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Original Contribution

# Current smokers with hyperlipidemia lack elevated preβ1-high-density lipoprotein concentrations

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**KEYWORDS:**
ABCA1;
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LCAT;
Prebeta-HDL

**BACKGROUND:** Preβ1-high-density lipoprotein (HDL) is an efficient acceptor of cell-derived free cholesterol, which is converted into lipid-rich HDL by lecithin–cholesterol acyltransferase. Previous studies have shown that preβ1-HDL is significantly higher in individuals with hyperlipidemia. Preβ1-HDL concentrations may be altered in smokers, who are at high risk for atherosclerosis.

**OBJECTIVE:** The aim of the present study was to investigate the effect of smoking on preβ1-HDL concentrations.

**METHODS:** We measured the preβ1-HDL concentration and lecithin–cholesterol acyltransferase–dependent conversion rate ($CHT_{pre\beta1}$) in 74 men (39 nonsmokers and 35 smokers) using an immunoassay.

**RESULTS:** The smoker and nonsmoker groups were further divided into normolipidemic and hyperlipidemic subjects. Among nonsmokers, the mean preβ1-HDL concentration was 27% higher in hyperlipidemics than in normolipidemics (25.5 ± 6.7 vs 20.3 ± 4.6 mg/L apoAI, $P < .01$). In contrast, mean preβ1-HDL concentrations did not differ between hyperlipidemic and normolipidemic smokers (19.9 ± 3.1 vs 22.4 ± 6.9 mg/L apoAI). We found a positive correlation between preβ1-HDL concentration and $CHT_{pre\beta1}$ in nonsmokers, but not in smokers. Smoking a single cigarette did not change preβ1-HDL concentrations or $CHT_{pre\beta1}$. Compared with nonsmokers, preβ1-HDL concentrations were relatively low in hyperlipidemic smokers but not in normolipidemic smokers, and $CHT_{pre\beta1}$ was not a significant determinant of preβ1-HDL concentrations in smokers.

**CONCLUSION:** Our findings suggest that smoking may be disadvantageous to individuals with hyperlipidemia because preβ1-HDL metabolism is altered.
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## Introduction

Previous epidemiologic studies have identified several risk factors for atherosclerotic disorders such as coronary heart disease (CHD) including hypertension, dyslipidemia, diabetes, and cigarette smoking.[1–4] The Japan

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Collaborative Cohort study group found that CHD-related mortality was 2.51-fold higher in current male smokers and 3.35-fold higher in current female smokers than in respective never smokers.[4] To elucidate the mechanisms underlying the association between smoking and atherosclerosis, previous investigators have focused on smoking-induced mild inflammation, endothelial dysfunction, oxidative stress, and dyslipidemia.[5–8] Furthermore, smokers consistently exhibit low concentrations of high-density lipoprotein-cholesterol (HDL-C),[9,10] a measure of HDL.

HDL is composed of several distinct subfractions with unique lipid and protein compositions.[11] The preβ1-HDL is a small but efficient acceptor of cell-derived free cholesterol that is converted into lipid-rich HDL by lecithin–cholesterol acyltransferase (LCAT).[12] Cell-culture studies have found that high preβ1-HDL concentrations are associated with enhanced cholesterol efflux.[13] However, clinical studies have shown that preβ1-HDL concentrations are elevated in patients with atherogenic and atherosclerotic disorders such as hypercholesterolemia,[14,15] hypertriglyceridemia,[16] coronary artery disease (CAD),[17–20] diabetes,[21,22] and those receiving hemodialysis.[23] We previously reported that the LCAT-dependent conversion rate of preβ1-HDL is the most important determinant of plasma preβ1-HDL concentration.[24] However, no previous studies have investigated the preβ1-HDL concentration and LCAT-dependent conversion rate in smokers. Thus, we investigated the chronic and acute effects of cigarette smoking on preβ1-HDL concentrations and the rate of conversion to α-migrating HDL.

## Materials and methods

### Recruitment of subjects

Through an advertisement on our Web site, we recruited male volunteers from the general public. Participants were grouped according to their smoking status (nonsmokers and smokers), and each group was further subdivided into normolipidemic and hyperlipidemic subjects. We selected 39 nonsmokers and 35 current smokers. We classified respective participants into normolipidemic (low-density lipoprotein-cholesterol [LDL-C] $<$ 160 mg/dL and triglycerides [TG] $<$ 200 mg/dL) and dyslipidemic (LDL-C $\geq$ 160 mg/dL and/or TG $\geq$ 200 mg/dL) groups according to their fasting lipid concentrations. The exclusion criteria were acute inflammation, severe liver dysfunction, use of lipid-lowering agents, CAD, and end-stage renal disease. Participants self-reported cigarette smoking and drinking habits on a simple questionnaire. Following the definitions issued by the Centers for Disease Control and Prevention, we placed only current smokers (who smoked at least 100 cigarettes in their lifetime and were still smoking either every day or some days) in the smoker group.[25] Nonsmokers were either former smokers or never smokers. In the nonsmoker group, all the normolipidemic subjects were never smokers; 6 hyperlipidemic subjects had a history of smoking and had abstained from smoking for at least 2 years (former smokers). We calculated the Brinkman index as the number of cigarettes smoked per day times smoking duration in years. Before the study, participants provided written informed consent. The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Juntendo University School of Medicine.

### Study protocol

The subjects were instructed to fast overnight and to refrain from smoking on the day of phlebotomy. Polyethylene terephthalate tubes containing $K_2$-EDTA were prechilled in ice water. Within 4 hours of awakening, venous blood was drawn into the tubes to stop the metabolism of preβ1-HDL immediately.[12,22–24,26] Plasma was maintained at 0°C during centrifugation at $\times 1500g$ for 5 minutes. In addition, in the case of some smokers, blood samples were collected at baseline and 4 h after smoking a single cigarette, using the same procedure. We prohibited study subjects from smoking until the second blood sampling was completed.

### Lipoproteins and LCAT

Total cholesterol (TC) and TG concentrations were determined enzymatically, and LDL-C and HDL-C were measured using homogeneous assays (Choletest LDL; Sekisui Medical, Tokyo, Japan; MetaboLead HDL-C; Kyowa Medex, Tokyo) that were verified for accuracy and precision in our previous studies.[27,28] Apolipoprotein (Apo) concentrations were measured by turbidimetric immunoassay. LCAT activity was measured using the NESCAUTO LCAT kit-S (Alfresa Pharma, Osaka, Japan) and expressed as the reduction in free cholesterol per hour at 37°C.

### Preβ1-HDL concentration and rate of conversion into α-migrating HDL

All plasma samples were freshly isolated and immediately cooled in ice water. Then, the plasma was pretreated with a 50% sucrose solution at a dilution of 1:20 for stabilization and kept at −80°C.[26] Preβ1-HDL concentrations in thawed plasma were measured by immunoassay using a 96-well plate coated with a monoclonal antibody (Mab55201) against preβ1-HDL.[26] The preβ1-HDL concentration was expressed as the amount of apoA1.

The method used to determine the LCAT-dependent rate of conversion of preβ1-HDL was reported in detail previously.[24,29] In brief, fresh plasma was incubated at 37°C with or without inhibition of LCAT using 2 mmol/L 5, 5′-dithiobis (2-nitrobenzoic acid) dissolved in 0.1 M phosphate buffer (pH 7.4). We collected samples at baseline (maintained at 0°C without incubation) and every 30 minutes for 120 minutes and incubated them at 37°C. The conversion halftime of preβ1-HDL ($CHT_{pre\beta1}$) was calculated as the incubation

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