Similar Myocardial Perfusion and Vascular Stiffness in Children and Adolescents with High Lipoprotein (a) Levels, in Comparison with Healthy Controls

Kyriaki Papadopoulou-Legbelou^a Areti Triantafyllou^b Olga Vampertzi^a
Nikolaos Koletsos^b Stella Douma^b Efimia Papadopoulou-Alataki^a

^a4th Department of Pediatrics, School of Medicine, "Papageorgiou" General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; ^b3rd Department of Internal Medicine, School of Medicine, "Papageorgiou" General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Keywords

Lipoprotein (a) · Subclinical atherosclerosis indices · Subendocardial variability ratio · Children

Abstract

Background and Aims: This study investigated the possible correlation between elevated lipoprotein (a) (Lp(a)) levels and early vascular aging biomarkers in healthy children and adolescents. **Methods:** Twenty-seven healthy children/adolescents, mean age 9.9 ± 3.7 years, with high Lp(a) levels without other lipid abnormalities and 27 age- and sex-matched controls with normal Lp(a) levels, were included in the study. The investigation of possible early vascular aging was assessed by measuring vascular function indices: carotid intima-media thickness (c-IMT), pulse wave velocity (PWV), augmentation index (AIx), and subendocardial viability ratio (SEVR). **Results:** Although serum lipid values were within normal levels, mean values of total cholesterol and apolipoprotein B were higher in the group of children with high Lp(a) levels than controls ($p = 0.006$ and $p < 0.001$, respectively). Vascular function indices did not show significant differences, neither between the 2 groups nor in the subgroups of children with increased Lp(a) levels. These subgroups

were defined by the presence or absence of family history of premature coronary artery disease. Lp(a) levels did not show a significant correlation with the other parameters studied, both regarding the whole sample (patients and controls), as well as in the subgroups of elevated Lp(a) levels. However, in the group of children with high Lp(a) levels, c-IMT and PWV were positively correlated with diastolic blood pressure ($r = 0.427$, $p = 0.026$ and $r = 0.425$, $p = 0.030$, respectively), while SEVR was negatively correlated with AIx ($r = -0.455$, $p = 0.017$). **Conclusions:** Healthy children and adolescents with high Lp(a) levels do not yet have impaired vascular indices, compared to controls. However, in order to prevent early atherosclerosis, it is crucial to early identify and follow up children with high Lp(a) levels and positive family history of premature coronary disease or other cardiovascular risk factors.

© 2021 S. Karger AG, Basel

Introduction

Dyslipidemia is a known risk factor associated with premature atherosclerotic cardiovascular disease (CVD) [1]. In addition, elevated lipoprotein (a) levels (Lp(a))

have been identified as an independent risk factor for CVD in adults, but also in children with a positive family history [1].

Elevated plasma Lp(a) has been related to coronary artery disease (CAD) and stroke in the offspring of parents with familial hypercholesterolemia (FH), and vice versa, children 3–18 years old with a parental or grandparental history of premature CAD have 2–3 times higher Lp(a) levels than children with negative family history [2].

Although the mechanisms of elevated Lp(a) levels in FH are still unclear, there is a genetic evidence that Lp(a) is the strongest risk factor for CAD [3]. Lp(a) levels stabilize at 2 years of age, remain constant throughout life, and may help to identify families with an increased risk of CAD [2].

The association of high Lp(a) levels with increased CVD risk is continuous, without dependence on other cardiovascular risk factors. However, when high Lp(a) levels are combined with high LDL-cholesterol (LDL-C) or triglyceride (TG) levels and/or low HDL-cholesterol (HDL-C) levels, the risk of early CAD is markedly increased [4]. In addition, when other atherosclerosis-promoting risk factors coexist, such as obesity, hypertension, and diabetes mellitus, the risk of early atherosclerosis also increases significantly [2].

Lp(a) accumulates in the arterial wall of adults with early atherosclerosis [5]. The risk is strongest before the age of 45 years and declines after the age of 55 years [2].

Early diagnosis of subclinical atherosclerosis is mandatory, especially in high-risk groups. There are several indices of subclinical atherosclerosis, such as carotid intima-media thickness (c-IMT) and arterial stiffness markers, that have been associated with increased cardiovascular risk in adults [6, 7].

