Atherosclerosis Plus 51 (2023) 1–7

Contents lists available at ScienceDirect

Atherosclerosis Plus

journal homepage: www.elsevier.com/locate/atherosclerosis

Lp(a) does not affect intima media thickness in hypercholesterolemic children −a retrospective cross sectional study

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ARTICLE INFO

Article history:
Received 20 June 2022
Received in revised form
30 October 2022
Accepted 21 November 2022
Available online 26 November 2022

ABSTRACT

Purpose: Combined hyperlipidaemia results in premature atherosclerosis and a high burden of cardiovascular morbidity and mortality. Early identification of highly affected subjects within this population is of utmost importance to enable informed treatment decisions. The measurement of intima media thickness (IMT) is a readily available, non-invasive method to investigate evidence of early atherosclerosis. To assess the usefulness of this method in pediatric subjects with hypercholesterolemia, we here examined a possible interaction of LDL-C and Lp(a) on IMT.

Methods: Blood lipids (Lp(a), LDL-cholesterol, total cholesterol, triglycerides, high density lipoprotein (HDL) -cholesterol, apolipoprotein A1, apolipoprotein B), anthropometric parameters (age, height, weight, body mass index (BMI)) and possibly existing early evidence of atherosclerotic lesions measured by intima media thickness (IMT zscore).as a surrogate parameter was examined retrospectively in 113 children and adolescents (aged 1−18 years) with elevated Lp(a) and/or LDL-cholesterol (Lp(a) > 30 mg/dL, LDL>130 mg/dL). Furthermore, we compared hsCRP levels between groups.

Results: There were no significant differences in IMT Zscore or hsCRP between groups. Regression analysis did not reveal a statistically significant interaction between Lp(a) and LDL-C.

Conclusions: At the age of 6−18 years, we found no significant differences in early markers of atherosclerosis between subjects with high Lp(a)- and/or high LDL-cholesterol with no detectable synergistic effects between the two lipoproteins.

1. Introduction

Lipoprotein(a) [Lp(a)] is a lipoprotein closely related to low-density lipoprotein cholesterol (LDL-C) as it contains an Apolipoprotein B-100 (ApoB 100) component and exhibits the distinctive ability to bind apolipoprotein (a) through plasminogen-like domains [1]. Interest into the lipoprotein has peaked in recent decades and even though it was first described in 1963 by Kare Berg, open questions remain [2].

Lp(a) is now recognized as an important risk factor for the development of premature atherosclerosis and coronary vascular disease (CVD) and relatively recently Mendelian randomization studies have proven that elevated plasma concentrations of Lp(a) are correlated with an increased risk for myocardial infarction, significant aortic valve stenosis and ischaemic stroke [3]. While the epidemiological data regarding the atherogenic role of Lp(a) is convincing, the molecular basis for these effects is less clear. However, several theories have been formulated based on convincing evidence from basic science experiments, as recently reviewed by Jang et al. [4].

Briefly summarized, much of the atherogenicity of Lp(a) can be contributed to its particular structure. The lysine-binding site of the kringle domains within an apo(a) molecule predisposes Lp(a) molecules to bind to the endothelial receptors, thereby contributing to atherogenicity. The structural homology of apo(a) to the

Abbreviations: ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; BMI, Body Mass Index; CCA, common carotid artery; cIMT, carotid intima media thickness; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; Lp(a), Lipoprotein a; SBP, systolic blood pressure; TC, Total cholesterol; TG, Triglycerides.

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https://doi.org/10.1016/j.athplu.2022.11.001

plasminogen molecule also confers thrombogenicity of Lp(a). Therefore, an excess concentration of Lp(a) abrogates the function of plasmin activators, decreases plasmin levels, and eventually leads to attenuated fibrinolysis activity [4].

Plasma levels of Lp(a) show high heterogeneity between individuals, can vary 1000-fold and are influenced almost exclusively by the number of pentanucleotide TTTTA-repeats in the apolipoprotein A-gene. For example small apolipoprotein (a) isoforms, small Lp(a) particle-sizes and a small number of "kringle IV type 2"-repeats lead to high plasma levels of Lp(a) [1]. Even though the individual genetic markup accounts of 90% of the inter-individual variation of serum Lp(a) levels, there is limited evidence that they may also be influenced by nutrition and other lifestyle factors to minor extents [5].

Since atherosclerosis typically remains subclinical in children (although some rare cases of early cardiovascular death are described in patients affected with aggressive forms of familial hypercholesterolemia) [6], early identification of those parts of the pediatric population that already exhibit early markers of atherosclerosis is of utmost importance in order to enable clinicians to manage cardiovascular risk factors with targeted treatments. The measurement of the carotid artery intima media thickness (cIMT) by means of ultrasound is a non-invasive method that enables clinicians to identify early subendothelial damage and can be performed in the setting of an outpatient clinic [7]. Furthermore, early-stage atherosclerosis leads to low levels of chronic inflammation may result in minor increases of C reactive protein (hsCRP), which is routinely measured in many centers. hsCRP was previously associated with the presence of cardiovascular risk factors, although existing literature in paediatric age regarding this is highly controversial as reviewed by Blinc et al. [8].

