ORIGINAL ARTICLE

Lipoprotein(a) Levels in Children and Adolescents: Ouro Preto Study

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Abstract

Background: Lipoprotein (a) is a cardiovascular risk factor in adult. Studies have shown the presence of this emergent risk factor in school children, which may contribute to the development of atherosclerosis in adulthood.

Objective: To evaluate the association between lipoprotein (a) and cardiovascular risk factors in school children.

Methods: Lipoprotein (a) levels were measured in 320 school children (6-14 years) selected from a population survey carried out in Ouro Preto (southeast of Brazil). Demographic (sex and age), biochemical (total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, and glucose), anthropometric (body mass index, waist circumference, body fat percentage), clinical (arterial blood pressure, pubertal stage and birth weight) and economic (family income) parameters, as well as family history (obese and/or hypertensive parents) were analyzed. Non-parametric analysis was used to evaluate lipoprotein (a) levels in each subgroup. Variables with $p \leq 0.20$ in the univariate analysis were included in binary regression logistic model. Differences with $p < 0.05$ were considered significant.

Results: Lipoprotein (a) levels were associated with total cholesterol (p=0.04), body fat (p=0.009), and mother´s systolic (p=0.02) and diastolic blood pressure (p=0.04). In a logistic regression analysis, children with high lipoprotein (a) levels and body fat, and children born from hypertensive mothers were, respectively, at 3.2(p=0.01) and 1.4 (p=0.03) times higher risk than other children. In clustering these factors, elevated lipoprotein (a) was 2.6 times more likely to be seen in school children with high body fat and born hypertensive mothers.

Conclusions: Lipoprotein (a) was correlated with cardiovascular risk factors in children and adolescents. Persistence of these risk factors in childhood suggests a contribution of elevated lipoprotein (a) to future cardiovascular disease. (Int J Cardiovasc Sci. 2021; 34(1):10-18)

Keywords: Children; Adolescents; Lipoproteins; Cholesterol; Hypertension; Body Mass Index; Adiposity; Bod Fat; Epidemiology.

Introduction

The high prevalence of cardiovascular diseases and associated risk factors has led to increased morbidity and mortality in various countries, including Brazil.[1] In many cities of Brazil, including Ouro Preto (Southern Brazil), cardiovascular diseases are the main cause of mortality and the second highest cause of hospitalization among adults aged 20 years or older.[1] Classical risk factors, such as high blood pressure, diabetes mellitus, dyslipidemia and obesity have been detected among children, adolescents,[2] and young adults, and may lead to cardiovascular diseases in adult life. In addition, these risk factors are associated with emerging risk factors, such as increased lipoprotein (a) levels, contributing to the process of atherosclerosis in childhood and adolescence.[3-5] Although the mechanisms by which lipoprotein (a) promotes atherosclerosis are not clearly understood, proposed mechanisms include increased lipoprotein (a)-associated cholesterol in the arterial

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intima, inflammatory cell recruitment, presence of proinflammatory oxidized phospholipids, impairment of fibrinolysis by inhibition of plasminogen activation, and enhancement of coagulation by inhibition of the tissue factor pathway inhibitor.[5] Studies have demonstrated an association of lipoprotein (a) with cardiovascular risk factors in children and adolescents, especially among those with a family history of cardiovascular diseases.[6,7] In a previous study in Ouro Preto city, it was observed that in the adult population, lipoprotein (a) levels were associated with ischemic heart disease and a high Framingham risk score.[8] The purpose of the present study is to evaluate whether serum lipoprotein (a) levels are associated with cardiovascular risk factors in a Brazilian paediatric population living in Ouro Preto.

Materials and Methods

A cross-sectional survey was conducted in Ouro Preto city (Brazil) among school children, chosen by simple random selection and stratified by age and gender, in all public (n=14) and private (n=2) schools of the city. Lipoprotein (a) was analyzed in 320 subsamples of the cross-sectional study. As a criterion for non-inclusion, children with special needs were not evaluated in this study. Participation in the study was entirely voluntary. Child's consent and signed informed consent from the parents or legal guardians of each participant were obtained before the study.