With regard to childhood, increased c-IMT has been observed in children with hypercholesterolemia, diabetes mellitus type 1, hypertension, and obesity [8]. Furthermore, studies in children suffering from FH showed increased c-IMT and arterial stiffness markers [9–11] or endothelial dysfunction [9, 12].

In addition, subendocardial viability ratio (SEVR), a new index of myocardial oxygen supply and demand, has been proposed as a measure of microvascular myocardial perfusion. In adults, lower values of SEVR are indicative of low perfusion in the subendocardium. Moreover, reduced values of SEVR have been found in adult patients with cardiovascular risk factors and have been associated with subclinical vascular damage, such as arterial stiffness [13]. However, SEVR has not yet been investigated, neither in children without CVD nor in children with elevated

Lp(a) levels or other serum lipid abnormalities. The aim of the present study was to investigate whether all above-mentioned early functional and structural vascular changes occur in healthy children and adolescents with high Lp(a) levels, using noninvasive early vascular aging biomarkers.

Materials and Methods

A total of 54 healthy children and adolescents, from January 2018 to December 2019, were enrolled in the study. Twenty-seven of them, 17 boys (mean age of 9.9 ± 3.7 years) had elevated Lp(a) levels, with normal levels of other serum lipids. The exclusion criteria for the study were the presence of abnormal lipid profile (except Lp(a)), hypertension, obesity, acute infection or chronic disease, autoimmune diseases, renal, hepatic, or thyroid disease, as well as the administration of any medication.

The control group consisted of 27 healthy age- and sex-matched controls (17 boys), with the mean age of 9.7 ± 3.0 years. They had volunteered or came from those who had attended the general pediatrics outpatient clinic of a tertiary care hospital. Acute or chronic disease, obesity, dyslipidemia, hypertension, and family history of dyslipidemia, hypertension, or premature CAD were the exclusion criteria for the control group. Parents of all participants (patients and controls) were asked if their children were born with assisted reproduction techniques (in vitro fertilization or intracytoplasmic sperm injection), as these techniques may adversely affect Lp(a) levels [14].

After a complete physical examination, blood pressure (BP) was measured using a validated oscillometric device (ProCare 300; General Electric, USA). The patient was placed in a sitting position for at least 3–5 min, and the measurements were made with the appropriate cuff size (40% of arm circumference) and length (80–100% of arm circumference). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured 3 times, with an interval of 3 min, and the average value of the last 2 was recorded. All measurements were estimated according to ESC guidelines for children and adolescences [15]. Central SBP and central DBP were also estimated with the SphygmoCor device (AtCor Medical, Sydney, NSW, Australia).

In all subjects (patients and controls), an extended lipid profile (total cholesterol [TC], LDL-C, HDL-C, triglycerides [TG], apolipoprotein A1 [ApoA1], apolipoprotein B [ApoB], and Lp(a)) was obtained. All of the above measurements have been performed in a morning blood sample, after overnight fasting, using an Architect c16000 Automatic Biochemistry Analyzer, Abbott Medical, Japan. Normal values of lipids in children and adolescents were estimated according to the Expert Panel Guidelines for dyslipidemia in children [16]. Levels of Lp(a) below 30 mg/dL were considered normal.

The investigation of possible early vascular aging was assessed by measuring c-IMT. In addition, indices of arterial stiffness, such as the pulse wave velocity (PWV) and the augmentation index (AIx), as well as of myocardial microcirculation (SEVR) were measured.

