterol levels, but also on the LCAT activity.

Trial registration: UMIN (https://upload.umin.ac.jp/cgi-bin/ctr ctr_reg_list.cgi) Study ID: UMIN000033228 retrospectively registered 2 July 2018.

Keywords: LCAT, TRLs, LDL-particle size

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Background
Lecithin cholesterol acyltransferase (LCAT) is reported to be closely involved in reverse cholesterol transport (RCT), which is an anti-atherogenic process by which excess cholesterol is removed from the cells by high-density lipoprotein (HDL) and delivered to the liver for excretion [1].

However, according to the results of evaluation of the LCAT activity using the currently available assay methods, including both the exogenous and endogenous substrate methods, it appears quite likely that an increased LCAT activity is associated with the progression of atherosclerosis. Furthermore, several investigations have also suggested the existence of a positive correlation between increase in the serum levels of triglyceride (TG)-rich lipoproteins (TRLs) and elevation of the LCAT activity [2–4].

Recently, we reported that increased LCAT activity, as measured in terms of the serum cholesterol esterification rate by the endogenous substrate method, might be associated with a decrease in the LDL-particle size via its association with an increase in the serum levels of TRL-related markers in patients at a high risk for progression of atherosclerosis [5]. However, because this aforementioned study was designed as a cross-sectional study, and not as a longitudinal study or an interventional study, it was difficult to arrive at any definitive conclusions about the causal relationships based on the results.

Therefore, we designed this longitudinal study in an attempt to verify the hypothesis that elevation of the LCAT activity is associated with an increase in the serum levels of TRL-related markers in patients at a high risk for progression of atherosclerosis [5]. However, because this aforementioned study was designed as a cross-sectional study, and not as a longitudinal study or an interventional study, it was difficult to arrive at any definitive conclusions about the causal relationships based on the results.

The present study, with a longitudinal study design, as mentioned above, was undertaken to analyze the relationships between changes in the LCAT activity and changes in the LDL-particle size, particularly between elevation of the LCAT activity and diminution in the LDL-particle size.

Methods
Study design and populations
This study was designed as a hospital-based longitudinal study to investigate the relationship between the changes in the LCAT activity and changes in the LDL-particle size in the subjects of our previous cross-sectional study [5] who were available for additional measurements 1 year after completion of the previous study. The subjects underwent follow-up hematologic and blood biochemical tests at this institution at least 1 year after their participation in the completion of our previous study [5]. The primary endpoint was to evaluate the association between the absolute changes (Δ) in the LCAT activity and the Δ LDL-particle size using a multi-logistic regression analysis with adjustments for confounding factors, and the secondary endpoint was to investigate the associations between the Δ LCAT activity and Δ TRL-related markers, which are closely associated with TG metabolism.

The criterion for patient registration was the presence of one or more risk factors for atherosclerotic cardiovascular disease (ASCVD). The diagnostic criteria for the ASCVD risk factors were as follows: hypertensive: systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg, and/or current treatment with antihypertensive medication; diabetes mellitus (DM): fasting plasma glucose concentration ≥126 mg/dL, HbA1c ≥6.5%, and/or current treatment with anti-diabetic agents; dyslipidemia: serum LDL cholesterol (LDL-C) ≥140 mg/dL, serum TG ≥150 mg/dL, serum high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL, and/or current treatment with lipid-lowering medication; hyperuricemia: serum uric acid level ≥7.0 mg/dL and/or patient taking medications for control of blood uric acid levels; CKD: eGFR < 60 mL/min/1.73 m², with the severity of chronic kidney disease (CKD) being determined based on the estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation, modified by a Japanese coefficient [7]; Obesity: body mass index (BMI) ≥25 kg/m².

 Patients were not enrolled if they met any of the following exclusion criteria: hepatic dysfunction (serum alanine aminotransferase and aspartate aminotransferase ≥2 times the upper limit of normal), known malignant disease, refusal to provide consent for participation in the study, diagnosis of acute coronary syndrome within 3 months prior to the study, and/or serum TG ≥400 mg/dL. The design and purpose of the study were approved by the Nihon University Surugadai Hospital Ethics Committee.

