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Decreased lipoprotein lipase activity and increased postprandial concentrations of triglyceride-rich lipoproteins in offspring of elderly survivors of myocardial infarction

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KEYWORDS
Postprandial hypertriglyceridemia;
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Myocardial infarction

Abstract *Background and aim:* A family history of myocardial infarction (MI) is an independent risk factor for future coronary events. Decreased plasma lipoprotein lipase (LPL) activity is associated with delayed clearance of triglyceride-rich lipoproteins (TRL) and low fasting HDL cholesterol. The aim of the study was to investigate the relations between plasma LPL activity, postprandial TRL and HDL cholesterol in offspring of MI patients.
Methods and results: A case-control study was performed in 17 healthy middle-aged offspring of MI patients and 13 healthy age-and sex-matched controls. Fasting blood samples were collected and each subject was given a standardized oral fat load (1 g fat/kg body weight) with subsequent blood samples collected for an 8-h period. Offspring of MI patients had significantly lower postheparin LPL activity (62.9 mU/ml $\pm$ 22.8 mU/ml) (mean $\pm$ SD) than healthy controls (93.0 mU/ml $\pm$ 21.7 mU/ml) ($p = 0.002$). Decreased postheparin LPL activity was accompanied by significantly increased and delayed clearance of postprandial TRL and subsequent lower fasting HDL cholesterol in offspring of MI patients. Postheparin LPL activity was associated with HDL cholesterol ($r = 0.40$, $p = 0.036$) and trend analysis revealed a decrease in incremental area under the curve (AUCi) for chylomicrons with increasing LPL activity ($p = 0.013$).
Conclusions: Offspring of MI patients had decreased postheparin LPL activity accompanied by increased postprandial TRL and subsequent decreased HDL cholesterol, an unfavourable lipid profile which may contribute to their increased risk for future coronary events.

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Introduction

A family history of myocardial infarction (MI) is an independent risk factor for coronary artery disease (CAD) in offspring [1,2]. Epidemiological studies have shown that offspring with familial CAD had higher levels of total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides, and lower high density lipoprotein (HDL) cholesterol [3]. Low serum concentration of HDL cholesterol is a strong and independent risk factor for CAD [4,5], also among offspring of CAD patients [3,6].

More than twenty years ago, Zilversmit proposed that atherosclerosis is a postprandial disease, and hypothesized that accumulation of triglyceride-rich lipoproteins (TRL) promoted formation of atherosclerosis, due to reduced clearance and thereby prolonged exposure of TRL to the vascular wall [7]. The hypothesis was supported by more recent studies showing a particularly efficient penetration and selective retention of chylomicron remnants in sites of lesion formation [8,9]. Patients with CAD have delayed elimination of postprandial TRL [10,11], and plasma concentrations of postprandial remnants are related to the progression of coronary lesions [12].

Lipoprotein lipase (LPL) is the major lipase in lipoprotein metabolism [13] and exerts its function by hydrolysis of TG in chylomicrons and very low-density lipoproteins (VLDL), providing fatty acids to the underlying tissues [14]. Deficiency of LPL or its cofactor apolipoprotein CII (apo-CII) promoted accumulation of chylomicrons in plasma, suggesting that triglyceride hydrolysis is important for clearance of these particles [15]. Low levels of LPL activity, as encountered in patients with partial LPL deficiency, are associated with premature atherosclerosis and accelerated progression of atherogenesis [16]. In humans, LPL activity contributes to the regulation of HDL cholesterol and may partly explain the inverse relation between postprandial TRL and HDL cholesterol [13]. Furthermore, postheparin LPL activity was associated with HDL cholesterol [17,18] and inversely correlated to the magnitude of postprandial hyperlipidemia in normolipidemic patients [19]. Unfractionated heparin has higher affinity for LPL than heparan sulphate, and heparin infusion will therefore displace LPL from the endothelial surface into circulating blood [14]. The amount of LPL released after a bolus dose of heparin is used as a measure of functional LPL and assumed to reflect the LPL availability at the endothelial surface [17].

Previous studies in offspring of CAD patients have reported of delayed postprandial clearance of TRL [20] and high fasting triglycerides have been related to an increase in postprandial TRL [21]. The aim of the present study was to investigate the relations between plasma LPL activity, postprandial TRL and HDL cholesterol in offspring of MI patients and healthy controls. To address these questions we performed a case-control study in healthy middle-aged offspring of MI patients and healthy controls without a family history of CAD.

Methods

Patients and study design

Medical records for patients between 65 and 85 years of age with the diagnosis acute myocardial infarction one to four years earlier, and no later hospitalizations for coronary heart disease (CHD) were obtained from the archives at the University Hospital of Northern-Norway in Tromsø. The diagnosis acute myocardial infarction was verified by diagnostic criteria such as chest pain, pathological ECG and increase in serum concentration of cardiac markers. The verified MI patients were invited to participate in a case-control study on postprandial hyperlipidemia in MI. Forty-four elderly MI patients responded positive to the invitation and met the inclusion criteria. Offspring of these patients were requested to be included in the present study. The inclusion criteria were: apparently healthy offspring from MI patients, both genders, and age between 35 and 50 years at the time of the study. The exclusion criteria were: regular use of drugs interfering with the coagulation system (i.e. warfarin and heparins), chronic inflammatory diseases, renal or liver disease, cancer, hypothyroidism, serious hypertension, abuse of alcohol or drugs, and major psychiatric diseases. Persons who responded positive to our invitation letter to participate in the study were invited to a screening visit. One age- and sex matched apparently healthy person for each case was recruited from the general population and invited to a screening visit. At the screening visit, a complete medical history, physical examination and blood samples were taken with special emphasis on exclusion criteria. A detailed interview on the occurrence of cerebrovascular events, myocardial infarction, angina pectoris, serious hypertension, diabetes, chronic inflammatory diseases, renal or liver disease, cancer, hypothyroidism, abuse of alcohol or drugs, major psychiatric diseases and smoking habits was obtained. Invited control persons with a medical history or blood tests indicating any of the earlier mentioned diseases were excluded. Height and weight were measured with the patients in light clothing without shoes; body mass index (BMI) was calculated as weight per height squared (kg/m^2). Blood pressure was recorded in seated position by the use of an automatic device (Dinamap Vital Signs Monitor). Three recordings were made at 1-min intervals, and the mean of the 2 last values is used in this report. Eligible persons (17 cases and 13 controls) were invited to a second visit during which the participants were subjected to a fat tolerance test. Informed written consent was obtained from the participants, and the regional ethical committee approved the study. The study was conducted at the Clinical Research Center at the University Hospital of Northern-Norway in Tromsø.

Blood collection and storage

Blood was drawn in the morning at 7:45 am from an antecubital vein on the right arm after 12 h of overnight fasting using a 19-gauge needle into a vacutainer system with minimal stasis. Serum was prepared by clotting whole blood in a glass tube at room temperature for 1 h and then centrifuged at 2000 $\times$ *g* for 15 min at 22 °C. Aliquots of 1 ml were transferred into sterile cryovials (Greiner laboratechnik, Nürtringen, Germany), flushed with nitrogen, and frozen at −70 °C until further analysis. Blood for plasma preparation was collected into vacutainers (Becton Dickinson, Meylan Cedex, France) containing 0.129 M sodium