Furthermore, in order to identify possible effects of early vascular aging, the studied population was, subsequently, classified

Table 1. Demographic, clinical characteristics, and vascular function indices in the study population (children/adolescents with high Lp(a) levels and controls)

	High Lp(a) levels (n = 27)	Controls (n = 27)	p value
Age, years	9.9±3.7	9.7±3.0	0.808 (NS)
Gender (M/F)	17/10	17/10	1.0 (NS)
Height, cm	140.6±20.4	137.5±15.8	0.534 (NS)
BMI, kg/m ²	16.5 (14.9–19.4)	17.6 (16.3–18.5)	0.161 (NS)
SBP, mm Hg	104.5±9.2	108.8±7.6	0.066 (NS)
DBP, mm Hg	57.4±7.2	59.6±5.3	0.210 (NS)
HR, beats/min	78.6±10.7	82.8±13.6	0.214 (NS)
cSBP, mm Hg	89.5±8.8	91.3±6.7	0.386 (NS)
cDBP, mm Hg	60.2±7.7	62.0±5.1	0.315 (NS)
TC, mg/dL	182.0 (157.5–199.5)	161.0 (150.5–168.5)	0.006
TG, mg/dL	53.0 (41.0–83.5)	58.0 (50.0–83.5)	0.350 (NS)
HDL-C, mg/dL	58.0 (49.5–63.5)	51.0 (47.0–56.5)	0.100 (NS)
LDL-C, mg/dL	107.6±22.2	92.7±15.4	0.06 (NS)
ApoA1, mg/dL	150.0±24.7	149.8±17.8	0.972 (NS)
ApoB, mg/dL	83.8±13.6	70.2±10.0	<0.001
Lp(a), mg/dL	84.0 (68.8–133.9)	9.0 (5.0–16.0)	<0.001
c-IMT, mm	0.43±0.04	0.43±0.04	0.796 (NS)
PWV, m/s	4.3 (3.9–4.9)	4.4 (4.1–5.2)	0.240 (NS)
AIx, %	8.4±12.8	7.4±10.3	0.763 (NS)
SEVR, %	128.5 (113.5–141.0)	123.0 (105.3–139.5)	0.324 (NS)

Data are presented as mean ± standard deviation or median (interquartile range). n, number of children/adolescents; M/F, male/female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglycerides; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein (a); c-IMT, carotid intima-media thickness; PWV, pulse wave velocity; AIx, augmentation index; SEVR, subendocardial viability ratio; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol.

according to the sex-, age-, and height-dependent percentiles of PWV in children [17]. Hemodynamic parameters and lipid profile of the total population sample were compared with PWV values, above or below the 90th percentile, according to age and height.

Carotid Intima-Media Thickness

The c-IMT was estimated as the mean c-IMT value of the left and right common carotid artery. In each artery, c-IMT was calculated from 3 consecutive measurements taken in the far wall of the common artery and in the distal 10 mm of each artery. Images were obtained with carotid ultrasound (ProSound A7 Ultrasound System, Aloka, Tokyo, Japan).

Pulse Wave Velocity, Augmentation Index, and Subendocardial Viability Ratio

Early vascular aging biomarkers (PWV, AIx, and SEVR) were assessed by applanation tonometry, with a SphygmoCor device (AtCor Medical, Sydney, NSW, Australia). Measurements were made in the supine position, after a 15-min resting period.

Carotid-femoral PWV was estimated as the gold-standard measure of arterial stiffness. Two sequential recordings of the pulse wave were obtained in the carotid and femoral artery. Wave transit time was calculated from a simultaneously recorded electrocardiogram. The distance was calculated from the difference between the distances from sternal notch to the carotid or femoral

artery, respectively, over the body surface in a direct line. PWV was calculated as the distance traveled by the pulse wave between the carotid and femoral sampling sites, divided by time ($PWV = \Delta d / \Delta t$). All measurements of PWV were performed twice, and the mean of both measurements was recorded. If measurements were differing >0.5 m/s, a third measurement was obtained and the mean value of the 2 closest was included in the analysis. Normal values in children and adolescents were additionally estimated according to the study by Reusz et al. [17].

AIx was calculated as the augmentation pressure to central pulse pressure, which has been estimated as the difference between central systolic and diastolic pressures. Aortic augmentation pressure was calculated as the difference between the first and second systolic peaks of the ascending aortic waveform. For the present analysis, we used AIx corrected for the mean (75) heart rate (AIx75). The average of 2 successive, high-quality recordings of AIx (operator quality index >80) was included in the present analysis.

Finally, SEVR, a new noninvasive measure of microvascular coronary perfusion, was calculated as the ratio of the area under the diastolic segment of the derived aortic pressure waveform (diastolic pressure time index) to the area under the systolic segment of the waveform (tension time index). This index reflects the balance between coronary perfusion and arterial load, and lower values of SEVR are indicative of impaired myocardial oxygen demand and supply.

