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Influence of race and sex on lipoprotein-associated phospholipase A2 levels: Observations from the Dallas Heart Study

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Abstract

Aims: Most lipoprotein-associated phospholipase A2 (Lp-PLA2) studies included mainly white men. We sought to determine whether Lp-PLA2 levels differ according to race and sex.

Methods: Lp-PLA2 mass and activity were measured in 3332 subjects age 30–65 participating in the Dallas Heart Study, a multiethnic, population-based, probability sample. Lp-PLA2 levels were compared between different race and sex groups.

Results: Mean age was 45 ± 9 years and 44% were men; 30% were white, 17% hispanic, and 53% black. Mean Lp-PLA2 activity and mass were 146 ± 40 nmol/min/mL and 191 ± 60 ng/mL, respectively. Lp-PLA2 activity was lower in women compared with men (134 ± 35 vs. 161 ± 40, $p = 0.001$) and was lowest in black (136 ± 38), intermediate in hispanic (151 ± 36), and highest in white subjects (161 ± 39) (trend $p = 0.0001$). In multivariable linear regression models, after adjusting for age, body mass index (BMI), smoking, total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides and high sensitivity C-reactive protein (hsCRP), Lp-PLA2 activity was 19 nmol/min/mL higher in men vs. women ($p < 0.001$); compared with black subjects, adjusted Lp-PLA2 activity was 11 and 20 nmol/min/mL higher in white and hispanic subjects, respectively (both $p < 0.001$). Similar race and sex differences were observed for Lp-PLA2 mass.

Conclusion: Race and sex independently influence Lp-PLA2 activity and mass. Thresholds to define Lp-PLA2 elevation may need to be sex and race specific.

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Keywords: Lipoprotein-associated phospholipase A2; Race; Sex factors

1. Introduction

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an enzyme that circulates in blood, mainly bound to low-density lipoprotein (LDL) cholesterol particles. Lp-PLA2 hydrolyzes oxidized phospholipids, leading to the generation of lysophosphatidylcholine and oxidized free fatty acids, and is increasingly recognized as a novel atherosclerosis risk marker. A recent systematic review of 14 studies showed an adjusted odds ratio of 1.60 for the association between Lp-PLA2 and prevalent cardiovascular disease [1], and higher Lp-PLA2 levels have been associated with an increased incidence of first-ever cardiac events in population-based studies [2–4], and with recurrent cardiovascular events in patients with clinically manifested coronary artery disease [5–8] and with initial [4,9] and recurrent [10] stroke. However, some of these studies have included only men [3,11], and most studies have included mainly white subjects [3–7,11,12], except the Atherosclerosis Risk in Communities study that included 25% black subjects [2] and the Northern Manhattan Stroke

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Study that included 53% hispanic and 27% black subjects [10]. Moreover, independent of race and sex considerations, very little is known about the population distribution of Lp-PLA2, which is important for interpretation of the Lp-PLA2 assay results [13].

We measured Lp-PLA2 mass and activity in a large multiethnic population-based study of adult residents of Dallas, Texas to determine: (a) the population-based range of Lp-PLA2, and (b) whether sex and racial differences in Lp-PLA2 distribution exist.

2. Methods

2.1. Study population

The Dallas Heart Study is a population-based, multiethnic, probability sample of 6101 subjects in Dallas County designed to study cardiovascular disease [14–19]. Briefly, a stratified random sample of Dallas County residents age 18–65 was obtained from a pool of 841,943 eligible subjects using the U.S. Postal Service Delivery Sequence File, with deliberate oversampling of African Americans. An initial visit for 6101 participants included a detailed in-home interview for demographic and health-related data, as well as measurements of weight, heart rate, and 5 sequential blood pressure measures. All subjects between the ages of 30–65 who completed the initial visit were invited to participate in a second home visit to collect fasting venous blood and urine samples, and if they completed the second visit, invited to a third detailed clinic visit, consisting of a 12-lead electrocardiogram, cardiac and aortic magnetic resonance imaging, electron beam computed tomography (EBCT) to assess coronary artery calcification, and dual-energy X-ray absorbtometry (DEXA) scanning to evaluate fat distribution and bone density. For the present analyses, we included data from the 3332 subjects in whom plasma was available for Lp-PLA2 measurement and whose (self-reported) race was white, Hispanic, or black. Study definitions for various covariates have been previously reported [14].

2.2. Lp-PLA2 assay

Blood samples were obtained in EDTA tubes and were stored for $\leq$4 h at 4 °C before processing. Plasma was frozen in aliquots of 100 μL at −80 °C.

Lp-PLA2 activity was measured with a colorimetric activity method provided by Glaxo Smithkline (Research Triangle Park, NC, USA). Samples, standards, or controls were added to wells of a non-binding 96-well microplate, followed by addition of reaction buffer containing substrate. In the presence of Lp-PLA2 enzyme, the substrate is converted upon hydrolysis by the phospholipase enzyme. The change in absorbance was immediately measured at 405 nm over 60–180 s. The level of Lp-PLA2 activity in nmol/min/mL was calculated from the slope (OD405/min), based on a standard conversion factor from a *p*-nitrophenol calibration curve. The mean duplicate coefficient of variation was 2.94% for the low controls and 3.85% for the high controls. Samples that had activity values outside the range of 2–300 nmols/min/mL exceeded the dynamic range of the assay and were reported as such. All samples were assayed in duplicate on consecutive microtiter plates (mean values were reported). The mean duplicate CV% for samples was 3.87%. Analysis of Lp-PLA2 mass was performed by diaDexus, Inc. (South San Francisco, CA, USA) using a dual monoclonal antibody immunoassay standardized to recombinant Lp-PLA_2, as previously reported [5]. The mean duplicate coefficient of variation was 2.89% for the low controls and 3.23% for the high controls. Samples were run in single point.

2.3. Statistical analysis

Categorical data are reported as proportions and continuous data as mean values with standard deviations, or as medians (interquartile range) for non-normally distributed variables. Subjects were divided into 6 groups based on their race and gender. Baseline demographic variables and CV risk factors were compared across the different groups with the χ^2 trend test for categorical variables and the test for trend or the Kruskall–Wallis test across ordered groups for continuous variables. The association between Lp-PLA2 levels and continuous variables was explored using Spearman correlation coefficients. Multivariable stepwise linear regression analysis was used to determine variables independently associated with Lp-PLA2 levels. The stepwise linear regression model included all baseline covariates with a univariable association of $p < 0.1$ with Lp-PLA2 activity, as well as race and sex, and used backward selection to derive the final models. All analyses were performed using Stata 9.0 (College Station, Texas).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study population stratified according to sex and race are shown in Table 1. Overall, mean age was 45 ± 9 years and 44% were men; 30% were white, 17% hispanic, and 53% black. Compared with men, women were more likely to have a family history of myocardial infarction, and less likely to smoke, or take aspirin. Women had higher high-sensitivity C-reactive protein (hsCRP) and high-density lipoprotein (HDL) cholesterol and lower LDL cholesterol and triglycerides. Compared with whites and hispanic subjects, black subjects were more likely to have hypertension and had higher median CRP. Mean and median Lp-PLA2 activity was 146 ± 40 and 144 nmol/min/mL, respectively. Mean and median Lp-PLA2 mass was 191 ± 60 and 187 ng/mL, respectively. There was