Measurement of laboratory parameters
Fasting blood samples were collected in the early morning hours after the subjects had fasted overnight for 12 h. Serum LCAT activity was determined by a self-substrate method (SRL Co., Ltd., Tokyo, Japan), in which the serum free cholesterol is measured enzymatically after incubation of the serum with synthetic dipalmitoyl lecithin using a commercially available kit (Nescoat LCAT kit-S, Alfresa Pharma, Osaka, Japan) [8]. The LCAT activity measured by the present method showed good correlation with the values measured by the endogenous substrate method using gas-liquid chromatography [8], and the exogenous substrate method [9], and
with the LCAT mass concentrations measured by enzyme-linked immunosorbent assay [10]. The serum total cholesterol (TC), HDL-C, and TG levels were measured using standard methods. Serum LDL-C levels were calculated using the Friedewald formula [11]. The serum RLP-C levels were measured using an immunoadsorption assay (SRL). The serum apo levels were determined using turbidimetric latex agglutination assays (Daichi Pure Chemicals Co., Ltd., Tokyo, Japan). Serum highsensitivity C-reactive protein (hs-CRP) levels were measured using a nephelometric assay (Behring Diagnostic Marburg, Germany).

**Measurement of the LDL-Rm value**

The relative LDL migration (LDL-Rm) value, an indicator of the LDL-particle size, was measured relative to the mobility value of LDL by polyacrylamide-gel electrophoresis (PAGE) using the LipoPhor system (Joko, Tokyo, Japan). The LDL-Rm value was calculated as the distance between the very LDL (VLDL) peak and the LDL peak divided by the distance between the VLDL peak and the HDL peak (Fig. 1). Several studies have reported that an LDL-Rm value of ≥0.40 suggests the presence of a large amount of small-dense (sd)-LDL in the LDL fraction [12]; a decrease of the LDL-Rm value indicates an increase in the LDL-particle size [13, 14].

In order to distinguish LDL-particle size phenotype A (large buoyant LDL) and phenotype B (sd-LDL), Hirano et al., established a cutoff value in LDL diameter of 25.5 nm as determined by PAGE, corresponding to an LDL-Rm value of 0.40. [13]. As described above, LDL-Rm value is often used for qualitative evaluation of the LDL-particle size in a clinical practice setting. Therefore, LDL-Rm value represents the average size of all LDL particles, which are aggregates of heterogeneously sized particles, and not the absolute amount of sd-LDL. However, the present study used LDL-Rm value as a continuous variable, which is keeping with previous drug interventional evaluating LDL-particle size conducted until now [15, 16].

**Statistical analysis**

Data are expressed as the mean ± standard deviation for continuous variables and as percentages for discrete variables. For variables with a significantly skewed distribution, the data are expressed as interquartile ranges. In a subset analysis performed according to quartiles of the ΔLCAT activity, we used analysis of variance (ANOVA) followed by Bonferroni’s adjustment for covariates if differences were detected. A multi-logistic regression analysis was performed to identify the variables associated with changes of the LDL-Rm value. Increase/decrease of the LDL-Rm value from the baseline was entered as the dependent variable, and the patient characteristics, risk factors for ASCVD, use/non-use of lipid-modifying drugs, and quartiles of ΔLCAT activity were entered as independent variables. Regression analysis was performed using linear regression, with estimation of the Spearman’s and Pearson’s correlation coefficients. All the statistical analyses were performed using the SPSS software program (SPSS Inc., Chicago, Illinois, USA) for Windows (version 12.0.1).

**Results**

**Patients**

The patient characteristics and laboratory profiles are shown in Tables 1 and 2. Among the subjects (n = 538) enrolled in our previous cross-sectional study [5], 335 subjects who were available for follow-up hematologic and blood biochemical tests at least 1 year after participation in completion of the previous study [5] were enrolled in the present study. Of these 335 patients, none had experienced any cardiovascular events during the 1-year interval from the previous study.

