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Evaluating the Potential Association Between Lipoprotein(a) and Atherosclerosis (From the MASALA Cohort)

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Abstract

We sought to report the distribution of Lp(a) levels in the Mediators of Atherosclerosis among South Asians Living in America (MASALA) cohort of participants who were free from clinical ASCVD at baseline and to evaluate the cross-sectional association with atherosclerosis measured by coronary artery calcification (CAC) and carotid intima media thickness (CIMT). Among 886 participants (mean [SD] age: 55.4 [9.4] years, 54% male), median lipoprotein (a) level was 17 (9, 33) mg/dl. Compared with the lowest quartile (9 mg/dl), individuals in the highest Lp(a) quartile (33–178 mg/dl) were more likely to be women (51% versus 37%, $p<0.01$) and had a higher mean (SD) total cholesterol (193 [37] mg/dl versus 181 [35] mg/dl, $p<0.01$). CAC was present in 42% and both the presence and degree of CAC was similar across Lp(a) quartiles ($p=0.58$). Median (IQR) common and internal carotid IMT thicknesses were 0.84 (0.73, 0.98) mm and 1.12 (0.95, 1.34) mm respectively and were also similar across Lp(a) quartiles. After adjustment for cardiovascular risk factors, Lp(a) quartile had no association with prevalent CAC ($p=0.98$), internal carotid IMT ($p=0.46$) or common carotid IMT ($p=0.97$). Among South Asian Americans, mean Lp(a) levels were higher than previous reports among Whites, Hispanic/Latino, and Chinese-

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Americans but lower than in Blacks. Unlike findings from other race/ethnic groups, Lp(a) levels were not associated with atherosclerosis among South Asian Americans.

Keywords

lipoprotein (a); South Asians; atherosclerosis; Lipids and Cholesterol; Race and Ethnicity

Introduction

South Asians have an increased risk for atherosclerosis hypothesized to be related to elevated lipoprotein (a) [Lp(a)] levels.[1] Elevated Lp(a) levels have been associated with incident coronary heart disease[2] and stroke in other race/ethnic groups.[3] However, data describing Lp(a) levels and its association with atherosclerosis among South Asians without overt cardiovascular disease are limited.[4] We evaluated the distribution of Lp(a) in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study participants who were free from clinical cardiovascular disease and evaluated the cross-sectional association with atherosclerosis measured by coronary artery calcification (CAC) and carotid intima media thickness (CIMT). We hypothesized that Lp(a) would be associated with the presence and degree of CAC but not with CIMT.

Methods

The MASALA study methods have been previously reported and are modeled after the Multi-Ethnic Study of Atherosclerosis (MESA).[5] From 2010 to 2013, 906 individuals of South Asian descent between the ages of 40 to 84 years without cardiovascular disease were recruited from the San Francisco Bay Area and greater Chicago field centers. Participants' home birth country primarily included India (84%) and Pakistan (5%) with < 5% of participants' birth country being Nepal, Sri Lanka, Bangladesh, Myanmar, or a South Asian diaspora country.[5] Lp(a) levels were measured by particle-enhanced immunonephelometry on a BNII nephelometer. Using standardized protocols, CAC was measured by cardiac computed tomography, and CIMT was measured by B mode ultrasound.

Due to the high positive skew as well as inflation at the lower detectible assay limit of 9 mg/dl, Lp(a) was categorized into quartiles for the primary analysis. Baseline characteristics were compared across quartiles using chi-squared test for categorical covariates and ANOVA or Kruskal-Wallis for continuous. We evaluated the association between Lp(a) quartile and the presence of CAC through multivariable logistic regression and with degree of CIMT through multivariable linear regression. We also created spline models to explore a potential threshold for Lp(a) and atherosclerosis. We used SAS v9.4 (Cary, NC; SAS) for our analyses. The study protocol was approved by the University of California San Francisco and Northwestern University institutional review boards, and all participants provided written informed consent.