Data were collected by a team of trained research assistants from March to December 2006. The following variables were included: demographic (sex and age); biochemical (levels of total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, and glucose); anthropometric (body mass index [BMI], waist circumference, and body fat percentage); clinical (arterial blood pressure, pubertal stage, and birth weight); physical activity (active and inactive); socioeconomic status (family income); and family history (obese and/or hypertensive parents).

Blood samples were collected via venipuncture after overnight fasting (12h). The samples were analysed by enzymatic-colorimetric assays using commercial kits (In Vitro Diagnóstica, Itabira, MG, Brazil) and an Airone 200 analyser (Crony Instruments, Rome, Italy). Lipid and fasting glucose levels were classified in accordance with the Brazilian Society of Cardiology[9] and the Brazilian Society of Diabetes[10] criteria, respectively. Apolipoprotein (a) values (units/L) were determined using the ELISA method (Mercodia In, Upsala, Sweden). Lipoprotein (a) levels were obtained by the conversion method suggested by the manufacturer: 1 unit of apo(a) is approximately equal to 0.7 mg lipoprotein (a) protein. This assay is very sensitive and highly specific and produces no measurable cross-reactivity with plasminogen and apolipoprotein B; in addition, it minimizes the possible interference of heterogeneity in apo(a) isoforms in the results; the detection limit is 0.0035 mg/dL; the overall coefficient of variation for lipoprotein (a) measurements in this study was 5.3%. Serum aliquots were stored at -80°C until analysis.

Weight was determined using a Tanita BF542® scale (Tanita Corporation of America, Arlington Heights, IL, USA), while height was determined using a WCS® stadiometer (Cardiomed, Curitiba, Brazil). Waist circumference was measured midway between the lowest rib and the iliac crest. In the absence of national reference values, the 90th percentile of the distribution was used to identify individuals at risk, considering their gender and age. The BMI for children and teenagers, which is gender and age specific, was defined according to the World Health Organization criteria.[11] Body fat was estimated with the bipolar foot-to-foot bioelectrical impedance technique using the Tanita BF542® scale and the tetrapolar bioelectrical impedance technique by Quantum II® BIA-T(RJL Systems Inc., Michigan, USA). Reference values for body fat percentage were defined as 25% for boys and 30% for girls, in accordance with Williams et al.[12] To assess subcutaneous fat, the skinfold thickness at the following sites was measured: suprailiac, subscapular, triceps, and biceps, using Cescorf® skinfold callipers (Cescorf Inc., Porto Alegre, Brazil). All measurements were obtained in triplicate on the right side of the body by a team of trained technicians. The average of the three measures taken from each site was calculated, and equations were used to predict the fat percentage, as proposed by Deurenberg et al.[13] Body fat percentage was defined in accordance with Lohman et al.[14]

Arterial blood pressure was measured three times at 10-min intervals using an Onrom 705CP® blood pressure monitor (Onrom Healthcare, Kyoto, Japan) while the children were sitting down with their left arm at the level of the heart. When mean values of blood pressure exceeded the 90th percentile, measurements were repeated with auscultation. The blood pressure range was classified by age, sex, and height percentiles. A systolic and/or diastolic blood pressure ≥90th percentile was classified as hypertension risk.[15]

Pubertal stage was determined based on Tanner's criteria and assessed using a self-report questionnaire: prepubertal (1–2 Tanner stage), pubertal (3–4 Tanner stage) and postpubertal (5 Tanner stage).

Information concerning birth weight, physical activity, and socioeconomic status was obtained from the participants and their parents or legal guardians by face-to-face interviews. Birth weight was initially self-referred and further checked by telephone for those parents or guardians who could not remember; cross verification was performed using the child's birth control card. School children were considered physically inactive sedentary if they performed less than 300 min/week of physical activity.[16] Sedentary activities included watching television, playing video games, and sitting in front of the computer for more than 2 h a day.[17] Family income was based on the Brazilian minimum wage at the time of the study (US$230/month).

The BMI and blood pressure values of the progenitors (father and mother) were analysed in accordance with the guidelines established by the World Health Organization[18]and the Brazilian Society of Cardiology,[15] respectively.