Table 2. Comparison between demographic, clinical characteristics, and vascular function indices in children/adolescents with elevated Lp(a) levels and positive or negative family history of premature CAD

Number, %	High Lp(a) levels and positive family history of premature CAD (<i>n</i> = 9) (34.62%)	High Lp(a) levels without family history of premature CAD (<i>n</i> = 17) (65.38%)	<i>p</i> value
Age, years	11.1±2.8	9.2±4.1	0.214
Gender (M/F)	4/5	12/5	0.189
Height, cm	146.2±13.7	136.6±23.0	0.263
BMI, kg/m ²	17.4 (15.3–20.4)	16.0 (14.6–17.9)	0.847
SBP, mm Hg	104.6±8.6	104.1±9.8	0.899
DBP, mm Hg	57.3±7.7	57.5±7.4	0.950
HR, beats/min	78.9±12.6	77.9±10.1	0.836
cSBP, mm Hg	87.8±8.6	90.4±9.3	0.487
cDBP, mm Hg	59.3±7.8	60.8±8.1	0.656
TC, mg/dL	162.0 (155.0–196.0)	189.0 (160.0–200.0)	0.285
TG, mg/dL	90.0 (41.0–107.0)	46.0 (41.0–69.0)	0.700
HDL-C, mg/dL	55.9±18.4	57.0±12.8	0.858
LDL-C, mg/dL	98.0±22.4	112.4±21.7	0.124
ApoA1, mg/dL	142.0±31.5	153.5±22.8	0.347
ApoB, mg/dL	86.7±15.0	82.3±13.6	0.540
Lp(a), mg/dL	106.1±46.0	94.7±41.3	0.524
c-IMT, mm	0.42±0.06	0.43±0.03	0.788
PWV, m/s	4.4±0.5	4.4±1.0	0.964
Alx, %	8.3±7.1	8.8±15.4	0.905
SEVR, %	132.0 (112.0–145.0)	128.5 (116.5–140.0)	0.500

One child from a single-parent family was not included in the comparisons. Data are presented as mean ± standard deviation or median (interquartile range). *n*, number of children/adolescents; M/F, male/female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; cSBP, central systolic blood pressure; cDBP, diastolic diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglycerides; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein (a); c-IMT, carotid intima-media thickness; PWV, pulse wave velocity; Alx, augmentation index; SEVR, subendocardial viability ratio; CAD, coronary artery disease; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol.

Statistical Analysis

Analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows version 25.0 (IBM SPSS Statistics, Chicago, IL, USA). Based on the normality of the distribution, continuous variables were described as mean ± standard deviation or as median ± interquartile range. Differences among groups were examined by independent samples *t* tests for normally distributed variables, while a nonparametric Mann-Whitney test was used for non-normally distributed variables. Qualitative variables were compared by the χ^2 test (with the Fisher's exact test when necessary), and results are expressed as percentages. Pearson's and Spearman's correlation coefficients were used for identifying significant correlations, based on the variable's normality of distribution. A probability value *p* < 0.05 was considered as statistically significant.

Results

There were no significant differences in age, gender, height, BMI, SBP, DBP, central SBP, and central DBP between children and adolescents with high Lp(a) levels and

controls (Table 1). Although serum lipid values were within normal levels, mean values of TC and ApoB were higher in the group of children with high Lp(a) levels than controls (*p* = 0.006 and *p* < 0.001, respectively) (Table 1). Furthermore, vascular function indices (c-IMT, PWV, Alx, and SEVR) did not show significant differences between the 2 groups (Table 1). None of the participants were found to have carotid plaques. In addition, in the overall population, there were no statistical significant differences, between lipid or hemodynamic parameters and PWV values, above or below the 90th percentile, according to age and height.

As for the assisted reproductive technology history, only 2/27 children (7.4%) with high Lp(a) levels and 1/27 controls (3.8%) were born by IVF (*p* = 0.504). No children were born by an intracytoplasmic sperm injection in either group.

