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Original article

HDL subpopulations containing apoA-I without apoA-II (LpA-I) in patients with angiographically proven coronary artery disease

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ABSTRACT

Background: High density lipoproteins (HDL) can be divided into two metabolically distinct fractions, one containing apolipoprotein (Apo) A-I but not ApoA-II [apolipoprotein A-I; lipoprotein (Lp) A-I] and the other containing both ApoA-I and ApoA-II (LpA-I/A-II). LpA-I fraction which, seeming to be more cardioprotective than LpA-I/A-II particles, is itself heterogeneous. Preβ1-HDL is a minor subfraction of LpA-I and the initial acceptor of cellular cholesterol in the process of reverse cholesterol transport. The aim of the study was to determine the usefulness of the determination of LpA-I fractions as indicators for the atherosclerotic process.
Methods: The study included 112 patients with angiographically-documented coronary artery disease (CAD+) and 51 patients with negative results of coronary angiography (CAD−). We evaluated LpA-I concentration in serum in HDL_2 and HDL_3 fractions as well as Preβ1-HDL concentration. Furthermore, we analyzed the association of the assessed parameters with the extent and severity of CAD assessed by Gensini score.
Results: CAD+ patients were characterized by a lower concentration of serum LpA-I by 19%, LpA-I in HDL_2 by 26%, higher level of Preβ1-HDL by 27%, and elevated Preβ1-HDL/LpA-I values by 62%. Univariate correlation analysis indicated that serum LpA-I and HDL-cholesterol concentrations were negatively correlated with Gensini score ($R = -0.279$; $p = 0.002$, $R = -0.227$; $p = 0.016$, respectively) whereas Preβ1-HDL/LpA-I values were positively correlated with the severity of CAD ($R = 0.529$; $p < 0.001$). In multiple linear regression, after adjusting for age, gender, preexisting hypertension, diabetes, and statin therapy, only the Preβ1-HDL/LpA-I values remained an independent determinant of atherosclerosis severity ($\beta = -0.499$; $p < 0.001$).
Conclusions: Our results show a lower level of LpA-I and higher concentration of Preβ1-HDL in the CAD+ patients compared to the CAD− group. We suggest that the distribution of LpA-I is different in CAD and the Preβ1-HDL/LpA-I ratio may have additional value in assessing anti-atherogenic potential of HDL particles and it is likely to become a clinically valuable indicator of atherosclerosis development.
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Introduction

Due to the important role of high-density lipoproteins (HDL) in the pathogenesis of atherosclerosis, the parameters which could be the best illustration of the antiatherogenic potential of HDL particles have been sought for several years. To this day, the most commonly used parameter for the clinical evaluation of HDL has been its cholesterol content. However, HDL represents heterogeneous groups of particles differing in their function, lipid and protein content, and an estimation of the number of circulating HDL particles by their cholesterol content may not clearly reflect the antiatherogenic potential of different HDL subpopulations [1–3]. There is a constant need to evaluate the subpopulations of HDL that can better denote the quality and cardioprotective function of HDL particles than HDL-cholesterol (C).

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Due to the important role that apolipoproteins play in the secretion, structural stability, and metabolism of lipoproteins, HDL particles are classified according to their apolipoprotein (ApoA) composition, between those that contain ApoA-I but are deficient in ApoA-II [lipoprotein (Lp)A-I] and those that contain both ApoA-I and ApoA-II (LpA-I/A-II). LpA-I and LpA-I/A-II fractions have different physiological properties and in vivo metabolism [4]. In vitro studies have demonstrated that LpA-I promotes cell cholesterol efflux, while LpA-I/A-II does not [5]. Some clinical studies have reported selective lowering of LpA-I in coronary artery disease (CAD) patients, suggesting its antiatherogenic properties, however not all trials have supported these observations. While some reported a selective reduction in LpA-I in CAD patients [4,6], others showed a lowering of both LpA-I, LpA-I/A-II [7], or did not show a significant reduction of LpA-I or LpA-I/A-II HDL subclasses [8,9]. This can be due to the fact that LpA-I, despite an apparent homogenous main apolipoprotein composition, is still a heterogeneous fraction and subfractions containing ApoA-I but not ApoA-II may differ both in size, density, and potentially in their antiatherogenic effects.

One of the LpA-I fractions, which in recent years is of particular interest because of its important role in reverse cholesterol transport, is the Preβ1-HDL fraction. Preβ1-HDL represents nascent or newly-formed HDL and consists of ApoA-I, small amounts of phospholipids, and unesterified cholesterol. Despite the fact that Preβ1-HDL is known as an initial plasma acceptor of cell-derived cholesterol, previous studies have shown that the elevation of this HDL subfraction in patients with CAD may be connected with delayed catabolism of Preβ1-HDL or its enhanced production [10–12].

