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ASSOCIATION OF LP-PLA₂ ACTIVITY WITH ALLELE-SPECIFIC LP(a) LEVELS IN A BI-ETHNIC POPULATION

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Abstract

Objectives—Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) and lipoprotein(a) [Lp(a)] have been implicated as cardiovascular disease risk factors, and are differentially regulated across ethnicity. We investigated the association between Lp-PLA₂ activity and allele-specific apolipoprotein(a) [apo(a)] levels in a bi-ethnic population.

Methods—Lp-PLA₂ activity, Lp(a) and allele-specific apo(a) levels were determined in 224 African Americans and 336 Caucasians.

Results—Lp-PLA₂ activity level was higher among Caucasians compared to African Americans (173 ± 41 vs. 141 ± 39 nmol/min/ml, $P < 0.001$), and positively associated with Lp(a), total and LDL cholesterol, triglyceride, apolipoprotein B-100, and negatively with HDL cholesterol levels in both ethnic groups. The association between Lp-PLA₂ activity and Lp(a) was stronger among African Americans compared to Caucasians ($R = 0.238$, $\beta_1 = 3.48$, vs. $R = 0.111$, $\beta_1 = 1.93$, respectively). The Lp-PLA₂ activity level was significantly associated with allele-specific apo(a) levels for smaller (< 26 K4 repeats) apo(a) sizes in both ethnic groups ($P = 0.015$ for African Americans, $P = 0.038$ for Caucasians). In contrast, for larger (> 26 K4 repeats) apo(a) sizes, high Lp-PLA₂ activity levels were associated with higher allele-specific apo(a) levels in African Americans ($P = 0.009$), but not in Caucasians.

Conclusion—The association between Lp-PLA₂ activity and allele-specific apo(a) levels differs across African American-Caucasian ethnicity.

Keywords

lipoprotein; allele-specific apo(a); K4 repeats; vascular inflammation marker; ethnicity

INTRODUCTION

Increased levels of lipoprotein-associated phospholipase A₂ (Lp-PLA₂), a leukocyte-derived enzyme circulating in plasma attached to lipoproteins, are associated with increased

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risk for cardiovascular disease (CVD) [1,2]. However, Lp-PLA₂ levels differ significantly across ethnicity after adjusting for differences in traditional risk factors and environmental exposures, with low mean levels in African Americans and high mean levels in Caucasians [3,4]. The explanation for this interethnic difference in Lp-PLA₂ level remains unclear.

Lp-PLA₂ preferentially associates with low-density lipoprotein (LDL), but also occurs on high-density lipoprotein (HDL) [5]. In addition, Lp-PLA₂ is associated with lipoprotein (a) [Lp(a)], in particular when Lp(a) levels exceed 30mg/dl, a level associated with cardiovascular risk [6,7]. Notably, Lp(a) particles carry proportionally more Lp-PLA₂ mass (1.5- to 2-fold) and activity (up to 7-fold) compared to equimolar amounts of LDL [7,8]. Recent studies have suggested the possibility of a direct link between Lp-PLA₂ and Lp(a) with regard to CVD risk [8]. Paradoxically, Lp(a) and Lp-PLA₂ levels are inversely regulated in African Americans and Caucasians with higher Lp(a) and lower Lp-PLA₂ levels among African Americans. Lp(a) levels are to a major extent regulated by genetic factors [9], and its apolipoprotein (a) [apo(a)] component has an extensive size polymorphism due to variable number of kringle 4 (K4) repeats [10]. A large number of studies have demonstrated an association between small size apo(a) and CVD [11–13]. Though smaller apo(a) sizes associate with higher plasma Lp(a) levels in general, there is a considerable variability in Lp(a) levels even for a given apo(a) size [14–16]. The use of allele-specific apo(a) levels offers opportunity to more accurately assess the relationship between apo(a) size and Lp(a) levels [17]. We have previously reported that presence of inflammation as detected by increased levels of C-reactive protein (CRP) and fibrinogen impacts allele-specific apo(a) levels in African Americans [17], with a selective increase in medium size apo(a) levels during proinflammatory conditions. Lp-PLA₂ has been identified as a more specific marker for vascular inflammation [18,19], and appears to capture a different inflammatory burden than CRP and fibrinogen. The present study was undertaken to evaluate the association between Lp-PLA₂ activity and allele-specific apo(a) levels in African American-Caucasian ethnicity.

