Lipoprotein(a) in Children of Asian Indian Descendants and Their Caucasian Neighbors: The Slovak Lipid Community Study

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Abstract To elucidate a higher rate of premature cardiovascular disease (CVD) in Asian Indian descendants (Roma) in Slovakia, we investigated frequency distribution, correlates and relationship of lipoprotein(a) [Lp(a)] to family CVD risk factors in Roma children and their Caucasian neighbors. The study sample consisted of 607 healthy children aged 7–18 years (55% Roma, 48% male) as part of the biracial (Roma–Caucasian) Slovak Lipid Community Study. Overall, frequency distribution data of Lp(a) were highly skewed to low concentrations, with markedly higher Lp(a) levels in Roma than in Caucasian children (median and range, mg/dL: 14.5; 0–159.2 vs 6.2; 0–112.3, $P < 0.001$), regardless of age and gender. Lp(a) was positively correlated with apo B (0.159, $P = 0.004$) in Roma, and LDL cholesterol (0.170, $P = 0.005$) in Caucasian children. In addition, daily income of the family was negatively related with Lp(a) in Roma (-0.134 , $P = 0.036$) while positively in Caucasians (0.136, $P = 0.047$). For both race groups, no significant association was found between Lp(a) and age, body mass index, mean arterial pressure, smoking, and physical activity. Also, no significant relationships were examined between serum Lp(a) levels >30 mg/dL in children and family CVD risk factors, except for diabetes mellitus in parents of Caucasian origin (OR 4.46; 95%CI: 1.23–16.20). In a multivariate analysis, daily income, LDL cholesterol or apo B explained $\sim 7\%$ of the variance of Lp(a). This study suggests a significantly higher serum

Lp(a) levels in Roma than in Caucasian children and a small effect, in general, of relevant CVD risk factors on the variation of Lp(a) levels in childhood.

Keywords Ethnicity · Asian Indians · Children · Cardiovascular disease · Lipoprotein(a) · Slovakia

Introduction

Lipoprotein(a) [Lp(a)] is a serum lipoprotein complex assembled from cholesterol-rich low-density lipoprotein (LDL) and the highly polymorphic glycosylated apolipoprotein(a) [apo(a)], which is close resembled to plasminogen [1]. In a given individual, serum Lp(a) concentration remains remarkably stable over time and is not influenced by age, diet, lifestyle, or drugs [2]. Within the same population, however, serum Lp(a) levels vary greatly and marked variation in distribution and concentration of Lp(a) also exists between ethnic groups [3, 4]. Asian Indians, native or overseas immigrants, have obviously a higher Lp(a) levels compared to Caucasian populations [5–7]. For most populations, including Asian Indians and European Caucasians, Lp(a) levels > 25 – 30 mg/dL seem to be strongly associated with a higher incidence of cardiovascular events [8, 9].

The term Roma (Gypsies) refers to descendants of Asian Indians that migrated in several waves from Pakistan, Bangladesh and northern India into Europe between the ninth and 14 centuries. The first written record of the existence of this racial group in the territory of Slovakia dates back to the year 1322. Although the size of the overall Roma population in Slovakia is uncertain today, it is estimated to be around 440,000, which means that they represent 8.1% of the general Slovak population, a 31.2% increase on the 1990 figure [10]. Their poor health status is

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notorious and stems from long-term bad economic circumstances, a low level of educational attainment, and an unhealthy lifestyle [11].

The exact prevalence of cardiovascular disease (CVD) in the Roma population of Slovakia is difficult to estimate because race/ethnicity-related evidence of the causes of morbidity and mortality is not consistent with EU anti-discrimination law implementing the principle of equal use of personal data irrespective of racial or ethnic origin. However, the results from one small case-study have shown that the occurrence of CVD in Slovak Roma people is approximately 1.5-fold higher than in the majority population [12]. Moreover, CVD in Roma, as in Asian Indians, is premature, aggressive, severe, and more often have dismal prognosis as compared to those occurring in Caucasian patients [13].

Therefore the purpose of this study was: (a) to investigate the distribution of Lp(a) levels by sex in Roma and Caucasian children, (b) to identify the relationship between serum Lp(a) levels to other CVD risk factors and thus identify possible predictors of Lp(a) levels, and (c) to assess the association between Lp(a) and family risk factors of atherosclerosis to identify children with a high adult CVD risk.