When children and adolescents with high Lp(a) levels were subgrouped according to the presence or not of fam-

Table 3. Comparison between demographic, clinical characteristics, and vascular function indices in children/adolescents with elevated Lp(a) levels and positive or negative family history of hypertension

	High Lp(a) levels and positive family history of hypertension (n = 12)	High Lp(a) levels without family history of hypertension (n = 14)	p value
Age, years	9.4±3.7	10.3±3.8	0.561
Gender (M/F)	8/4	8/6	0.701
Height, cm	136.3±20.1	143.0±21.1	0.420
BMI, kg/m ²	17.0 (14.9–18.4)	15.7 (14.9–20.2)	0.918
SBP, mm Hg	101.7±6.8	106.4±10.6	0.196
DBP, mm Hg	54.8±6.5	59.8±7.5	0.080
HR, beats/min	76.9±10.8	79.4±11.1	0.564
cSBP, mm Hg	86.3±8.7	92.3±8.5	0.087
cDBP, mm Hg	57.3±7.3	62.9±7.7	0.074
TC, mg/dL	174.0 (144.0–199.5)	185.0 (162.0–200.0)	0.377
TG, mg/dL	55.0 (44.5–83.5)	43.5 (39.0–90.0)	0.328
HDL-C, mg/dL	58.5 (46.0–61.5)	58.0 (50.0–69.0)	0.643
LDL-C, mg/dL	104.6±29.0	109.8±15.9	0.589
ApoA1, mg/dL	148.9±27.5	151.9±23.9	0.784
ApoB, mg/dL	85.1±15.1	81.4±12.4	0.546
Lp(a), mg/dL	76.5 (60.5–84.0)	121.7 (83.7–138.0)	0.036
c-IMT, mm	0.43±0.04	0.42±0.04	0.416
PWV, m/s	4.0 (3.5–4.6)	4.5 (4.3–4.9)	0.068
AIx, %	7.9±9.5	9.2±15.7	0.807
SEVR, %	130.0 (115.3–145.5)	125.8 (113.0–140.0)	0.520

One child from a single-parent family was not included in the comparisons. Data are presented as mean ± standard deviation or median (interquartile range). *n*, number of children/adolescents; M/F, male/female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; cSBP, central systolic blood pressure; cDBP, diastolic diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglycerides; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein (a); c-IMT, carotid intima-media thickness; PWV, pulse wave velocity; AIx, augmentation index; SEVR, subendocardial viability ratio; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol.

ily history of dyslipidemia, we found that 24/26 children/adolescents had a positive family history of dyslipidemia and only 2/26 had a negative family history ($p < 0.001$). In 1 child, the complete family history was not available because the child came from a single-parent family.

When children and adolescents with high Lp(a) levels were subgrouped according to the presence or not of family history of premature CAD, similarly all of the above studied parameters did not differ significantly (Table 2). The same was found when participants with high Lp(a) levels were subgrouped according to the presence or not of family history of hypertension (Table 3).

After the application of correlation analysis, it was revealed that Lp(a) levels did not present a significant correlation with the other parameters studied, both regarding the whole sample (patients and controls), as well as in the subgroups of elevated Lp(a) levels. However, in the group of children with high Lp(a) levels, c-IMT was positively correlated with DBP ($r = 0.427$, $p = 0.026$) and there was a statistical trend correlation with SBP ($r =$

0.372 , $p = 0.056$). PWV was also positively correlated with DBP ($r = 0.425$, $p = 0.030$), while SEVR was negatively correlated with AIx ($r = -0.455$, $p = 0.017$).

Discussion

This study shows that otherwise healthy children and adolescents with high Lp(a) levels do not yet have impaired micro- and macrovascular indices (SEVR, AIx, PWV, and c-IMT) compared to controls. One possible explanation may be the young age of the participants, as it takes several years from the preliminary damage of the endothelium, to the appearance of the vascular alterations, which we measure.

Furthermore, to our knowledge, this is the first study in healthy children and adolescents, which investigates the possible association between elevated Lp(a) levels and indices of myocardial microcirculation, using SEVR. In the present study, there was no statistically significant dif-

ference between the mean values of SEVR in children with elevated Lp(a) levels and the control group. However, the participants had lower values of SEVR than the adult values, but since this index has not yet been studied so far in healthy children and adolescents, there are no reference values in this age-group.