MATERIALS AND METHODS

Subjects

Subjects were recruited from a patient population scheduled for diagnostic coronary arteriography either at Harlem Hospital Center in New York City or at the Mary Imogene Bassett Hospital in Cooperstown, NY. The clinical characteristics of the study population and the study design including inclusion and exclusion criteria have been described previously, and notably, exclusion criteria included use of lipid lowering drugs, as well as hormone replacement therapies [14,16,17]. Briefly, a total of 648 patients, self-identified as Caucasian (n=344), African-American (n=232), or other (n=72) were enrolled. The present report is based on the findings in 560 subjects (336 Caucasians, 224 African Americans); 16 subjects were excluded due to incomplete data. The apo(a) allele sizes, circulating apo(a) isoforms, and allele-specific apo(a) levels were available on 426 subjects (167 African Americans, 259 Caucasians). The study was approved by the Institutional Review Boards at Harlem Hospital, the Mary Imogene Bassett Hospital, Columbia University College of Physicians and Surgeons, and University of California, Davis, and informed consent was obtained from all subjects.

Measurement of plasma lipid concentrations and Lp-PLA₂ activity

Participants were asked to fast for 12 hours, and blood samples were drawn approximately 2 to 4 hours before the catheterization procedure. Serum and plasma samples were separated and stored at –80°C prior to analysis. Concentrations of triglycerides (Sigma Diagnostics, St. Louis, MO), total and HDL cholesterol (Roche, Somerville, NJ) were determined using

standard enzymatic procedures. HDL cholesterol levels were measured after precipitation of apoB-containing lipoproteins with dextran sulfate [20]. Plasma Lp(a) levels were measured by an apo(a) size insensitive sandwich ELISA (Sigma Diagnostics, St Louis, MO) [16,17]. Lp-PLA₂ activity was measured with a colorimetric activity method with laboratory personnel blinded to all clinical data (diaDexus, Inc., South San Francisco, CA) [19].

Determination of apo(a) allele, isoform size and allele-specific apo(a) levels

To determine apo(a) allele sizes, we performed genotyping using pulsed-field gel electrophoresis of DNA from leucocytes embedded in agarose plugs [21,22]. Apo(a) isoform sizes were analyzed by SDS-agarose gel electrophoresis of plasma samples, followed by an immunoblotting. Allele-specific apo(a) levels were determined based on the computerized scanning of apo(a) protein bands on the Western blot as described previously [17,21,22].

Statistics

Analysis of data was done with SPSS statistical analysis software (SPSS Inc, Chicago, IL). Results were expressed as means $\pm$ SD. Triglyceride and Lp-PLA₂ activity levels were logarithmically transformed, and Lp(a) levels and allele-specific apo(a) levels were square root transformed to achieve normal distributions. Group means were compared using Student's *t*-test. Univariate relationship between Lp-PLA₂ activity and other variables were described by the Pearson correlation coefficients. One-way ANOVA and post hoc analyses were performed with the Bonferroni test for two independent samples. All analyses were two-tailed, and *P*-values less than 0.05 were considered statistically significant.

RESULTS

The characteristics of the study population are presented in Table 1. There was no significant difference in the levels of total and LDL cholesterol, and apolipoprotein B-100 between the two ethnic groups. African Americans had significantly higher levels of HDL cholesterol ($P<0.001$) and apolipoprotein A-1 ($P=0.003$) and lower level of triglyceride ($P<0.001$) compared with Caucasians.