Materials and Methods

Details of the study population, design, survey method, and laboratory procedures have been described in detail elsewhere [14]. The key points are summarized below.

Recruitment of Participants

Subjects were recruited from the Slovak Lipid Community Study (2005–2007) aiming to evaluate risk factors for CVD in a biracial (Roma–Caucasian) population of children aged 7–18 years. In total, 331 Roma children (165 males and 166 females) and 276 Caucasian children (128 males and 148 females) fulfilled the inclusion criteria, i.e. absence of acute or chronic diseases, lipid-lowering medication, and had assayed Lp(a) concentration. Evaluation of race according to skin, eye and hair color, including antecedents, cultural traditions and language was used to identify Roma individuals.

Informed Consent and Ethical Approval

The study protocol was approved by the Institutional Ethics Committee (F.D. Roosevelt Faculty Hospital, Banská Bystrica), and informed consent was obtained from the parents or guardians of these children.

Laboratory Procedures

To measure serum lipids and apolipoproteins, venous blood samples were drawn after an overnight fasting. After clotting and centrifugation, sera were collected, frozen at -20°C , and shipped to the Central laboratory (F.D. Roosevelt Faculty Hospital). Here, all serum samples were analyzed in a few analytical runs after short-term storage freezing period to reduce systematic bias and interassay variation. Lp(a) concentration (in mg/dL) was determined by rate nephelometry technique on an Immage 800 System analyzer (Beckman-Coulter Inc., Fullerton, CA, USA) using a commercially available LPAX Lipoprotein(a) test (Immage, Beckman-Coulter) with particle-bound polyclonal rabbit anti-Lp(a) antibody. Within- and between-run precision was 3.4 and 5.7%, respectively. Total cholesterol, HDL cholesterol and triglyceride standardized enzymatic methods were performed on an Olympus AU2700 analyzer (Olympus Diagnostics Systems, Melville, NY, USA) as described in detail previously [14]. LDL cholesterol was calculated using a Friedewald formula [15]. Total apo B and apo AI concentration was measured by an immunonephelometric technique on an Immage 800 System analyzer (Beckman-Coulter) using the diagnostics of the same manufacturer.

Anthropometric Measurements

Anthropometric measurements of height, weight and blood pressure were made by trained health personnel. Height and weight were measured to the nearest 0.5 cm and 0.5 kg, respectively. Body mass index (BMI, kg/m^2) was used as a measure of overall body fatness. Age- and gender-specific cutoff points were used to assess the overweight and obesity status [16]. Blood pressure values were measured on the right arms of the subjects in relaxed, sitting position with mercury-gravity manometer, in mmHg. Mean arterial pressure (MAP, diastolic blood pressure $+ 0.33 \times$ pulse pressure) was used in analysis.

Questionnaire Data Collection

Information about age, sex, race, family income, cigarette smoking, physical activity, parental clinical risk factors, and family history of CVDs was gathered from interview questionnaires. Socio-economic status was represented by per capita income, received from salaries coming from regular or occasional jobs and social welfare support allowance. The households were divided in three income groups: less than 2.5 € per capita/day (poverty), up to 15 € per capita/day (standard) and more than 15 € per capita/day (high standard). Current smoking status was assessed quantitatively using the number cigarettes smoked weekly.

According to self-reported data, the average number of hours per week of different types physical activity, in school and free time, was calculated. Data concerning the alcohol consumption in children were unreliable, therefore they were omitted from the final analysis. Information regarding the family history of premature CVD (myocardial infarction, stroke and peripheral vascular disease) as well as obesity, hypertension and diabetes mellitus among relatives was also obtained.

Statistical Analysis

The PASW statistics 17.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. The difference in categorical variables was assessed by the Chi-square test. Student's *t* test and the Mann–Whitney test was used to compare the difference of means between the study groups. Spearman correlation analysis was performed in order to examine the relationship between variables. Logistic and linear regression analysis was used wherever necessary. Significance was accepted at $P < 0.05$, two-tailed.