There is only 1 study in children suffering from heart failure with preserved ejection fraction, showing significantly lower SEVR values in patients than controls, while in another study of children, no significant differences in SEVR values were found [18, 19]. Lower values of SEVR, especially below 100%, are indicative of poor perfusion of the subendocardium in high cardiovascular risk adult patients [20].

In our study, SEVR was negatively correlated with AIx in patients with high Lp(a) levels. Similar results were found in adult patients suffering from peripheral arterial disease [21], but not in patients with rheumatoid arthritis [20].

There are also studies, which mainly investigate large vessels (by measuring c-IMT and PWV), with similar results to our study, even in less healthy populations of children or young adults [1, 22]. In our study, mean c-IMT was 0.43 mm, both in patients and in controls. In the study of Jourdan et al. [23], in healthy adolescents aged between 10 and 20 years, median values of c-IMT ranged between 0.38 and 0.4 mm. Ishizu et al. [24] also measured c-IMT in healthy children aged 5–14 years and found that the thickness increases by 9 μ m each year.

Other studies in pediatric patients with heterozygous FH (mean age 12 and 10.7 years, respectively) reported no significant differences in the carotid thickness between patients and healthy controls [11, 25]. However, Wiegman et al. [10] showed that children with FH had higher c-IMT values over the age of 12 years than controls. Furthermore, in the study by Jourdan et al. [23], c-IMT of healthy adolescents was more related to height than to the age and c-IMT was positively correlated with BMI and SBP. In addition, in the study by Vlahos et al. [25], Lp(a) was an independent predictor of c-IMT in children with heterozygous FH.

There are different non-invasive methods to assess arterial stiffness in adults that can provide reliable information for the detection of high-risk patients. Although most of these methods have not been standardized for children, the measurement of arterial stiffness under controlled conditions can give accurate information for the assessment of early vascular aging in children [26]. Among these methods, the measurement of PWV is considered the simplest and most accurate non-invasive method to determine arterial stiffness.

Increased PWV is an indicator of arterial stiffness and future risk of cardiovascular events in adults [7]. Furthermore, there are several conditions associated with arterial stiffness even in childhood, such as dyslipidemia, hypertension, diabetes, chronic kidney disease, and obesity [26].

In our study, mean values of PWV did not show significant differences between healthy children/adolescents with elevated Lp(a) levels and the control group. In the study by Riggio et al. [11], hypercholesterolemic children with the mean age of 12 years had increased PWV compared to controls. According to the above, in our study there were probably no differences in PWV, as most children (17/27, 63%) were <12 years old.

Furthermore, we did not find statistically significant correlations between elevated Lp(a) levels and the other studied parameters. However, data from the Third National Health Nutrition and Examination Survey (NHANES-III) showed a positive correlation between TC and Lp(a) levels in children/adolescents aged 4–19 years [27]. Vlachopoulos et al. [14] also reported higher Lp(a) levels in children born with IVF than naturally conceived children. However, since only 3 children were born with IVF, in the total sample of our study population, we believe that IVF did not affect our results.

There are also studies showing an association between Lp(a) levels and endothelial dysfunction in children, by using a brachial artery flow-mediated dilation (FMD) technique [25, 28]. More specifically, in the study by Vlahos et al. [25], FMD was significantly decreased in patients with heterozygous FH over the age of 10 years.

When high Lp(a) levels coexist with elevated levels of other serum lipids, especially in patients with FH, the early vascular aging biomarkers have been reported to be impaired even in childhood. Studies in children and adolescents with FH showed increased arterial stiffness and increased c-IMT [9–11]. Furthermore, decreased FMD was found to be attributed to high LDL-C levels, but not to high ApoB or Lp(a) levels in children with heterozygous FH [9, 25].

In our study, the 9/26 children with high Lp(a) levels (34.62%) had a positive family history of premature CAD. Previous studies in children have also shown a positive correlation between high Lp(a) levels and family history of premature CAD [1, 27, 29, 30]. There are also studies showing ethnicity-related differences, with higher Lp(a) levels observed in African-American children [1, 27].

