Elevated Lipoprotein(a) Levels in South Asians in North America

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This report demonstrates that South Asians living in North America have elevated levels of Lp(a) compared with North American whites. Elevated Lp(a) levels may account, in part, for the tendency of South Asians to develop premature coronary heart disease (CHD).

THERE IS COMPELLING EVIDENCE that South Asians who originate from India, Pakistan, Bangladesh, and Sri Lanka are at increased risk of coronary heart disease (CHD) both within their country of origin and abroad.[1] This excess is not explained by the established CHD risk factors such as hypertension, hypercholesterolemia, and cigarette smoking.[1] Multiple studies have demonstrated that South Asians have a high prevalence of glucose intolerance, abdominal obesity, and dyslipidemia, especially when they are exposed to urban life-styles.[2] Although other ethnic populations share the same tendency to develop metabolic abnormalities with migration to urban environments, they do not appear to develop premature CHD at the same rate as South Asians.[1] Elevated levels of lipoprotein(a) [Lp(a)], which is genetically determined, may be responsible, in part, for these high rates.

As part of an ongoing series of investigations to determine cardiovascular risk factors among ethnic populations, we studied the sociodemographic, anthropometric, and biochemical characteristics of three separate groups of South Asians living in North America. The first two study groups were "opportunistic" population samples, whereas the third was derived more rigorously by random sampling. We report that South Asians have higher levels of Lp(a) compared with North American whites.

SUBJECTS AND METHODS

Three separate studies were conducted:

Study 1

The Coronary Artery Disease in Asian Indians (CADI) Study represented the first systematic effort to study CHD risk factors in South Asians in North America. In 1992, 141 South Asian physicians who attended the annual meeting of the American Association of Physicians from India participated in this cross-sectional study. All participants, aged 40 to 57 years, completed a cardiovascular assessment consisting of a health survey, dietary evaluation, anthropometric measurements, and fasting blood samples. This study sample was matched by socioeconomic status to 138 caucasian physicians participating in the ongoing Meharry-Hopkins Study.[3] Lp(a) levels were measured on fasting blood samples with a Dynatech (Chantilly, VA) reader using an enzyme-linked immunosorbent assay (ELISA) with monospecific polyclonal antisera (Macra Lp(a); Terumo Medical, Elkton, MD) at the Mary Imogene Bassett Research Institute (Cooperstown, NY). All samples were stored at −70°C and assayed in duplicate, and the results were averaged for reporting. If the samples differed by more than 30%, the sample was reanalyzed. The intraassay coefficient of variation was 3.9% at 15 mg/dL and 4.8% at 36 mg/dL.

Study 2

This was a cross-sectional study of South Asian churchgoers in which 255 individuals between the ages of 22 and 70 years were recruited from Sunday services at two South Asian churches in Chicago, IL. All participants completed a health questionnaire, underwent physical testing, and provided fasting blood samples. This group was compared with a cohort of 246 white Americans who participated in the San Antonio Heart Study in Texas.[4] All blood samples from both studies were analyzed at the research laboratory of the University of Texas Health Science Center at San Antonio. Lp(a) levels were measured on fasting blood samples using an ELISA monoclonal anti-Lp(a) antibody technique (Terumo Medical). All samples were stored at −70°C for less than 12 months before analysis. The intraassay coefficient of variation was 4%.[5]

Study 3

This was a cross-sectional study conducted in preparation for a large cohort study of chronic disease risk factors in ethnic populations in Canada (Study of Health Assessment and Risk factors in Ethnic groups [SHARE]). Thirty South Asian and 21 white Canadians were randomly sampled from the community. All participants reported to the hospital, provided fasting blood samples, and completed a health questionnaire, dietary assessment, and physical testing. Lp(a) levels were measured by an immunoturbidimetric assay (Incstar, Stillwater, MN), which allows quantitative determination of Lp(a) by automated immunoprecipitation analysis. All specimens were centrifuged immediately and stored at −70°C for less than 1 month before Lp(a) assay. The intraassay coefficient of variation was 4.7%.