**Comparison of the ΔLDL-Rm value according to the ΔLCAT activity (as classified into quartiles)**

Among the subjects of this cross-sectional study [7], we investigated the association between the ΔLCAT activity, as classified into quartiles, and the ΔLDL-Rm values in the 335 patients who could be followed up for at least 1 year. The ΔLCAT activity was correlated positively with the ΔLDL-Rm value (Fig. 2a). Moreover, a positive correlation between ΔLCAT activity and ΔLDL-Rm value was also found in both patients receiving and not receiving lipid-modifying drug treatment (Fig. 2b). The ΔLCAT activity ranged from −41.8 to 43.4 nmol/ml/hr/37 °C (mean ± SD: −1.7 ± 13.8 nmol/ml/hr/37 °C, median;
interquartile range in parentheses: −1.5 (−9.9/6.3 nmol/ml/hr/37 °C). The patients were divided into quartiles according to the ΔLCAT activity, as follows: first quartile, −41.8 to −10.0 nmol/ml/hr/37 °C (n = 83), second quartile, −9.9 to −1.7 nmol/ml/hr/37 °C (n = 83), third quartile, −1.6 to 6.2 nmol/ml/hr/37 °C (n = 84), and fourth quartile, 6.3 to 43.4 nmol/ml/hr/37 °C (n = 85). The Δ LDL-Rm value increased with increasing quartile of ΔLCAT activity, the differences (p = 0.023) (Fig. 3) indicating that the higher the Δ LCAT activity, the smaller the Δ LDL-particle size.

Multi-logistic regression analysis to identify variables that were independently correlated with the changes of the LDL-Rm value, an estimate of the LDL-particle size

To investigate the relationships between elevation of the LCAT activity and diminution in the LDL-particle size, multiple logistic regression analysis in the 335 patients conducted with adjustments for age, gender, risk factors

for ASCVD, and history of use of lipid-modifying drugs revealed that Δ LCAT activity in the fourth quartile was an independent predictor of increased LDL-Rm values, namely, smaller LDL-particle sizes (Table 3). However, no association between increased Δ LCAT activity and decreased Δ LDL-Rm value was found in the cases with serum LDL-C < 100 mg/dL, (1Q vs. 4Q, OR: 1.711; 95% CI: 0.649–4.510; p = 0.277).

Relationship between Δ LCAT activity and Δ TRL-related markers

Investigation of whether changes in the serum levels of TRL-related markers specifying the LDL-particle size might be correlated with changes in the LCAT activity was then pursued, inasmuch as the research hypothesis that elevation of LCAT activity was an independent predictor of diminution of the LDL-particle size had been verified. Figure 4 shows the simple correlations between the Δ LCAT activity and Δ serum TRLs-related markers. Positive correlations were noted between the Δ LCAT activity and all Δ TRL-related markers.

Discussion

This longitudinal study yielded the following findings. Elevation of LCAT activity, as measured in terms of the serum cholesterol esterification rate by the endogenous substrate method, was associated with a decrease in LDL-particle size, which exhibit potent atherogenic activity, and increased LCAT activity may be depend on increased serum levels of TRL-related markers in patients at high risk for ASCVD.
The present longitudinal study on the correlations among LCAT activity, serum levels of TRL-related markers and the LDL-particle size was conducted in the same subject cohort as that in our previously reported cross-sectional study [5], and demonstrated that an increase in the LCAT activity may bring about elevations of the serum TRL-related markers, i.e., indicators of disordered triglyceride metabolism, and down-sizing of the LDL-particle size, and thereby possibly trigger an atherosclerogenic effect rather than exerting an anti-atherosclerogenic effect associated with activation of the RCT system. This is consistent with the findings reported heretofore [2-4].

Importantly, only cross-sectional study was unable to establish a causal relationship between the results, but the results of the two studies with different (cross-sectional [5] and longitudinal) designs taken together strongly suggests that an increase of the LCAT activity was associated with a decrease of the LDL-particle size.

It has been reported that the increased serum cholesterol esterification generated by the LCAT reaction may be the result of an increase in TRLs, and that it may, therefore, represent potentially decreased LDL-particle size through activities of cholesteryl ester transfer protein and hepatic lipase [3, 17, 18]. These reports provide support for what have been demonstrated in the present study, i.e., that elevation of LCAT activity constitutes a determinant of diminution of the LDL-particle size and that a positive correlation exists between absolute changes in LCAT activity and changes in the TRL-related markers from the baseline.

However, the RCT system represents a complicated network mediated not merely by the bioactivity of LCAT, but by the activities of many other enzymes as well, to exert an anti-atherosclerogenic effect of HDL in toto [19, 20]. We may have to interpret the present findings, solely focused upon the LCAT activity, TRL-related markers and LDL-particle size, as implying nothing...
more than a demonstration of a causal relationship of these three factors with atherosclerogenic effect.