Results

Baseline Characteristics of Studied Children

Baseline characteristics of Roma and Caucasian children at the time of blood sampling are summarized in Table 1. Roma children, compared to Caucasians, were slightly younger and much leaner, and had significantly lower values of MAP, without hypertension in both ethnic groups. By contrast, the proportion of persons who smoked and reported a very low level of physical activity was higher in Roma than in Caucasian neighbors. Levels of total cholesterol, triglycerides, LDL- and HDL-cholesterol, and apo B were similar in Roma and Caucasians, whereas apo AI levels were significantly higher in Roma than in Caucasians. Similarly, low family income and rates of family history of premature CVD or diabetes mellitus were also substantially higher among the relatives of Roma children.

Race-Specific Difference

The mean, median and selected percentiles of Lp(a) levels by race and gender are shown in Table 2. Overall, Roma children had markedly higher Lp(a) concentration than Caucasian children (median and range, mg/dL: 14.5; 0–159.2 vs. 6.2; 0–112.3, $P < 0.001$), especially in males (14.7; 0–125.6 vs. 5.1; 0–112.3, $P < 0.001$) than in females (14.1; 0–159.2 vs. 7.5; 0–108.6, $P = 0.002$), and among the older (12–18 years) (17.1; 0–125.1 vs. 7.2; 0–109.0, $P < 0.001$) than younger (7–11 years) age group (12.7;

0–159.2 vs. 5.5; 0–112.3, $P = 0.008$). The frequency distribution was highly positively skewed in both racial groups, reflecting the wide difference between the median and the mean values for each race-sex group (Fig. 1). Forty-three percent of the Caucasian children had Lp(a) concentrations < 5 mg/dL; in contrast, only 26% of Roma children fell into this category. The proportion of subjects with Lp(a) > 30 mg/dL was greater in Roma than in Caucasians, while the proportion of those with an undetectable levels of Lp(a) (less than 2 mg/dL) was significantly higher in Caucasian group (Caucasians, 25% vs. Roma, 13%, $P < 0.001$).

Age and Gender

To examine the age-related trends, the polynomial regression function (age³) was used (Fig. 2). The higher Lp(a) levels in Roma were already seen in the youngest children, especially among the females. Overall, the similar pattern of age-related changes in Lp(a) concentration was seen in both males and females. The levels of Lp(a) tended to increase in the younger children and to decrease in the older children, although with different age-related timing in both genders. However, the correlation analysis by age group showed that the poor age-related trend was significant only in older Roma males (14–18 years: $r = -0.338$, $P = 0.005$). No significant male–female difference in Lp(a) was seen in both racial groups, with males having higher values than females in the Roma and vice versa in the Caucasian population.

Correlates of Lp(a) with Anthropometric, Lipid and Lifestyle Data

Relations of Lp(a) to anthropometric, lipid and lifestyle data are presented in Table 3. Lp(a) levels were significantly positively associated with apo B in Roma (0.159, $P = 0.004$), and LDL cholesterol in Caucasian children (0.170, $P = 0.005$). For both race groups, no correlation was found between Lp(a) and BMI or MAP, respectively. Lifestyle data showed that only family income was significantly correlated with Lp(a) levels, but in opposite directions for Roma (-0.134 , $P = 0.036$) versus Caucasian children (0.136, $P = 0.047$). Only in Roma children, family income was positively associated with physical activity (0.331, $P < 0.001$) and negatively with smoking (-0.217 ; $P = 0.001$). In addition, gender per se had no considerable effect on the magnitude or direction of the correlation analysis (data not shown).

Table 4 shows the results of the final linear regression model for both race groups. Apo B, LDL cholesterol and family income, in that order, were the major factors that contributed to the explained variance ($\sim 7\%$) of Lp(a). Other covariates such as age, sex, BMI, smoking, and