Statistical Methods

All continuous data were examined and corrected for nonnormality by logarithmic transformation. The SAS program (SAS Institute, Cary, NC) was used to perform chi-square significance tests between dichotomous variables, and *t* tests were used to compare groups on continuous measures. Categorical variables were adjusted for age and sex using logistic regression, and continuous variables were age- and sex-adjusted using one-way factorial ANOVA with age and sex as covariates.

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Submitted March 6, 1997; accepted July 11, 1997.

Supported in part by the American Association of Physicians from India, a Heart and Stroke Foundation of Canada Research Fellowship (S.S.A.), and Medical Research Council of Canada Career Scientist Award (S.Y.).

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0026-0495/98/4702-0011$03.00/0

RESULTS

Study 1

From the CADI sample, the mean Lp(a) concentration for South Asian physicians was 19.6 mg/dL compared with 17.5 mg/dL for white American physicians ($P = .55$). The median Lp(a) values were 15 and 11 mg/dL, respectively ($P = .17$). The percentage of Lp(a) values greater than 30 mg/dL was 25% in South Asians and 19% in White Americans ($P = .25$) (Table 1).

Study 2

Among 255 South Asian churchgoers from Chicago, 216 (85%) were born in the state of Kerala, India, and the mean duration of residence in the United States was 14 years. Significant differences in age and sex distribution between South Asians and non-Hispanic whites were identified such that all reported comparisons between these groups have been age- and sex-adjusted. Logistic regression was performed on data transformed for nonnormality. The mean Lp(a) concentration was significantly elevated in South Asians (20.2 mg/dL) compared with white Americans (16.3 mg/dL, $P < .002$). The median Lp(a) values were 16.1 and 9.1, respectively ($P < .0001$). Although the percentage of Lp(a) values greater than 30 mg/dL was higher in South Asians compared with white Americans (23% *v* 19%, $P = .27$), this difference was not statistically significant ($P = .08$) (Table 2).

Study 3

The SHARE investigation in Hamilton, Ontario, Canada, showed that South Asians had significantly higher mean Lp(a) concentrations compared to white Canadians (34.1 *v* 17.3 mg/dL, $P < .013$) after adjustment for age and sex differences. The median concentration was 28.4 and 11.3 mg/dL, respectively ($P < .014$), and the percentage of South Asians with Lp(a) values greater than 30 mg/dL was 50%, compared with 24% in the European Canadian group ($P < .003$) (Table 3).

DISCUSSION

Our data from three separate cross-sectional studies demonstrate that people of South Asian origin living in North America have higher concentrations of Lp(a) than North American whites. In two of the studies the difference was statistically significant, and in the third there was a trend.

Lp(a) has been demonstrated to be a powerful and independent promoter of cardiovascular disease, including CHD, stroke, and peripheral vascular disease, among whites in several but not all studies.[6] Lp(a) is a genetically determined lipoprotein consisting of LDL and apolipoprotein B (apo B) linked to an apo(a) moiety. Although the functional significance of Lp(a) is not known, elevated Lp(a) concentrations may be related to both accelerated atherogenesis and thrombogenesis.[7] The primary structure of apo(a) is homologous to plasminogen, making Lp(a) a potential inhibitor of plasminogen.[7]

The inconsistent nature of the association between Lp(a) and CHD across populations may be partly explained by comparison of the mean Lp(a) value, differences in study design, and differences in the collection, storage, and processing of blood samples.[6] Lp(a) is not normally distributed, and because it is markedly skewed to the lower end of the range, the use of mean Lp(a) concentrations may be potentially misleading. However, a threshold value above which the risk of cardiovascular events appears to increase has been established (>30 mg/dL) in males, and has recently been supported by data in females.[8] Given the

Table 1. CADI Study

Variable	South Asians	White Americans	P*
No. of subjects	141	138	
Mean age (yr)	47	58	.0001
Current smokers (n)	2	10	.005
Prevalence of CHD (%)†	11	15	.34
Hypertensives (%)	10	18	.05
Diabetics (%)	1	4	.30
Serum cholesterol (mmol/L)	5.32	5.63	.01
Mean Lp(a) (mg/dL)	19.5 ± 17.11	18.3 ± 18.4	.55
Median Lp(a)	15 (6.7-29.2)‡	11 (5.5-26.0)‡	.17
Lp(a) > 30 mg/dL (%)	25	19	.25

*Age-adjusted.
†ECG criteria.
‡Interquartile range.