It has also been reported that the anti-atherosclerogenic effect of RCT is dependent on the state of lipid metabolism which has a profound bearing on progression of atherosclerosis. Several investigations suggest that in the presence of abnormal lipid metabolism that can cause ASCVD, RCT may be activated and LCAT may stimulate esterification of free cholesterol, possibly resulting in changes in the direction toward suppressed progression of atherosclerosis [20–22]. In support of these reported findings, a negative correlation between the plaque volume assessed by intravascular ultrasonography and the LCAT mass concentration has been documented in coronary artery disease patients in recent years, and the authors have suggested that LACT activity is up-regulated with a consequent facilitation of RCT, leading to a reduction in coronary artery plaques in patients with coronary artery disease [23].

There are few reports yet of large-scale prospective cohort studies investigating LCAT activity in relation to the prognosis of coronary artery disease. Most recently, in a prospective cohort study carried out in the general population in Japan, a positive correlation was observed between the LCAT activity, measured in terms of the serum cholesterol esterification rate assessed by the endogenous substrate method, and the serum levels of the TRLs, and the group with elevated LCAT activity showed a significantly higher incidence of sudden death and coronary artery disease [24]. This may provide evidence in support of our study results, although the cited study did not examine the relation between TRLs and the LDL-particle size.

Interestingly, what would deserve special mention here is that the coefficient of correlation between the Δ LCAT activity and Δ LDL-Rm was higher in the patient group receiving lipid-modifying drugs (mostly statins) as compared to that in the group that was not receiving lipid-modifying drugs (Fig. 2-2). Lipid-modifying drugs seem likely to suppress the downsizing of the LDL-particle size associated with elevation of the LCAT activity, although this may only be stated parenthetically in the presence of intergroup differences in sample size and patient background characteristics.

In the preceding investigation conducted as a cross-sectional study, a correlation was shown to exist between increase of LCAT activity and diminution of the LDL-particle size in patients with serum LDL-C levels of < 100 mg/dL. In this study, however, which was conducted using the data of patients at high risk for ASCVD, a multivariate logistic regression analysis indicated that in patients with serum LDL-C levels of < 100 mg/dL, who are assumed to have only a low tendency towards progression of atherosclerosis, increase of the LCAT activity had no impact on the LDL-particle size. This would be interpreted as being due to a decline in the statistical detection rate owing to the small case-sample size of this study. We propose to further verify the present research hypothesis through increasing the case-sample size. Figure 5 illustrated our hypothesis that increased LCAT activity might be associated with an increase in TRL-related markers and a reduction of LDL-particle size, possibly leading to the development of ASCVD.

| Variable                  | OR     | 95% CI   | p value |
|---------------------------|--------|----------|---------|
| Age                       | 0.973  | 0.951–0.995 | 0.018   |
| Male gender               | 1.108  | 0.645–1.903 | 0.710   |
| BMI                       | 0.991  | 0.929–1.056 | 0.776   |
| Current smoking           | 0.625  | 0.240–1.627 | 0.336   |
| Diabetes mellitus         | 0.822  | 0.475–1.422 | 0.483   |
| Hypertension              | 0.618  | 0.367–1.041 | 0.484   |
| Dyslipidemia              | 1.704  | 0.768–3.781 | 0.190   |
| Lipid-modifying drugs     | 1.368  | 0.734–2.552 | 0.324   |
| ΔLCAT 1Q                  | Reference |        |         |
| ΔLCAT 2Q                  | 1.498  | 0.738–3.039 | 0.263   |
| ΔLCAT 3Q                  | 1.784  | 0.884–3.601 | 0.163   |
| ΔLCAT 4Q                  | 2.028  | 1.019–4.035 | 0.044   |

OR odds ratio, CI confidence interval, BMI body mass index, Δ absolute change from baseline, LCAT lecithin-cholesterol acyltransferase, Q quartile
Study limitations and clinical implications