Most available studies have focused on investigating associations of elevated Lp(a) with a family history of premature CVD [9,10]. Relatively recently, a study by Qayum et al. reported that isolated Lp(a) elevation does not lead to increased IMT thickness when the values are compared to a cohort of non-hyperlipidaemic children that had been referred to a specialised outpatient clinic for the management of cardiovascular risk factors [11]. These findings suggest that measurement of carotid intima media thickness is most likely not suitable for early identification of paediatric subjects with isolated Lp(a) or LDL-C elevation. However, it is currently unclear if- and how elevated levels of Lp(a) and LDL-C interact on early markers of atherosclerosis in childhood as it is plausible that the presence of both independent risk factors may result in additional thickening of the carotid intima media. Furthermore, due to the heterogenous nature of Lp(a) particles between individuals, it may be possible to identify a particularly vulnerable subgroup in this population.

Thus, the present study reports the effects of serum Lp(a) and LDL-C levels on early evidence of atherosclerotic lesions (measured by surrogate parameters IMT Zscore) in paediatric- and adolescent patients.

2. Materials and methods

2.1. Patient cohort

We reported on pooled data from the patient collective treated at the paediatric outpatient clinic for nutritional- and metabolic disorders of the Medical University of Vienna in a cross-sectional study. Data presented here were obtained at the initial presentation after referral to our outpatient clinic between 1994 and 2011; our results thus represent values measured prior to the initiation of any form of specific treatment of the underlying disorder of lipid metabolism.

Patients were included into the assessment if they met the following criteria:

Age >6 years but <18 years at the time of initial presentation.

Lp(a) at initial presentation >30 mg/dL and/or LDL-Cholesterol levels >130 mg/dL.

The cut-off value for Lp(a) of 30 mg/dL was chosen based on previous meta-analyses and mendelian randomization trials demonstrating that higher levels are associated with increased cardiovascular risk. It represents a commonly used reference range to identify clinically relevant Lp(a) elevations in central Europe and was recently recommended to be used in young subjects by the 2016 Canadian Cardiovascular Society Guidelines [12,13]. Furthermore, we used a cut-off for LDL-C consistent with the recommendations issued by the National Heart, Lung, and Blood Institute, the American Academy of Pediatrics, and the American Heart Association/American College of Cardiology [14–16]. All patients with LDL-C elevations were also genetically tested for familial hypercholesterolemia.

Additionally, subjects were excluded from the analysis if they were affected with at least one of the following conditions: diabetes mellitus, liver diseases, acute or chronic viral- or bacterial infection, renal disease, an anamnesis of having received cortisone therapy in the last 8 weeks before initial presentation at our department, hormonal disorders, autoimmune diseases, ongoing treatment with hepatotoxic drugs at the time of initial presentation, pregnancy, known or suspected genetic disorders and/or syndromes except familial hypercholesterolaemia and familial combined hyperlipidaemia. An LDL-C cut-off of 130 mg/dL was chosen based on current clinical recommendations regarding normal LDL-C reference ranges in children [16].

Since there is evidence from adult populations that the coexistence of high LDL-C and high Lp(a) increases the risk of premature cardiovascular- and cerebrovascular events, we hypothesized that subjects with both risk factors present would exhibit increased IMT as an early marker of atherosclerosis [17,18]. To this end, we perfomed two types of analysis. First, we performed a multivariate linear regression analysis to assess if serum Lp(a) and LDL-C levels predict IMT-thickness. Second, subjects were divided into three groups based on the clinically established cut-offs of their lipoprotein levels for the purpose of this analysis:

Group 1: LDL-Cholesterol > 130 mg/dL *and Lp(a)* > 30 mg/dL *(LDL-C+/Lp(a)+)*.

Group 2: LDL-Cholesterol > 130 mg/dL *and Lp(a)* < 30 mg/dL *(LDL-C+/Lp(a)-)*

Group 3: LDL-Cholesterol < 130 mg/dL *and Lp(a)* > 30 mg/dL *(LDL-C-/Lp(a)+)*.

This was done to assess the impact of Lp(a)- and LDL-C elevations based on clinical definitions, assuming a dichotomous-rather than a linear correlation with increased IMT. The following parameters were recorded for all participants at the time of initial presentation at our specialised outpatient clinic: age in years, BW in kg, height (H) in cm, BMI *z* score, systolic BP (SBP) and diastolic BP (DBP) in mm Hg, cIMT in mm, hsCRP in mg/dL and a full lipid profile after an overnight fast.

An initial cohort of 252 subjects was identified. Complete measurements were available for 113 subjects, which are reported here.

2.2. Clinical and laboratory evaluation

All biochemical analyses were performed in the central laboratory of the Vienna General Hospital. Total cholesterol (TC), LDL-C, high density lipoprotein-cholesterol (HDL-C), triglycerides (TGs), apolipoprotein A1 (apoA1), apoB, and lipoprotein (a) [Lp(a)] levels were evaluated in serum, after an overnight fast (water was allowed).