Statistical analysis

Non-parametric analysis (Wilcoxon and Kruskal-Wallis test) was used to evaluate statistically significant differences in lipoprotein (a) levels (non-normal distribution) between each category of the demographic (gender, age, pubertal stage, skin color), economic (familiar income), anthropometric (body mass index, waist circumference, body fat by skinfold thickness, bipolar body fat, tetrapolar body fat, mother's/father´s BMI), biochemical (LDL-c, total cholesterol, HDL-c, triglycerides, fasting glucose), life style (physical activity, sedentary habits) and clinical parameters (systolic and diastolic blood pressure, mother's/father´s systolic and diastolic blood pressure, weight at birth) using median and interquartile range levels to guide interpretation. For binary logistic regression analysis, associations between lipoprotein (a) (above and below median) and each category of independent variables were assessed. Variables with p≤0.20 in the univariate analysis were included in binary regression logistic model. The analysis was carried out using the SPSS software (version 20.0; SPSS Inc, Chicago, IL, USA). Differences between values were considered statistically significant for p-values < 0.05.

This study was approved by the Institutional Review Board of the Federal University of Ouro Preto (Protocol Number 2004/46).

Results

The total sample was composed of 320 individuals, 49.1% (n=157) girls, with a mean age of 10.4±2.4 years. Lipoprotein (a) exhibited an asymmetrical distribution in this population, with a mean ± standard deviation of 33.7±27.6mg/dL, and median of 25.5mg/dL. Lipoprotein (a) levels above 30mg/dL and null values occurred in approximately 43.8% and 2.5% of the individuals, respectively. Table 1 presents median/range the lipoprotein (a) levels by demographic and economic variables. No significant difference was found in lipoprotein (a) serum levels between these subgroups.

Table 1 - Lipoprotein(a) levels by demographic and economic variables

Variables	n	Median / range	p*
Gender			0.24
Female	157	26.1 / 107.2	
Male	163	24.7 / 106.6	
Age (years)			0.25
6-9	126	24.2 / 107.2	
10-14	194	26.0 / 106.6	
Pubertal Stage			0.37
Pubertal	145	23.3 / 105.1	
Prepubertal	100	27.4 / 107.2	
Postpubertal	75	25.9 / 106.6	
Skin color			0.55
White	50	21.7 / 98.5	
Mixed race	248	25.7 / 107.2	
Black	12	35.3 / 85.2	
Family Income†			0.25
>4	29	22.1 / 95.4	
1-4	228	24.9 / 107.2	
<1	26	42.7 / 101.8	

** Kruskal Wallis test; † Based on the minimum wage (MW)*

Table 2 presents median (range) of lipoprotein (a) levels by biochemical and clinical variables. Non-significant associations were found for lipoprotein (a) levels and low-density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, or fasting glucose. However, in children with a high range of total cholesterol, lipoprotein (a) levels [38.7mg/dL (106.6)] were significantly higher than those in individuals with normal and moderate total cholesterol levels [24.3mg/dL (102.3) and 20.3mg/dL (107.2), respectively]. Lipoprotein (a) levels did not vary significantly with changes in clinical variables, or changes in systolic (p=0.17) and diastolic blood pressures (p=0.68). Additionally, no associations were observed between lipoprotein (a) levels and weight at birth (p=0.46).

In Table 3, no associations of lipoprotein (a) levels with BMI, waist circumference, or body fat measured by skinfold thickness were found. However, lipoprotein (a) levels were significantly higher in school children with excess weight [31.2mg/dL (107.2)] than in those with normal body fat [24.5mg/dL (106.6)]. Furthermore, median lipoprotein (a) levels were higher in individuals with excess weight, as measured by tetrapolar methods, than in individuals with normal weight [22.9mg/dL (107.2) and 38.6mg/dL (105.1), respectively]. No associations were observed between lipoprotein (a) levels and sedentary habits (p = 0.77). However, a consistent upward trend in lipoprotein (a) levels was observed in sedentary school children [26.0 mg/dL (107.2)] in comparison with active individuals [21.8 mg/dL (106.6)].