First, this study did not incorporate analysis of changes in the properties of the atherosclerotic lesions by diagnostic imaging [25]. Secondly, interventional studies using drugs which have the potential to modify LCAT activity (e.g., lipid-modifying drugs) may be useful for clarifying the relationship between LCAT activity and lipid metabolism [26]. It is expected that interventional studies with various drugs will be conducted in the future to examine the effect of LCAT on the progression of arteriosclerosis. We previously reported, in our original article, a patient with obesity who responded to prescribed dietary control with weakening of arteriosclerotic plaque. We hypothesized that...
weight reduction accompanied by lowering of the serum levels of TRLs and LCAT activity, and a decrease of the LDL-Rm value [27]. Similarly, there have been reports of lowering of the serum levels of TRLs and sd-LDL and LCAT activity associated with controlled weight reduction [28]. Thus, further evidence needs to be accumulated to establish the exact relation between the serum LCAT activity and LDL-heterogeneity. Thirdly, this study does not demonstrate the relationship between LCAT activity and clinical indices and/or outcomes, because it was only a pilot study. Finally, we have pursued the argument in this paper on the premise that LCAT activity represents an atherosclerosis-promoting factor; however, we may have to discuss with great deliberation whether LCAT facilitates, or in fact, suppresses atherosclerosis on the ground of evidence heretofore accumulated, by taking account of differences in LCAT assay procedure and characteristics of the study subjects (general population, high-risk cases of cardiovascular disease, gender) and of the expression profile of the LCAT gene in the pathophysiological state [29, 30]. In fact, no unified view has been obtained so far, based on carotid artery ultrasound study reports, as to the relation of the serum LCAT activity with progression/suppression of atherosclerosis [2, 31, 32].

In this study, we investigated the factors involved in the progression of atherosclerosis with our attention focused on the serum LCAT activity, TPL-related markers and LDL particle size. However, atherosclerosis progresses through a complex network also involving other elements than the above-mentioned factors alone [33]. Further verification of the results of this study will have to take into consideration these other factors as well.

**Conclusions**

In this longitudinal study, we confirmed that increased LCAT activity, measured in terms of the serum cholesterol esterification rate by the endogenous substrate method, might be associated with a decrease of the LDL-particle size through its association with an increase in the serum levels of TRL-related markers and sd-LDL and LCAT activity associated with controlled weight reduction [27]. Similarly, there have been reports of lowering of the serum levels of TRLs and sd-LDL and LCAT activity associated with controlled weight reduction [28]. Thus, further evidence needs to be accumulated to establish the exact relation between the serum LCAT activity and LDL-heterogeneity. Thirdly, this study does not demonstrate the relationship between LCAT activity and clinical indices and/or outcomes, because it was only a pilot study. Finally, we have pursued the argument in this paper on the premise that LCAT activity represents an atherosclerosis-promoting factor; however, we may have to discuss with great deliberation whether LCAT facilitates, or in fact, suppresses atherosclerosis on the ground of evidence heretofore accumulated, by taking account of differences in LCAT assay procedure and characteristics of the study subjects (general population, high-risk cases of cardiovascular disease, gender) and of the expression profile of the LCAT gene in the pathophysiological state [29, 30]. In fact, no unified view has been obtained so far, based on carotid artery ultrasound study reports, as to the relation of the serum LCAT activity with progression/suppression of atherosclerosis [2, 31, 32].

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**Abbreviations**

ANOVA: Analysis of variance; apo: apolipoprotein; ASCVD: Atherosclerotic cardiovascular disease; BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; eGFR: estimated glomerular filtration rate; Hb: Hemoglobin; HDL: High-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LCAT: Lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; LDL-Rm = relative LDL migration; ASCVD = atherosclerotic cardiovascular disease; RCT = reverse cholesterol transport; HDL = high-density lipoprotein; TRL = triglyceride-rich lipoprotein; VLDL: Very-low density lipoprotein

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors’ contributions
ST has designed this study in whole and drafted this manuscript. KY, RM, and NM have contributed to collect data. ST has contributed to statistical analyses in this study. ST and KY have contributed to provide advice on interpretation of the results. ST revised this manuscript critically for important intellectual content and approved finally the manuscript submitted. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Committees of Nihon University Hospital. All participants were consistent to participate the study. This study was approved by the Institutional Ethics Committees of Nihon University Hospital.

Consent for publication
If the manuscript is accepted, we approve it for publication in BMC Cardiovascular Disorders.

Competing interests
The authors declare that they have no competing interests.

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