The main limitation of this cross-sectional observational study is the small sample size. Furthermore, the majority of children were <12 years old, where the lesions

of subclinical atherosclerosis as well as the signs of early vascular aging are not usually apparent, especially in healthy children. Longitudinal studies in low-risk children are also needed, in order to collect normative data.

In conclusion, healthy children and adolescents with high Lp(a) levels, but normal levels of other serum lipids, do not have yet impaired micro- and macrovascular indices (SEVR, AIx, PWV, and c-IMT) than their healthy counterparts. However, as other studies in children with increased Lp(a) levels and other comorbidities have found endothelial dysfunction or changes in early vascular aging biomarkers, it is crucial to early identify and follow up these children. At the same time, emphasis should be given on early identification of other cardiovascular risk factors (such as other underlying lipid abnormalities, obesity, or hypertension), in order to prevent premature CAD. In addition to genetic factors, dietary habits and lifestyle may play an important role. Therefore, intervention programs are needed to prevent or reduce other atherogenic risk factors, which may coexist.

Acknowledgments

We would like to thank the patients and their parents for their participation in the study.

Statement of Ethics

The study was approved by the Institutional Ethics Committee of “Papageorgiou” General Hospital (decision no. 512, April 26, 2018), and written informed consent was obtained from all parents

of the participants, before inclusion in the study. The authors also certify that all procedures comply with the internationally accepted ethical standards, according to the Helsinki Declaration.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

Funding Sources

This study did not receive any specific funding.

Author Contributions

Kyriaki Papadopoulou-Legbelou designed the study, contributed to the interpretation of data, and drafted the manuscript. Areti Triantafyllou involved in the design of the study, analyzed the data, and critically reviewed the manuscript. Olga Vampertzi collected data and contributed to the writing of the manuscript. Nikolaos Koletsos collected and statistically analyzed the data and contributed to the interpretation of the data. Stella Douma was contributed to the conception of the study and critically reviewed the manuscript. Efimia Papadopoulou-Alataki was involved in the design of the study and critically reviewed the manuscript.

Availability of Data and Material

All data generated or analyzed during this study have not been made publicly available on ethical grounds and are held by the authors. Further enquiries can be directed to the corresponding author.

References

- 1 Qayum O, Alshami N, Ibezim CF, Reid KJ, Noel-MacDonnell JR, Raghuveer G. Lipoprotein (a): examination of cardiovascular risk in a pediatric referral population. *Pediatr Cardiol*. 2018;39(8):1540–6.
- 2 Enas EA, Chacko V, Senthilkumar A, Puthumana N, Mohan V. Elevated lipoprotein(a) – a genetic risk factor for premature vascular disease in people with and without standard risk factors: a review. *Dis Mon*. 2006;52:5–50.
- 3 Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med*. 2013; 273(1):6–30.
- 4 Luc G, Bard JM, Arveiler D, Ferrieres J, Evans A, Amouyel P, et al. Lipoprotein(a) as a predictor of coronary heart disease: the PRIME study. *Atherosclerosis*. 2002;163(2):377–84.
- 5 Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301(22): 2331–9.
- 6 Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–67.
- 7 Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318–27.
- 8 Järvisalo MJ, Jartti L, Nantö-Salonen K, Irjala K, Rönnemaa T, Hartiala JJ, et al. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. *Circulation*. 2001;104(24):2943–7.
- 9 Aggoun Y, Bonnet D, Sidi D, Girardet JP, Brucker E, Polak M, et al. Arterial mechanical changes in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2000;20(9):2070–5.
- 10 Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet*. 2004;363(9406):369–70.
- 11 Riggio S, Mandraffino G, Sardo MA, Iudicello R, Camarda N, Imbalzano E, et al. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. *Eur J Clin Invest*. 2010;40(3): 250–7.
- 12 de Jongh S, Lilien MR, Bakker HD, Hutten BA, Kastelein JJ, Stroes ES. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. *Atherosclerosis*. 2002;163(1): 193–7.