The distributions of both Lp(a) and Lp-PLA₂ activity levels differed between Caucasians and African Americans (Figure 1). As expected, Caucasians had significantly lower level of Lp(a) (24 vs. 110 nmol/l, $P<0.001$) and higher level of Lp-PLA₂ activity (171 vs. 140 nmol/min/ml, $P<0.001$) compared with African Americans. We next analyzed the relationship of Lp-PLA₂ activity with other variables across ethnicity. As seen in Figure 2, the Lp-PLA₂ activity levels were significantly and positively associated with Lp(a) levels in both ethnic groups. Further, the association between Lp-PLA₂ and Lp(a) was stronger among African Americans compared with Caucasians ($R=0.238$, $\beta_1=3.48$ vs. $R=0.111$, $\beta_1=1.93$, respectively). Irrespective of ethnicity, Lp-PLA₂ activity was positively associated with total and LDL cholesterol, triglyceride and apolipoprotein B-100, and negatively with HDL cholesterol levels (Table 2).

We next studied the association between Lp-PLA₂ activity and allele-specific apo(a) levels. We dichotomized apo(a) sizes by using the median apo(a) size (26 K4 repeats), as in our previous studies [14,16]. For smaller (<26 K4 repeats) apo(a) sizes, Lp-PLA₂ activity levels were significantly associated with allele-specific apo(a) levels in both ethnic groups ($P=0.015$ for African Americans, $P=0.038$ for Caucasians, Supplemental Figure 1). In contrast, for larger (>26 K4 repeats) apo(a) sizes, Lp-PLA₂ activity levels were associated with allele-specific apo(a) levels in African Americans ($P=0.009$), but not in Caucasians. To investigate this association in more depth, we divided the subjects with larger (>26 K4 repeats) apo(a) sizes into 2 groups using the respective median Lp-PLA₂ activity levels

(170.9 nmol/min/ml for Caucasians and 139.6 nmol/min/ml for African Americans). As seen in Figure 3, among African Americans, high Lp-PLA₂ activity levels were significantly associated with higher allele-specific apo(a) levels for larger (>26 K4 repeats) apo(a) sizes ($P=0.037$). In contrast, we did not observe any association between Lp-PLA₂ activity and allele-specific apo(a) levels for larger (>26 K4 repeats) apo(a) sizes among Caucasians, confirming our initial finding. In agreement with the previous studies [14,16], there was a significant interethnic difference in the allele-specific apo(a) levels for larger (>26 K4 repeats) apo(a) sizes across low and high Lp-PLA₂ activity groups, with 2- to 4-fold higher allele-specific apo(a) levels among African Americans compared with Caucasians ($P<0.001$) (Figure 3).

DISCUSSION

The main novel finding in our study was that increased levels of Lp-PLA₂ activity, an established biomarker of vascular inflammation, were associated with higher Lp(a) levels across African American-Caucasian ethnicity, with the strongest association among African Americans. Further, Lp-PLA₂ activity levels were associated with allele-specific apo(a) levels over the entire apo(a) size spectrum in the latter group. Among Caucasians, we observed a significant association between allele-specific apo(a) levels for smaller (< 26K repeats) apo(a) size and Lp-PLA₂ activity. Thus, our findings suggest the potential for an additive effect between Lp(a), in particular Lp(a) carrying small size apo(a), and Lp-PLA₂ in promoting cardiovascular risk.

The approach focused on a vascular inflammation marker was informed by our previous study [17], where we demonstrated an association between systemic inflammatory markers, such as CRP and fibrinogen, and allele-specific apo(a) levels for smaller (<26 K4 repeats) apo(a) sizes in African Americans. Further, Tsimikas *et al.* have suggested that Lp(a)-associated Lp-PLA₂ may have an important pro-atherogenic role impacting on oxidized phospholipids [8,23]. In a recent study by the same group of investigators, Lp-PLA₂ activity was shown to correlate with Lp(a) levels, with no major differences among ethnic groups [24]. However, there is strong evidence that apo(a) size impacts on Lp(a) atherogenicity and there is a paucity of information on the relation between Lp-PLA₂ activity and allele-specific apo(a) levels.