Results

Among 886 participants with Lp(a) measurements (98% of MASALA cohort), mean (SD) age was 55.4 (9.4) years, 54% were men, and 58% had prediabetes or diabetes (Table 1). Median Lp(a) level was 17 (9, 33) mg/dL. Compared with the lowest quartile (Q1: 9 mg/dl), individuals in the highest Lp(a) quartile (Q4: 33 to 178 mg/dL) were more likely to be women (51% in Q4 versus 37% in Q1, p<0.01) and have a higher mean (SD) total cholesterol (193 [37] mg/dL in Q4 versus 181 [35] mg/dL in Q1, p<0.01). CAC was present in 42%, but both the presence and degree of CAC was similar across Lp(a) quartiles (p=0.58). Median (IQR) common and internal CIMT were 0.84 (0.73, 0.98) mm and 1.12 (0.95, 1.34) mm, respectively, and were similar across Lp(a) quartiles.

After adjustment for cardiovascular risk factors (age, sex, smoking, systolic and diastolic blood pressure, hypertension medication, total cholesterol, HDL cholesterol and diabetes status), prevalent CAC (p=0.98), internal CIMT (p=0.46) and common carotid IMT (p=0.97) were not associated with Lp(a) quartile (Table 2). We did not identify any Lp(a) threshold that was associated with atherosclerosis in our adjusted spline models.

Discussion

These data do not demonstrate an association between Lp(a) levels and atherosclerosis measured by CAC and CIMT among South Asians. Further, the distribution of Lp(a) was not elevated among MASALA participants compared with other race/ethnic groups. For example, data from the Atherosclerosis Risk in Communities (ARIC) cohort demonstrate median (IQR) Lp(a) levels of 12.8 (7.1, 21.7) mg/dL in black participants and 4.3 (1.8, 10.7) mg/dL among white participants.[3] In the MESA cohort, median Lp(a) levels were 35.1 mg/dL for black participants, 13.0 mg/dL for white participants, 12.9 mg/dL for Chinese participants, and 13.1 mg/dL for Hispanic participants.[2] MESA investigators also have demonstrated race-specific thresholds for increased coronary heart disease risk, including ≥ 30 mg/dl for black participants and ≥ 50 mg/dl for white, Hispanic, and Chinese-American participants.[2] The lack of an association in the current study even at higher thresholds may be driven by: 1) the relatively high rate of atherosclerosis due to other factors such as dysglycemia, including among individuals with relatively low Lp(a); 2) evaluation of subclinical atherosclerosis rather than clinical events due to the low number of cardiovascular events that have accrued thus far in MASALA; 3) methods of Lp(a) measurement, or 4) limited statistical power to detect the proposed relationship between Lp(a) and CAC, which has been demonstrated in some,[6,7] but not all,[8] community-based cohorts of other race/ethnic groups.

Our study has several strengths, including being the largest to evaluate the relation between Lp(a) and atherosclerosis among South Asians. We also used standardized methods for assessing Lp(a), CAC, and CIMT to minimize variability. However, our study also has limitations, including being cross-sectional, potentially underpowered, and limited to the San Francisco Bay and Chicago metropolitan areas, though MASALA participant characteristics are broadly similar to South Asian data from the 2010 US Census.[5] It may also be possible that Lp(a) does not confer elevated risk for atherosclerosis among South

Asians, but this hypothesis warrants additional, longitudinal investigation across multiple cohorts. Seeking other biomarkers or pathways to identify novel causal factors may better help to explain the observed, elevated risk for atherosclerosis among South Asians.

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Table 1.

Baseline demographic, anthropometric, laboratory, and imaging covariates by quartile of lipoprotein (a) level among MASALA cohort participants (n=886).