Table 1 Baseline characteristics of the studied children

Characteristic	Roma	Caucasians	<i>P</i> value
Number of persons	331	276	0.007
Age (years)	12.4 ± 3.8	13.2 ± 3.8	
Body mass index (kg/m ²)	18.1 ± 3.8	19.7 ± 3.9	<0.001
% overweight or obesity	12.1	20.6	0.004
Mean arterial pressure (mmHg)	78.9 ± 9.5	82.6 ± 9.0	<0.001
Total cholesterol (mmol/L)	3.91 ± 0.73	3.93 ± 0.67	0.798
LDL cholesterol (mmol/L)	2.30 ± 0.56	2.32 ± 0.55	0.665
HDL cholesterol (mmol/L)	1.18 ± 0.27	1.19 ± 0.28	0.797
Triglycerides (mmol/L)	0.94 ± 0.49	0.95 ± 0.47	0.669
Apo AI (g/L)	1.27 ± 0.26	1.21 ± 0.22	0.009
Apo B (g/L)	0.70 ± 0.17	0.69 ± 0.17	0.281
% smokers	22.1	11.9	0.001
% physical activity < 2 h/week	79.5	57.2	<0.001
% income < 2.5€ per capita/day	58.0	9.1	<0.001
% family history of CVD	12.1	4.3	<0.001

The values for age, BMI, MAP and lipid analytes are mean ± standard error of deviation. Abbreviations as defined in text

Table 2 Serum lipoprotein(a) levels in Roma and Caucasian children stratified by sex

	<i>n</i>	Mean Lp(a) (mg/dL)	SD	Percentiles					>30 mg/dL (%)
				5th	25th	50th	75th	95th	
Roma*									
Males [†]	165	26.0	28.4	<2.0	5.3	14.7	35.8	94.2	33.9
Females [†]	166	23.6	26.3	<2.0	4.1	14.1	34.5	76.8	27.7
All	331	24.8	27.3	<2.0	4.8	14.5	34.9	85.9	30.8
Caucasians*									
Males [†]	153	15.4	22.8	<2.0	<2.0	5.1	15.9	69.1	17.6
Females [†]	123	18.5	23.6	<2.0	2.5	7.5	26.1	75.9	22.0
All	276	16.8	23.1	<2.0	<2.0	6.2	18.3	71.1	19.6

* Race difference (all children), *P* < 0.001

[†] Sex difference (all children), *P* = 0.471

Fig. 1 Frequency distribution of serum lipoprotein(a) in Roma and Caucasian children

physical activity contributed to a negligible extent to the observed variance of Lp(a).

Parental Risk Factors and Family History of CVD

The odds ratio (95%CI) for Lp(a) levels >30 mg/dL with identified parental risk factors and grandparental history of CVD is shown in Table 5. Parental risk factors were defined as hypertension (174 events), obesity (155), and diabetes mellitus (46). The parents, however, were too young to have sufficient myocardial events or stroke (before age of 55 years in a parent) for valid statistical analysis. In Roma, despite the significantly higher incidence of reported family risk factors and CVD mortality, we found no significantly increased risk between Lp(a) >30 mg/dL and any given parental clinical risk factor and family history for CVD. In contrast, the relationship between an increased

Fig. 2 Relation of serum lipoprotein(a) to age in children by race and sex, estimated by a polynomial regression model

Table 3 Spearman correlations of lipoprotein(a) with anthropometric, lipid, and lifestyle data in Roma and Caucasian children

Variable	Roma	Caucasians	Total
Age	0.105	0.017	0.048
Body mass index	−0.025	0.014	−0.054
Mean arterial pressure	0.086	0.039	0.019
Total cholesterol	0.101	0.149	0.130 ^b
LDL cholesterol	0.083	0.170 ^b	0.126 ^b
HDL cholesterol	0.055	0.061	0.059
Triglycerides	−0.049	−0.017	−0.045
Apo AI	0.052	−0.086	0.073
Apo B	0.159 ^a	0.120	0.166 ^b
Smoking	0.065	−0.046	0.036
Physical activity score	−0.114	0.038	−0.047
Family income	−0.136 ^a	0.133 ^a	−0.099 ^a

Statistical significance ^a $P < 0.05$; ^b $P < 0.01$

Lp(a) concentration in Caucasian children and diabetes mellitus of their parents was significant (odds ratio, 4.46; 95% CI 1.23–16.20). Furthermore, Caucasian children with three or more risk factors for CVD in their relatives had a risk

for Lp(a) >30 mg/dL four times greater (95% CI 1.10–14.60, $P = 0.040$) than those with neither or one parental risk factor.