In the present study, African Americans had significantly lower level of Lp-PLA₂ activity and higher levels of Lp(a), allele specific apo(a) and HDL cholesterol compared to Caucasians. It has been demonstrated that Lp-PLA₂ circulates in plasma predominantly associated with LDL, whereas a minor proportion is associated with HDL [5]. However, the distribution of Lp-PLA₂ can be influenced by the presence of Lp(a), in particular when levels exceed 30 mg/dl [6,7]. Notably, studies have shown that Lp(a) particles carry proportionally more Lp-PLA₂ mass (1.5- to 2-fold) and activity (up to 7-fold) compared to equimolar amounts of LDL [7]. In the present study, several of the lipoproteins associated with Lp-PLA₂ differed substantially among the two ethnic groups. Notably, compared to Caucasians, our African American subjects had significantly lower Lp-PLA₂ activity in spite of having considerably higher Lp(a) and HDL cholesterol at comparable total and LDL cholesterol levels. This raises the apparent paradox that although the amount of potential lipoprotein carriers for Lp-PLA₂ was higher in African Americans, the enzyme activity was lower. Our findings therefore indicate that Lp-PLA₂ may be differentially distributed among lipoprotein fractions across African American-Caucasian ethnicity. While further studies are needed to verify these results, it is well recognized that presence of inflammatory conditions impact on lipoprotein properties which might contribute to this difference. However, beyond the potential for carrier differences, we cannot exclude that genetic variants associated with Lp-PLA₂ activity might explain this interethnic difference. A loss of function single

nucleotide polymorphism (Val-279→Phe) in the Lp-PLA₂ gene is seen in approximately 30% of Japanese subjects (4% homozygous) and has been associated with higher risk of CAD [25] and stroke [26] though not confirmed in larger studies [27,28]. Another polymorphism, Ala-379→Val, is seen in Caucasians and appears to result in a secreted enzyme with reduced catalytic activity and lower risk of CAD [29]. However, there are virtually no data currently available identifying specific genetic variants associated with Lp-PLA₂ activity among African Americans.

It has been demonstrated that the attachment of Lp-PLA₂ on Lp(a) particles requires participation of the apoB-100, but not apo(a) [30]. There are marked differences in Lp-PLA₂ catalytic properties among various Lp(a) isoforms, where Lp-PLA₂ associated with smaller apo(a) isoforms exhibit higher apparent Michaelis constant and maximum velocity values [6]. These results may suggest that molecular properties of apo(a) may influence the association of Lp(a) with Lp-PLA₂, as well as its activity and potential physiological impact. Previously, we have shown that among Caucasians, dominance by smaller apo(a) isoforms was more common, increasing with higher Lp(a) levels, whereas codominance of smaller and larger apo(a) isoforms was more common among African Americans [22]. It is tempting to speculate that this difference might affect the association pattern between Lp(a) and Lp-PLA₂. Thus, a more pronounced dominance of smaller apo(a) among Caucasians might promote the formation of the Lp(a)-Lp-PLA₂ complex, which subsequently could contribute to the difference in the levels of Lp-PLA₂ activity among the two ethnic groups.

Lp-PLA₂ activity levels were significantly associated with allele-specific levels for both larger and smaller apo(a) sizes among African Americans, while this association was seen only for allele-specific smaller apo(a) levels in Caucasians. Thus, compared to the findings of our previous study [17], where CRP and fibrinogen levels were associated with allele-specific smaller apo(a) levels only in African Americans, Lp-PLA₂ showed more pronounced association with allele-specific levels of small size apo(a) across the two ethnic groups. This difference between the two studies suggest a stronger link between allele-specific apo(a) levels and Lp-PLA₂ than for CRP or fibrinogen, markers of systemic inflammation. As smaller apo(a) sizes have been associated with cardiovascular risks, our results suggest a strong impact of vascular inflammation on atherogenic Lp(a) particles, irrespective of ethnicity. Beyond underscoring an impact of inflammation on Lp(a) levels, our findings reinforce the concept that inflammation associated events may contribute to the well established African American-Caucasian interethnic difference in Lp(a) levels.

We acknowledge some of the limitations of this study. Subjects in our study were recruited from patients scheduled for coronary angiography and are likely more typical of a high-risk patient group than the healthy population at large. However, none of the patients had a history of acute coronary symptoms or surgical intervention within 6 months, arguing against any secondary increase in inflammatory parameters due to an acute CAD. Further, clinical and laboratory parameters were in agreement with differences generally observed between healthy African American and Caucasian populations from other studies. Although the subjects in our study may not be fully representative of the healthy population, our findings still suggest that even within a high-risk population, pro-inflammatory conditions may differentially influence Lp(a) levels among African-American and Caucasian ethnicity.