Table 4 presents lipoprotein (a) levels by family variables. There was no association between lipoprotein (a) levels of school children and blood pressure of their fathers, although this result may be unreliable because many fathers did not allow measurement of their blood pressures. Similarly, there was no association between lipoprotein (a) levels and familial BMI. However, lipoprotein (a) levels were significantly higher in children born from mothers with high systolic (p=0.02) and diastolic (p=0.04) blood pressure than in those with normotensive mothers.

In a logistic regression analysis adjusted by sex and pubertal stage, it was observed that lipoprotein (a) levels vary significantly in school children with high body fat measured by tetrapolar technique (p=0.01) and those whose mothers had elevated systolic blood pressure (p = 0.03). High lipoprotein (a) levels amongst

Table 2 - Lipoprotein(a) levels by biochemistry and clinical variables

Variables	n	Median / range	p*
LDL-c (mg/dL)			0.19
<100	233	23.3 / 107.2	
100-129	69	38.6 / 106.6	
≥ 130	18	22.8 / 91.9	
Total Cholesterol (mg/dL)			0.04
<150	139	24.3 / 102.3	
150-169	79	20.3 / 107.2	
≥ 170	102	38.7 / 106.6	
HDL-c (mg/dL)			0.73
≥ 45	278	25.5 / 107.2	
< 45	42	25.6 / 102.3	
Triglycerides (mg/dL)			0.71
<100	286	25.2 / 107.2	
100-129	34	29.0 / 102.3	
Fasting glucose (mg/dL)			0.70
<110	316	25.5 / 107.2	
≥110	4	32.3 / 95.1	
Systolic blood pressure (percentile)			0.17
< 90	294	26.1 / 106.6	
≥ 90	16	21.2 / 44.2	
Diastolic blood pressure (percentile)			0.68
< 90	298	26.0 / 106.6	
≥ 90	12	22.8 / 41.8	
Weight at birth (g)			0.46
≥ 2,500	208	21.7 / 101.1	
< 2,500	48	35.5 / 104.0	

** Kruskal Wallis test*

Table 3 - Lipoprotein(a) levels by anthropometric and lifestyle variables

Variables	n	Median / range	p*
Body mass index (percentile)			0.30
85	266	24.8 / 107.2	
≥ 85 < 95	39	28.9 / 102.4	
≥ 95	15	27.4 / 86.6	
Waist circumference (percentile)			0.83
≤ 50	214	25.2 / 107.2	
> 50 < 75	53	24.3 / 81.0	
≥ 75< 90	27	31.8 / 95.4	
≥ 90	24	25.4 / 97.9	
Body fat by skinfold thickness (%)			0.26
≤20† , ≤25‡	250	25.1 / 107.2	
20.1-25 † , 25.1-30‡	47	28.9 / 105.1	
>25.1† , >30.1‡	23	26.1 / 67.8	
Body fat (%)			0.05
≤25† , ≤30‡	231	24.5 / 106.6	
>25† , >30‡	87	31.2 / 107.2	
Tetrapolar body fat (%)			0.009
≤25† , ≤30‡	248	22.9 / 107.2	
>25† , >30‡	69	38.6 / 105.1	
Physical activity (min/week)			0.07
≥ 300	58	21.8 / 106.6	
< 300	226	26.0 / 107.2	
Sedentary habits (h/week)			0.77
< 2	36	26.8 / 95.4	
> 2	280	25.3 / 107.2	

** Kruskal Wallis test, † boys, ‡ girls*

Table 4: Lipoprotein(a) levels by family variables

Variables	n	Median / range	p*
Mother's systolic blood pressure (mmHg)			0.02
<130	156	20.7 / 105.1	
≥130-139	34	20.4 / 97.9	
≥140	83	28.9 / 107.1	
Mother's diastolic blood pressure (mmHg)			0.04
<85	132	20.1 / 101.1	
≥85-89	34	36.2 / 105.1	
≥90	107	26.1 / 107.2	
Father's systolic blood pressure (mmHg)			0.42
<130	44	19.2 / 105.1	
≥130-139	30	32.1 / 97.5	
≥140	74	30.1 / 102.3	
Father's diastolic blood pressure (mmHg)			0.22
<85	47	19.2 / 105.1	
≥85-89	29	24.3 / 98.5	
≥90	60	35.4 / 99.9	
Body mass index (Kg/m²)			0.76
<24.9	123	23.0 / 100.2	
≥25.0-29.9	96	24.8 / 100.2	
≥30.0	71	28.9 / 107.2	

