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Prognostic value of lipoproteins and their relation to inflammatory markers among patients with coronary artery disease

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Abstract

Background: Lipoproteins and their subfractions are associated with the incidence of atherosclerotic diseases. In patients with coronary artery disease (CAD), low serum concentrations of high density lipoprotein (HDL) and high low-density lipoproteins (LDL) are correlated to myocardial infarction and cardiovascular death. There is growing evidence indicating that those lipoprotein factors are related to the inflammatory process in atherogenesis.
Methods: We investigated in a median follow up of 3.9 years the association of HDL, apolipoprotein A-I (apoA-I), LDL, apolipoprotein B (apoB), and triglycerides with the incidence of a combined endpoint (myocardial infarction and cardiovascular death) and their relation to markers of inflammation in 1298 patients with angiographically documented CAD.
Results: In univariate analysis, serum concentrations of apoA-I were significantly and inversely related to the combined endpoint, whereas serum concentrations of LDL, apoB, and triglycerides were not. HDL was not significantly related to the endpoint in univariate analyses (p=0.057). Multivariate analyses showed that only apoA-I is an independent predictor. ApoA-I (and HDL) was significantly related to markers of inflammation.
Conclusion: Serum apoA-I levels were an independent predictor for fatal and non-fatal cardiovascular events in patients with CAD. This may be related to its anti-inflammatory effect.

Keywords Apolipoprotein A-I; Inflammation; Lipoproteins; Coronary artery disease

1. Introduction

In the past few years, numerous studies revealed that decreased serum high density lipoproteins (HDL) and apolipoprotein A-I (apoA-I), or increased low density lipoproteins (LDL), triglycerides, and apolipoprotein B (apoB) elevate the risk for atherosclerotic diseases [1–5]. There is growing evidence indicating that those lipoprotein factors are not only related to the cholesterol metabolism but also related to the inflammatory process in atherogenesis [6].

It is known that some lipoproteins are related to inflammation in atherosclerotic diseases. Remnants of very low density lipoproteins (VLDL) and chylomicrons upregulate endothelial expression of ICAM-1 and VCAM-1 [7], which in turn accelerate the recruitment of monocytes to the arterial wall and initiate the process of atherosclerosis [6]. Small dense LDL downregulates mRNA-levels of endothelial nitric oxide syntase, which has anti-inflammatory effects on endothelial cells [8]. Oxidized LDL promotes the differentiation of monocytes to macrophages and the differentiation of macrophages to foam cells in the atherosclerotic plaque [9]. Macrophages and foam cells release a

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variety of cytokines that activate endothelial cells to express adhesion molecules [10].

HDL appears to play an important role in modulating the inflammatory process. HDL-cholesterol (HDL-C) levels are decreased under acute and chronic inflammatory conditions [11–13]. HDL has been shown to bind and neutralize lipopolysaccharide (LPS), which is directly involved in the acute inflammatory process [14]. HDL can reduce the formation of foam cells by promotion of cholesterol efflux [15], and can inhibit cytokine-induced expression of endothelial cell adhesion molecules [16]. HDL is capable of destroying oxidized lipids that generate an inflammatory response [17].

ApoA-I is the major protein constituent of HDL. ApoA-I levels are also decreased in acute and chronic inflammatory states [18–20]. Functional assays and flow cytometry analyses show that apoA-I inhibits contact-mediated activation of monocytes by binding to stimulated T cells, thus inhibiting TNF-α- and IL-1β-production [21]. Furthermore, apoA-I downregulates neutrophile function [22], and inhibits monocyte inflammatory functions in peripheral blood monocytes activated by either specific antigens or lectins without affecting cell proliferation [21].

The aim of this study was to investigate whether HDL-C, apoA-I, LDL-C, apoB, or triglycerides could predict future cardiovascular events in patients with angiographically proven coronary artery disease (CAD) and whether the prediction is related to the inflammatory status.

2. Methods

2.1. Study population

A total of 1298 patients (873 patients with symptoms of stable angina pectoris, 421 with unstable angina pectoris) in whom a diameter stenosis of at least 30% was diagnosed by visible estimation in a major coronary artery after sublingual administration of 0.2 mg nitroglycerin were included in our study. All patients had been admitted to the II. Medical Department of the Johannes Gutenberg University Mainz for diagnostic angiography between November 1996 and June 2000. Patients with no evidence of CAD as defined above and patients with evidence of grave concomitant diseases, febrile conditions, or age higher than 80 years were excluded from the study. At study entry, patients completed a questionnaire that provided information about smoking habits, any history of diabetes mellitus, hypertension, hyperlipoproteinemia, current drug use, and family history of premature CAD (documented CAD of one first-degree relative before the age of 65 years). Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment or received additional oral antidiabetic or insulin medication or who had a current fasting blood sugar level >125 mg/dl; hypertension was diagnosed in patients who had received antihypertensive treatment or had been diagnosed as hypertensive (blood pressure>160/90 mm Hg); hyperlipoproteinemia was diagnosed in patients who had been given lipid-lowering medication or had a history of cholesterol levels >240 mg/dl. Smoking was defined as current smoking.

A total of 1294 patients (99.7%) were followed up for a mean of 3.9 years (from 49 weeks up to 5.2 years). The majority of the patients presented at our clinic for follow up; a small number of them were interviewed by telephone by trained medical staff. Follow-up information was obtained about cardiovascular death (n=115) or non-fatal myocardial infarction (n=43). Information about the cause of death or clinical events was obtained from hospital or general practitioner charts.

The patients had German nationality and the majority were inhabitants of the Rhein-Main area.

The study was approved by the ethics committee of the Johannes Gutenberg-University Mainz, Germany. Participation was voluntary and each participant gave written informed consent.

2.2. Laboratory methods

Blood was drawn from all subjects under standardized conditions after a overnight fasting period before coronary angiography was performed. Samples were placed on ice immediately and within 30 min blood was centrifuged at 4.000 rpm for 10 min, divided into aliquots and frozen at −80 °C until analysis.

C-reactive protein (CRP) was determined by a highly sensitive, latex particle enhanced immunoassay (detection range of 0 to 20 mg/l, Roche Diagnostics, Germany). Serum IL-6 was measured by the ELISA technique (EASIA, Biosource Europe). The detection range was 0–1540 pg/ml. Fibrinogen was determined by a derived method (Innovin, Dade Behring, Marburg, Germany). Leukocyte count was performed by ADVIA 120 (Bayer Diagnostics, Bayer-Vital, Leverkusen, Germany). ApoA-I- and apoB-concentrations were determined by immunoturbodimetric assays (Tina-quant, Roche Diagnostics), HDL-C, LDL-cholesterol (LDL-C), and triglycerides by enzymatic assays (Randox and Roche Diagnostics).

2.3. Statistical considerations

Mean levels of variables were compared across quartiles of lipoproteins by ANOVA for normal variables, Kruskall–Wallis test for skewed variables, and chi-square test for categorial variables. Survival analysis was performed by Kaplan–Meyer method and log-rank test. In all survival analysis, the end point was a combined endpoint from death from cardiovascular causes and non-fatal myocardial infarction, data on patients who died of other causes were censored at the time of death. The association of the lipoproteins with outcome was evaluated by Cox regression analysis adjusted for potential