In conclusion, this is to our knowledge the first study to examine the relationship between apo(a) size, allele-specific apo(a) levels and Lp-PLA₂ in a biethnic population. An important finding was that elevated levels of Lp-PLA₂ activity were significantly associated with increased Lp(a) levels for smaller (< 26 K4 repeats) apo(a) sizes in both ethnic groups, emphasizing the importance of small size apo(a) as a cardiovascular risk factor. For larger (> 26 K4 repeats) apo(a) sizes, an association between Lp-PLA₂ and Lp(a) was seen among

African Americans, but not in Caucasians. Further studies are needed to verify these results in other populations and to explore whether inflammation-associated events, including vascular inflammation, contribute to the interethnic difference in Lp(a) levels and impact on the role of Lp(a) as risk factor for CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Distribution of plasma Lp(a) (A) and Lp-PLA₂ activity (B) levels across ethnicity. Data represent median and interquartile ranges.

Figure 2.

Correlations of Lp-PLA₂ activity with plasma Lp(a) levels across ethnicity. Values for Lp-PLA₂ were logarithmically transformed, and values for Lp(a) were square root transformed before analysis. The transformed values are shown in the graph.

Figure 3.

Association between Lp-PLA₂ activity and allele-specific apo(a) levels for larger (>26 K4 repeats) apo(a) sizes across ethnicity. Subjects with larger (>26 K4) apo(a) sizes were dichotomized into 2 groups using respective median Lp-PLA₂ activity levels (170.9 nmol/min/ml for Caucasians and 139.6 nmol/min/ml for African Americans). Square root transformed allele-specific apo(a) levels and logarithmically transformed Lp-PLA₂ activity levels were used for statistical analysis. Data are expressed as means $\pm$ SE. * $P < 0.001$

Table 1

Characteristics of study population.

Characteristics	Caucasians (n=336)	African Americans (n=224)	P-value
Men/Women (n)	217/119	126/98	NS
Diabetes (n)	69 (20.5%)	66 (29.5%)	0.016
Hypertension (n)	188 (55.9%)	164 (73.2%)	< 0.001
Postmenopausal (n)	94 (79.7%)	65 (66.3%)	0.036
Age (yrs)	56.8±10.3	54.8±9.2	0.025
Total cholesterol (mg/dl)	197±41	198±45	NS
LDL cholesterol (mg/dl)	122±35	126±42	NS
HDL cholesterol (mg/dl)	41±12	49±17	< 0.001
Triglycerides (mg/dl)	153 (114–222)	106 (80–144)	< 0.001
Apolipoprotein A-1 (mg/dl)	122±23	130±28	0.003
Apolipoprotein B-100 (mg/dl)	136±36	134±40	NS

NS, not significant. Data are means ± SD or for non-normally distributed variables as median (interquartile range). Group means were compared using t-test. Value for triglyceride was logarithmically transformed before analysis.

Table 2Correlations of Lp-PLA₂ activity with other variables across ethnicity.

	Lp-PLA₂ activity	
	R	P-value
Caucasians		
Total cholesterol (mg/dl)	0.286	< 0.001
LDL cholesterol (mg/dl)	0.390	< 0.001
HDL cholesterol (mg/dl)	−0.358	< 0.001
Triglyceride (mg/dl)	0.127	0.021
Apolipoprotein A-1 (mg/dl)	−0.272	< 0.001
Apolipoprotein B-100 (mg/dl)	0.428	< 0.001
African Americans		
Total cholesterol (mg/dl)	0.417	< 0.001
LDL cholesterol (mg/dl)	0.488	< 0.001
HDL cholesterol (mg/dl)	−0.197	0.006
Triglyceride (mg/dl)	0.164	0.022
Apolipoprotein A-1 (mg/dl)	−0.119	NS
Apolipoprotein B-100 (mg/dl)	0.495	< 0.001

NS, non-significant. Values for triglyceride were logarithmically transformed before analyses.