** Kruskal Wallis test*

children with high body fat and born from currently hypertensive mothers were, respectively, 3.2 and 1.4 times higher than those of subjects not included in these categories (data not shown). In clustering higher tetrapolar body fat and mother´s systolic blood pressure, we observed that school children with high

body fat, born from hypertensive mothers and those with the two characteristics were 2.7 times, 2.3 times and 2.6 times more likely to have elevated lipoprotein (a) levels compared with normal children (Table 5).

Discussion

In our study, lipoprotein (a) distribution was skewed, with a high frequency of null (2.5%) or low values among children living in Ouro Preto, similar to that observed in the adult population[8] and that reported in another study.[7] This study showed an association of lipoprotein (a) with anthropometric, biochemical and behavioral data, as well as with the progenitors. Serum levels of lipoprotein (a) were not independent predictors of cardiovascular risk factors, but were associated with body fat and the mother's systolic blood pressure.

In contrast to some studies,[19,20] in our study, lipoprotein (a) levels were not associated with any demographic variables. Pubertal stage seems to influence lipoprotein (a) levels. Chen et al.[20]analysed 314 same-sex Chinese twin pairs aged 5–18 years and observed that lipoprotein (a) increased after the onset of puberty and was significantly higher in girls than in boys.

Although we did not find significant associations regarding skin color, this study contributes to the existing literature, in terms of the peculiarities of lipoprotein (a) distribution in a mixed paediatric population. Several studies have shown that lipoprotein (a) levels are higher in blacks than in whites.[21] Unlike the studies conducted in well-defined racially segregated populations, our study was conducted in Ouro Preto city, which has a mixed Brazilian population, including individuals with black ancestry. The reason for this racial difference between lipoprotein (a) levels has not been found. More studies are needed to clarify the influence of mixed race on lipoprotein (a) levels in children and adolescents.

As with other studies, we observed only a significant association between lipoprotein (a) and total cholesterol levels. Dirisamer et al.[13]analysed lipoprotein (a)levels and apo(a) isoforms in children and adolescents with familial hypercholesterolemia and observed that 46% of these individuals had higher lipoprotein (a) levels and lower apo(a) isoform levels than the control group. They concluded that elevated small-isoform lipoprotein (a) levels might be a strong and independent cardiovascular risk factor in hypercholesterolemic children and adolescents. An increase in lipoprotein (a)-associated cholesterol in the arterial intima can trigger mechanisms that lead to atherothrombosis.[5] In childhood, the role of lipoprotein (a) in the onset of atherosclerosis is uncertain. Weigmanet al.[22] have shown that elevated lipoprotein (a) in children with familial hypercholesterolemia is predicative of a parent with premature cardiovascular disease risk. However, Sirachainanet al.[23]demonstrated that lipoprotein (a) levels did not differ between children with thromboembolism and controls. In our study, we expected to find an association between low density lipoprotein-cholesterol and lipoprotein (a), since the dyslipidemic adults of Ouro Preto city, and likely children and adolescents with dyslipidemia,

Table 5 - Distribution of lipoprotein(a) levels by the combined variables: tetrapolar body fat and mother´s systolic blood pressure

Variables		Lipoprotein (a) (mg/dL)		Odds ratio (IC 95%)	p*
Tetrapolar body fat (%)	Mother's systolic blood pressure (mmHg)	< 25.5 *n*	>25.5 *n*		
≤ 25† , ≤30‡	< 130	92	54	1	
> 25† , >30‡	< 130	13	21	2.7 (1.20 – 6.38)	0.01
≤ 25† , ≤30‡	≥ 130	27	37	2.3 (1.23 – 4.45)	0.008
> 25† , >30‡	≥ 130	10	15	2.6 (0.99 – 6.64)	0.05

** Pearson's X^2 test, † boys, ‡ girls.*

have higher frequency of ApoE4 and lower frequency of ApoE2.[24] However, research has shown isolated hyperlipoproteinemia(a) in the presence of normal low-density lipoprotein-cholesterol.[25] More research is needed to answer these questions in children and adolescents.