- 13 Anyfanti P, Gkaliagkousi E, Triantafyllou A, Dipla K, Zarifis H, Arseniou P, et al. Noninvasive assessment of myocardial perfusion in different blood pressure phenotypes and its association with arterial stiffness indices. *Am J Hypertens*. 2019;32(6):557–63.
- 14 Vlachopoulos C, Kosteria I, Sakka S, Gkourogianni A, Terentes-Printzios D, Koutagiar I, et al. PCSK9 and Lp(a) levels of children born after assisted reproduction technologies. *J Assist Reprod Genet*. 2019;36(6):1091–9.
- 15 Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens*. 2016;34(10):1887–920.
- 16 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128: S213–56.
- 17 Reusz GS, Cseprekal O, Temmar M, Kis E, Cherif AB, Thaleb A, et al. Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension*. 2010;56(2):217–24.
- 18 Masutani S, Kuwata S, Kurishima C, Iwamoto Y, Saiki H, Sugimoto M, et al. Ventricular-vascular dynamics in pediatric patients with heart failure and preserved ejection fraction. *Int J Cardiol*. 2016;225:306–12.
- 19 Murakami T, Takei K, Ueno M, Takeda A, Yakuwa S, Nakazawa M. Aortic reservoir function after arterial switch operation in elementary school-aged children. *Circ J*. 2008;72(8):1291–5.
- 20 Anyfanti P, Triantafyllou A, Gkaliagkousi E, Triantafyllou G, Koletos N, Chatzimichailidou S, et al. Subendocardial viability ratio in patients with rheumatoid arthritis: comparison with healthy controls and identification of prognostic factors. *Clin Rheumatol*. 2017;36(6):1229–36.
- 21 Scandale G, Dimitrov G, Recchia M, Carzaniga G, Minola M, Perilli E, et al. Arterial stiffness and subendocardial viability ratio in patients with peripheral arterial disease. *J Clin Hypertens*. 2018;20(3):478–84.
- 22 Grebe MT, Schoene E, Schaefer CA, Boedeker RH, Kemkes-Matthes B, Voss R, et al. Elevated lipoprotein(a) does not promote early atherosclerotic changes of the carotid arteries in young, healthy adults. *Atherosclerosis*. 2007;190(1):194–8.
- 23 Jourdan C, Wühl E, Litwin M, Fahr K, Trelewicz J, Jobs K, et al. Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. *J Hypertens*. 2005;23(9):1707–15.
- 24 Ishizu T, Ishimitsu T, Yanagi H, Seo Y, Obara K, Moriyama N, et al. Effect of age on carotid arterial intima-media thickness in childhood. *Heart Vessels*. 2004;19(4):189–95.
- 25 Vlahos AP, Naka KK, Bechlioulis A, Theoharis P, Vakalis K, Moutzouri E, et al. Endothelial dysfunction, but not structural atherosclerosis, is evident early in children with heterozygous familial hypercholesterolemia. *Pediatr Cardiol*. 2014;35(1):63–70.
- 26 Savant JD, Furth SL, Meyers KE. Arterial stiffness in children: pediatric measurement and considerations. *Pulse*. 2014;2:69–80.
- 27 Obisesan TO, Aliyu MH, Adediran AS, Bond V, Maxwell CJ, Rotimi CN. Correlates of serum lipoprotein (A) in children and adolescents in the United States. The Third National Health Nutrition and Examination Survey (NHANES-III). *Lipids Health Dis*. 2004;3:1–10.
- 28 Lapinleimu J, Raitakari OT, Lapinleimu H, Pahkala K, Rönkämaa T, Simell OG, et al. High lipoprotein(a) concentrations are associated with impaired endothelial function in children. *J Pediatr*. 2015;166(4): 947–2.
- 29 Gaeta G, Cuomo S, Capozzi G, Foglia MC, Barra S, Madrid A, et al. Lipoprotein(a) levels are increased in healthy young subjects with parental history of premature myocardial infarction. *Nutr Metab Cardiovasc Dis*. 2008;18(7):492–6.
- 30 Guardamagna O, Abello F, Anfossi G, Pirro M. Lipoprotein(a) and family history of cardiovascular disease in children with familial dyslipidemias. *J Pediatr*. 2011;159(2):314–9.