Discussion

This study provides distribution and predictor variables of serum Lp(a), and its relationship to several family clinical risk factors for CVD in a biracial (Roma–Caucasian) population of children. The observed Roma excess of Lp(a) is consistent with previous data showing higher levels of Lp(a) both in adult native Asian Indians and Asian Indian immigrants around the world [5–7]. In these studies, median/mean Lp(a) levels were similar or to a high degree twice of those of Europeans, Caucasian Americans, and Australians. To our knowledge, there is no report of the Asian Indian–Caucasian difference on the Lp(a) levels in children. However, other Asian pediatric populations, for example Japanese, Chinese, and Korean, were investigated [17–19]. The medians of Lp(a) in these studies, which ranged from 7.5 mg/dL in Japanese to 11.9 mg/dL in Chinese females, were substantially lower than those obtained for Roma males and females in the present study.

Also the highly skewed distribution and the wide range of Lp(a) values in the studied children were not surprising because similar ranges and distributions have been previously reported for several Caucasian and Asian populations [3, 4, 19, 20]. These race-specific differences may be significantly determined by genetic factors. It is known that, in general, a strong inverse relationship exists between the size of the apo(a) isoforms and the Lp(a) concentrations [21]. In Asian Indians, however, only less than 35% (obviously 30–70%) of the variability of Lp(a) concentration was explained by the size heterogeneity of apo(a) [4].

It is postulated that Lp(a) levels are remarkably stable throughout the life of an individual. Data from the biracial (black–white) Bogalusa Heart Study have shown a slight rise of Lp(a) levels with increasing age in children aged 7–17 and also a weak positive association with the Tanner stage [22]. In contrast, no consistent association of age and

Table 4 Multivariate fitted regression model in predicting serum lipoprotein(a) levels by race

Roma ^a					Caucasians ^b			
	Regression coefficient	SE	<i>t</i>	<i>P</i> value	Regression coefficient	SE	<i>t</i>	<i>P</i> value
Constant	160.659	69.994	2.295	0.023	−193.693	92.734	−2.089	0.038
LDL-C					109.001	28.630	3.807	0.000
Apo B	273.965	89.367	3.066	0.002				
Income	−92.017	29.419	−3.128	0.002	53.017	33.708	1.573	0.117

^a R -square = 6.3% (adjusted R -square = 5.8%)

^b R -square = 7.8% (adjusted R -square = 6.9%)

Table 5 Prevalence odds ratio for association between Lp(a) >30 mg/dL and risk factors for CVD among first- and second-stage relatives

Risk factor	Roma Odds ratio (95%CI) ^a	<i>P</i> value	Caucasians Odds ratio (95%CI)	<i>P</i> value
Parents				
Obesity	0.65 (0.35–1.20)	0.167	0.81 (0.39–1.71)	0.583
Hypertension	0.91 (0.52–1.61)	0.751	1.05 (0.49–2.26)	0.920
Diabetes mellitus	0.95 (0.42–2.14)	0.887	4.46 (1.23–16.20)	0.028
Grandparents				
Myocardial infarction	0.65 (0.24–1.81)	0.410	2.45 (0.68–8.80)	0.234
Stroke	1.63 (0.52–5.08)	0.529		

^a Adjusted for age, gender, BMI, LDL cholesterol, and apo B

gender with Lp(a) was found in subjects below age 20 in a large-scale multiethnic NHANES survey [23].

The present study reveals a great variation in the age–sex specific levels of the Lp(a) in children of both populations. However, we observed an apparently universal pattern of a progressive rise, and a remarkable fall in mean values of Lp(a) by age from the early childhood to adolescent males. In contrast, an early shortlived rise, a comparable decline, and a subsequent rise during puberty (only in Caucasians) was found in females. Observed no significant gender difference in Lp(a) levels is consistent with findings reported by several studies [23–25], but not by others demonstrating significantly higher Lp(a) values in females [19, 22, 26]. Further research is required to link the evidence concerning the effect of sex hormones on the Lp(a) metabolism in prepubertal and pubertal children. We should note that apo(a) synthesis, although still in the transgenic mice model, may suppress not only estrogen but testosterone as well [27].