Our study verified that lipoprotein (a) levels were higher in school children with higher body fat than in school children with normal body fat. After adjusting for age, pubertal stage, cigarette smoking, and alcohol drinking, Chu et al.[26] showed that low-density lipoprotein-cholesterol, Apo B and Apo A were significantly associated with lipoprotein (a) levels, while BMI and waist circumference had no significant correlation. This demonstrated that the association of lipoprotein (a) with other blood lipids was more important than with anthropometric parameters. Of particular importance in this analysis is the evidence that BMI is not a specific anthropometric measurement for determination of body fat,[27] and thus is not the ideal index to evaluate the association between lipoprotein (a), obesity, and cardiovascular diseases. The role of obesity in lipoprotein (a) levels should not be underestimated. Moreover, the location of body fat deposits seems to be especially important in predicting changes in lipid metabolism[28] and consequently, in lipoprotein (a) levels.

Clinical variables such as birth weight, and sedentary habits are not correlated with lipoprotein (a) levels, in contrast to the findings of Cunningham et al.[4] In agreement with Taimela et al.,[29] we observed that school children who performed less than 300 min of physical activity per week had consistent upward trend in lipoprotein (a) levels than those who were physically active. Physical activity must influence lipid parameters[30] and may consequently modify lipoprotein (a) levels.

A family history of cardiovascular diseases is a risk factor associated with lipoprotein (a) levels in children and adolescents.[6,31] In our study, we observed that high arterial blood pressure in the mother is predictive of elevated lipoprotein (a) levels. In a logistic regression analysis, lipoprotein (a) levels vary significantly in school children with high body fat and those whose mothers had elevated systolic blood pressure. We suggest that the presence of familial risk factors for cardiovascular diseases, as well as high body fat or both, may be predictive of elevated lipoprotein (a) levels in children and adolescents.

Our study had some limitations. First, despite the non-parametric analysis, the limited number of subjects in some of the subgroups may have influenced the results. Further studies are needed to identify these possible associations. Second, we did not assess apo(a) isoforms. Apo(a) isoform size is inversely correlated with lipoprotein (a) concentration,[5] and low-molecular-weight apo(a) patterns have been reported as independent risk factors for atherosclerosis.[6,19] Therefore, the evaluation of the apo(a) genotype would have allowed a better understanding of the biological relationship between lipoprotein (a) and risk factors. Lipoprotein (a) was defined by median levels. The values obtained were similar to the age-dependent reference values established by Langer et al.[32]

This study is in agreement with reports by Ferrettiet al.,[5] and Cunningham et al.,[4] who suggested that lipoprotein (a) should be measured once in all subjects at risk for cardiovascular diseases and that this screening should begin in childhood.

Conclusion

Measurement of serum lipoprotein (a) levels in children and adolescents with familial hypertension and obesity might be a useful tool for identifying patients at increased cardiovascular risk. This practice will enable more effective preventative actions against cardiovascular diseases.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal de Ouro Preto* under the protocol number 2004/46. All the procedures in this study were in accordance with the 1975 Helsinki Declaration,

updated in 2013. Informed consent was obtained from all participants included in the study.

Author Contributions

Conception and design of the research: Cândido APC, Machado-Coelho GLL. Acquisition of data: Cândido APC, Mendonça-Mendes A, Cândido DRC, Roney LC Nicolato RLC. Analysis and interpretation of the data: Cândido APC, Mendonça-Mendes A, Cândido DRC, Nicolato RLC, Machado-Coelho GLL. Statistical analysis: Cândido APC, Machado-Coelho GLL. Obtaining financing: Machado-Coelho GLL. Writing of the manuscript: Cândido APC, Cândido DRC, Nicolato RLC, Machado-Coelho GLL. Critical revision of the manuscript for intellectual content: Cândido APC, Mendonça-Mendes A, Machado-Coelho GLL.

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