	Lipoprotein(a) quaritile (mg/dL)				
Variable	**9 (n=244)**	**10-17 (n=207)**	**18-32 (n=212)**	**33-178 (n=223)**	**p-value***
Age (years)	54.9 (8.9)	56.3 (9.1)	55.1 (10.0)	55.3 (9.4)	0.41
Sex					<.01
Male	153 (63%)	106 (51%)	106 (50%)	109 (49%)	
Female	91 (37%)	101 (49%)	106 (50%)	114 (51%)	
Menopause†					0.28
Pre-	37 (41%)	35 (35%)	39 (37%)	32 (28%)	
Post-	54 (59%)	66 (65%)	67 (63%)	82 (72%)	
Income category					0.60
<$40,000	25 (11%)	28 (14%)	29 (14%)	31 (14%)	
$40,000–74,999	35 (15%)	27 (13%)	25 (12%)	30 (14%)	
$75,000–100,000	20 (8%)	21 (10%)	28 (14%)	17 (8%)	
>$100,000	157 (66%)	125 (62%)	123 (60%)	139 (64%)	
Body mass index (kg/m^2)	25.5 (23.0, 27.8)	25.1 (22.7, 28.1)	25.5 (23.6, 27.9)	25.8 (23.2, 28.3)	0.50
Systolic blood pressure (mmHg)	124.7 (15.1)	125.3 (16.7)	124.1 (14.5)	124.5 (16.7)	0.90
Diastolic blood pressure (mmHg)	74.4 (8.9)	73.1 (9.4)	73.4 (9.9)	72.9 (10.9)	0.34
Smoker					0.28
Current	11 (5%)	3 (1%)	11 (5%)	5 (2%)	
Former	36 (15%)	30 (14%)	24 (11%)	31 (14%)	
Never	197 (81%)	174 (84%)	177 (83%)	187 (84%)	
Total cholesterol (mg/dL)	181.3 (35.2%)	183.0 (35.1)	192.6 (39.1)	193.1 (36.8)	<0.01
High density lipoprotein cholesterol (mg/dL)	47.9 (13.3)	50.7 (13.3)	51.3 (13.9)	50.5 (12.6)	0.03
Triglycerides (mg/dL)	121 (89–173)	119 (86–154)	116 (89–152)	117 (88–156)	0.53
Cholesterol medication	66 (27%)	69 (33%)	55 (26%)	71 (32%)	0.26
Glucose tolerance category					0.29
Normal	98 (40%)	88 (43%)	91 (43%)	91 (41%)	
Prediabetes	76 (31%)	59 (29%)	78 (37%)	79 (35%)	
Diabetes	69 (28%)	60 (29%)	43 (20%)	53 (24%)	
Coronary artery calcium, 3 categories					0.58
Coronary artery calcium score = 0	134 (55%)	115 (56%)	131 (62%)	133 (60%)	
Coronary artery calcium score 1–400	91 (37%)	78 (38%)	68 (32%)	70 (31%)	
Coronary artery calcium score >400	19 (8%)	14 (7%)	13 (6%)	20 (9%)	
Common carotid intima media thickness (mm)	0.84 (0.73, 0.99)	0.84 (0.74, 0.96)	0.83 (0.71, 0.95)	0.84 (0.72, 0.98)	0.55
Internal carotid intima media thickness (mm)	1.11 (0.97, 1.26)	1.10 (0.94, 1.36)	1.10 (0.90, 1.29)	1.14 (0.96, 1.41)	0.40

*Based on Chi-squared, ANOVA or Kruskal-Wallis test

†Among women only

Table 2.

Association of Lp(a) quartile with prevalent coronary artery calcium, internal carotid intima media thickness and common carotid intima media thickness-adjusted for cardiovascular risk factors in MASALA cohort participants (n=886).

	Lipoprotein(a) quartile (mg/dL)				
	9 (n=244)	**10-17 (n=207)**	**18-32 (n=212)**	**33-178 (n=223)**	**Type III effect p-value**
Coronary artery calcium, Odds ratio (95% CI)	Referent	0.93 (0.58 to 1.47)	0.92 (0.58 to 1.46)	0.98 (0.62 to 1.55)	0.98
Common carotid intima media thickness, mm, Beta (95% CI)	Referent	−0.01 (−0.04 to 0.03)	0.00 (−0.04 to 0.03)	0.00 (−0.03 to 0.04)	0.97
Internal carotid intima media thickness, mm, Beta (95% CI)	Referent	0.02 (−0.05 to 0.10)	0.01 (−0.06 to 0.09)	0.06 (−0.02 to 0.13)	0.46