Table 2. Study of Churchgoers and Non-Hispanic Whites

Variables	South Asians	White Americans	P*
No. of subjects	255	246	
Mean age (yr)	46	54	.0001
Females (%)	40	56	.001
Current smokers (%)	13.2	18.3	.016
History of MI (%)	2.1	4.9	.838
Hypertensives (%)	18.5	19.5	.053
Diabetics (%)	11.3	6.1	.0004
Cholesterol (mmol/L)	5.45	5.61	.6183
Mean Lp(a) (mg/dL)	20.2 ± 15.8	16.3 ± 18.3	.002
Median Lp(a)	16.1 (7.3-28.6)†	9.1 (3.7-22.0)†	.0001
Lp(a) > 30 mg/dL (%)	23.1	19.1	.080

Abbreviation: MI, myocardial infarction.
*Age- and sex-adjusted.
†Interquartile range.

Table 3. SHARE Study

Variable	South Asians	White Canadians	P*
No. of subjects	31	20	
Mean age (yr)	48	49	NS
Females (%)	40	57	NS
Mean residence in Canada (yr)	18	48	.001
Current smokers (%)	3.7	29	.0005
History of CHD (%)	7	14	.36
Diabetics (%)	7	0	NS
Hypertensives (%)	29	23	NS
Cholesterol (mmol/L)	5.10	4.99	NS
Mean Lp(a) (mg/dL)	34.13 ± 25.3	17.26 ± 19.4	.013
Median Lp(a)	28.4 (14.8-52.6)†	11.3 (0.8-27.3)†	.014
Lp(a) > 30 mg/dL (%)	50	24	.003

Abbreviation: NS, nonsignificant.
*Age- and sex-adjusted.
†Interquartile range.

nonnormal distribution of Lp(a), we present the median value and associated interquartile range for Lp(a) in each study and provide the percentage of participants with Lp(a) values greater than 30 mg/dL. Furthermore, in each of our studies, Lp(a) concentrations for both ethnic groups were measured using a standard Lp(a) assay under the same laboratory conditions. In studies 1 and 2 an ELISA monoclonal antibody technique was used, and in study 3 an immunoprecipitation technique was used. Each method has been validated for use in clinical studies.[9] Furthermore, none of these Lp(a) assays cross-reacted with apo B or plasminogen. Before processing, all blood samples were stored at −70°C and analyzed shortly after collection. Therefore, in each study, Lp(a) values were not significantly influenced by the type of Lp(a) assay or variations in laboratory processing.

There is strong evidence to suggest that Lp(a) concentrations in the blood are genetically determined through autosomal dominant transmission,[10] and are not greatly influenced by environmental factors such as smoking, diet, or exercise.[7,10] Preliminary data from cross-sectional studies indicate that Lp(a) may vary significantly between white, African-American, and Hispanic populations, although the impact of these differences on CHD rates remains unclear.[11]

Furthermore, in Japanese and Spanish populations with type II diabetes, the Lp(a) level has been demonstrated to be an independent predictor of future atherosclerotic events.[12,13] These observations are potentially important, as South Asians have an excess prevalence of type II diabetes compared with other populations, and we have demonstrated that they have elevated Lp(a) levels. Perhaps it is within this environment of glucose-metabolic abnormalities that the atherothrombotic activity of Lp(a) is initiated. Further research is needed to study the potential association between elevated Lp(a), glucose intolerance, and the development of CHD in this population.

While the results of our studies are provocative, caution must be exercised in their interpretation. Each study was cross-sectional, and two examined populations of South Asian volunteers. Although both the CADI Study and the churchgoers study are limited in their generalizability, the results of these studies are supported by our third and most recent study, SHARE, in which we used community-based stratified random sampling techniques.

Although the importance of Lp(a) as a risk factor for CHD in various ethnic groups remains unknown, this report provides the first evidence that South Asians possess elevated concentrations of Lp(a) compared with North American whites. The association between Lp(a) and CHD in South Asians needs to be tested in future studies.

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