LpA-I is also found in two main HDL subfractions, fractionated according to their density and size: both in large, less dense, relatively cholesterol-rich HDL_2 and in small, denser, relatively cholesterol-poor HDL_3. It has been suggested that particles in the HDL_2 subfraction may be more cardioprotective than those in the HDL_3 [13,14]. However the attempts to assess the clinical utility of measurement of LpA-I in HDL_3 and HDL_2 subfractions are not conclusive and require further study [9,15].

The aim of the present study was to determine the usefulness of LpA-I fractions as indicators for the atherosclerotic process. We evaluated LpA-I concentration in serum, in HDL_2, and in HDL_3 fractions as well as Preβ1-HDL concentration. Furthermore, we analyzed the association of the assessed parameters with the extent and severity of angiographically proven CAD assessed by Gensini score.

Methods

Patients

The study included 112 patients with confirmed atherosclerosis by coronary angiography (CAD+) and the HDL-C matched control group consisted of 51 patients who received negative results of coronary angiography (CAD−). None of the subjects had sustained a myocardial infarction within 6 months prior to taking part in the study. Patients with acute coronary syndrome, hepatic or renal disorders were excluded. The study was approved by the Independent Ethics Committee of the Medical University of Gdańsk and all patients gave their informed consent.

Coronary angiography

Coronary angiography was performed using the transradial or femoral approaches in all the recruits. The severity and extent of coronary atherosclerosis were quantified for each patient using the Gensini score, an assessment with prognostic significance for predicting the incidence of death or other cardiovascular events [16]. The Gensini score was assigned according to a previously described protocol [17], in which Gensini score was defined according to stenosis severity as 1 point for <25% stenosis, 2 points for 26–50% stenosis, 4 points for 51–75% stenosis, 8 points for 76–90% stenosis, and 32 points for total occlusion. The score was then multiplied by a factor that represents the importance of the lesion's position in the coronary arterial system (the left main – 5; the proximal left anterior descending or proximal left circumflex – 2.5, the mid-region – 1.5, the distal left anterior descending arteries – 1). The patients were divided into two groups: those with CAD (Gensini score ≥1; CAD+) and those without (Gensini score = 0; CAD−) according to angiographic results.

Laboratory measurements

Blood samples were obtained between 7 and 8 a.m. on the day of and prior to coronary angiography following an overnight fast. The samples (serum or plasma) were separated after centrifugation at $1000 \times g$ for 15 min and stored at −80 °C pending analysis.

Total cholesterol (TC), HDL-C, and triacylglycerols were measured in serum using standard enzymatic colorimetric tests. Low-density lipoprotein cholesterol level (LDL-C) was calculated using the Friedewald formula. Total HDL and HDL_3 were isolated using the earlier described dual-step precipitation method [18]. Total HDL fraction was isolated after precipitation of apolipoprotein B with combined precipitant consisting of heparin and $MnCl_2$ (final concentration 200 U/ml and 100 mmol/L respectively). HDL_3 subfraction was obtained by precipitation of HDL_2 particles with dextran sulphate 10,000 (final concentration: 1.3 mg/ml) in supernatant after precipitation with heparin/$MnCl_2$ solution. ApoA-I and ApoB concentration were determined by nephelometric methods with antibodies from Dade Behring (Deerfield, IL, USA) on a Behring laser nephelometer. LpA-I concentration (ApoA-I content of LpA-I) was assayed by an electroimmunodiffusion technique (Hydragel LpAI, Sebia, France). LpA-I concentration was determined in HDL and HDL_3, while LpA-I content in HDL_2 was calculated as a difference between HDL and HDL_3. LpA-I/A-II particles concentration (ApoA-I content of LpA-I/A-II) was calculated as a difference between total ApoA-I and ApoA-I in LPA-I particles (LpA-I concentration). Preβ1-HDL levels (ApoA-I content of Preβ1-HDL) were measured by a sandwich enzyme immunoassay (Bio-Connect Diagnostics, Huissen, the Netherlands; Pre-β1-HDL ELISA).

Statistics

All statistical analyses were performed using STATISTICA software, version 10 (StatSoft, Dell Statistica). The Shapiro–Wilk test was used to test the distribution of variables following a Gaussian pattern. Continuous variables were expressed as mean ± SD (standard deviation) or medians with 25th and 75th percentiles. Student's unpaired *t*-test or the Mann–Whitney *U*-test was used to assess the differences between the two groups. The Pearson's chi-squared test was used to compare categorical variables. Univariate correlations were assessed using standardized Spearman coefficients. Multilinear regression was assessed using standardized β coefficients. Values of $p < 0.05$ were considered statistically significant.

Results

The clinical characteristics of patients with angiographically proven CAD (CAD+) and patients with negative results from coronary angiography (CAD−) are shown in Table 1. The groups were matched for HDL-C concentration. Concentrations of ApoA-I,

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