Positive correlations of Lp(a) with apo B and LDL cholesterol in Roma and Caucasian children, respectively, corresponded with previous data, including our own, showing higher Lp(a) levels in subjects with hypercholesterolemia [19, 24, 28]. The fact that Lp(a) and LDL have a common synthetic pathway is likely to be an explanation for the positive association of Lp(a) and LDL cholesterol. Furthermore, Lp(a) cholesterol is a significant component of serum cholesterol and apo B occurs as a basic structural compound in the Lp(a) particle [1, 29].

In developed countries, the lower socioeconomic status groups tend to have a worse lipid risk profile (data on the Lp(a) are scarce) and higher CVD mortality than the better off [30]. Socioeconomic status is a major determinant of health, lifestyle and health-related behaviour, sufficient quantities of food and quality of nutrition, and opportunities for education [11]. In one from a few Asian studies, the socioeconomic status did not have a consistent influence on the Lp(a) levels in evenly earner stratified ethnic Chinese Taiwan population [24].

Interestingly, in this study, we found race differences in the relationship between Lp(a) levels and household income. Roma children from low income families had often under-weight, lower BMI and low rate of physical activity, and higher prevalence of smoking. In conformity with some former reports [31–33], these characteristics were associated with higher levels of Lp(a) which is reflected in the negative relationship between Lp(a) and family income. Furthermore, it has been repeatedly observed that Slovak Roma have an elevated consumption of cheap, fatty pork meat, animal fats, white bread, sweets, and soft drinks [34]. These findings, along with excessive smoking can contribute to obesity, CVD, and cancer in the adult Roma population. The reason for the reversed trend between Lp(a) and income of households found in our Caucasian children remains unclear. Future studies would attempt to take into consideration the ramifications of income, education, physical activity, and dietary intake in both populations.

Multiple regression analysis was used to assess possible non-genetic predictors of Lp(a) levels. Apo B and LDL cholesterol, sometimes triglycerides, insulin resistance, and smoking, but not daily income, are often listed as independent variables in predicting Lp(a) concentration [19, 20, 24]. It is possible that the relationship between Lp(a) and daily income, observed in our study, may be a random cohort-effect phenomenon. In Slovakia, however, the Roma community constitutes the poorest and most uneducated part of the general population, with limited job opportunities. In general, little of the variability in Lp(a) levels was explained using these models, indicating that Lp(a) levels are mainly determined genetically.

Contradictory findings have been published regarding the relationship between increased Lp(a) levels and the risk of contracting CVD. Our observations of no significant relation of high Lp(a) in children to family cardiovascular events are consistent with findings of some studies [17, 35], but not in others [18, 20, 23, 25]. Although the reasons for these contrasting findings remain unclear, different experimental designs, different numbers and characteristics of recruited

subjects, different CVD outcomes, ethnical differences, and lack of standardized methods for Lp(a) determination might at least in part explain the discrepancies among the studies. Relating to parental risk factors, only diabetes mellitus was an independent predictor of Lp(a) >30 mg/dL in Caucasian children. Furthermore, Caucasian children whose family members reported having three or more clinical risk factors for CVD had a higher concentration of Lp(a) than those whose relatives had one or no risk factors, as shown by a certain study examining young French children of Caucasian origin [36].

Our study had several potential limitations. There was a cross-sectional analysis of existing data, which hampers discussion on cause and effect. Furthermore, the sample size may have been relatively small, particularly when the population sample was subdivided into more groups. A major limitation, however, was a relatively low number of reported premature cardiovascular events for each race, which may limit the validity of the study.

Conclusion

Results from the study suggest a race-specific difference in Lp(a) levels, with higher concentrations of Lp(a) in Roma than in Caucasian children. A range of potential non-genetic predictors of Lp(a) levels explained little of the variance in Lp(a) levels. Even though the absence of significant association between higher Lp(a) levels in the Roma children and family risk factors for CVD in this study, an increased Lp(a) levels may be considered as important cardiovascular risk factor for this race group. Further prospective studies are needed to elucidate the relationship between Lp(a) levels and CVD among different Roma subgroups in Slovakia and other European countries.

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Conflict of Interest There is no conflict of interest.

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