Total cholesterol, HDL-C, and TG were measured using an enzymatic method (Roche Diagnostics) on an automatic analyzer (Cobass Integra 800). Apolipoprotein A1, apoB, and Lp(a) were evaluated by an immunonephelometric assay (Siemens BNII Nephelometer Analyzer). HsCRP was measured using an immunoturbidimetric assay (Diazyme).

The LDL-C levels were calculated by the Friedewald equation: LDL-C = TC − (HDL-C) − 1/5 TG (in mg/dL) and non-HDL-C levels by subtracting HDL-C from TC. All other parameters were measured using standard laboratory methods according to the manufacturers' instructions.

2.3. IMT measurements

IMT was measured as a routine clinical parameter in accordance with the standard operating procedure of the division of angiology of the Medical University of Vienna. In detail, in all children, cIMT was measured using a high-resolution B-Mode ultrasound system with a 40 mm linear 12 MHz probe.

Children were examined by ultrasound in the supine position with the neck extended and turned 45° opposite to the side being scanned. The probe was adjusted to ensure that the 2-dimensional ultrasound beam was perpendicular to the arterial walls. The images were magnified, and the ultrasound settings were optimised so that the walls of the common carotid artery (CCA) were clearly identified for 10 mm in length. The cIMT measurements were taken from the far wall of the CCA. The cIMT was defined as the distance between the lumen and the media-adventitia interface of the far wall of the carotid artery. The cIMT was measured manually (in mm) at the right and the left CCA, 1 cm proximal to the carotid bulb, not including the beginning of the bulb (5 mm below the bulb). Three end-diastolic measurements were manually obtained by placing electronic callipers at the edge of the far wall of each segment in a region of interest of 10 mm length from three separate frames. The average of these three measurements was calculated for each side respectively (referred to here as IMT *sin* for the left side and IMT *dext* for the right carotid artery) [19].

The average of both IMT *sin* and IMT *dext* was adjusted to age and sex of the respective subject by calculating the IMT percentile in accordance with the reference values published from a German sample of healthy children by Doyon et al. [20]This cohort was chosen due to the similarity in the methodology of the IMT measurements, the fact that both samples represent a central European population and the fact that the data were collected in a comparable timeframe to our own.

2.4. Family history

Information regarding a family history of premature CVD (pCVD) was recorded as part of the routine clinical assessment based on self-reporting. pCVD was defined as having been diagnosed with atherosclerotic narrowing of coronary arteries in males <55 years old or in females <65 years in accordance with established guidelines [21,22]. History of pCVD is reported for first-degree (parents, sibling) and second degree relatives (grandparents, uncles, aunts, half-siblings).

2.5. Statistics

The statistical analysis and evaluation of the data was performed with R Version 4.0.3 (R Foundation, Vienna, Austria) using the following packages: ggpubr, ggplot2, lmboot. For power calculations we used the free statistical software G*Power [18].First, the distribution of the data was visually inspected and assessed using histograms and Q-Q plots.

All parameters except gender and hsCRP were in relatively close approximation of a normal distribution. We analysed these data by performing two different statistical tests: in order to delineate the impact of the clinical definitions of hyperlipidaemia on IMT-Zscore, we performed a group-wise comparison with a residual bootstrap using an ANOVA omnibus test. In the case of statistical significance, defined as a p-value for the respective F-statistic of <0.05, we performed post-hoc tests by calculating the Bonferroni-corrected p-value for the mean difference between two respective groups in the original sample.

Additionally, the effects of LDL-C and Lp(a) on IMT Z-score were analysed by bootstrapped linear regression.

A 2-sided p-value of <0.05 was considered statistically significant. hsCRP levels are analysed using non-parametric rank sum tests. Differences between groups regarding a family history of pCVD were analysed by Chi-Square test. Values for all descriptive statistics are reported as mean plus/minus one standard deviation, except the sex of the subjects, for which absolute numbers are reported, as well as the percentages of subjects with a family history of pCVD and FH variants. Due to expected differences in the percentage of subjects with FH variants due to group makeup no statistical analysis was performed. All lipid, lipoprotein, apolipoprotein and hsCRP values are expressed in mg/dL.

3. Results

Of the 113 children and adolescents with complete data 28 had isolated Lp(a) elevation ([LDL-/Lp(a)+], 31.6%), 45 exhibited isolated LDL-C isolation ([LDL+/Lp(−)+], 50,9%) and 40 had combined elevations of Lp(a) and LDL-C ([LDL+/Lp(a)+], 50,9%). Group characteristics including age, anthropometric and laboratory data are reported in Table 1. Analysis of the mean difference in IMT thickness between groups showed high compatibility with the null hypothesis (Fig. 1). Furthermore, hsCRP did not differ significantly between groups (Fig. 2).

Both absolute LDL-C and Lp(a) failed to predict IMT Zscore in our cohort of paediatric subjects at high cardiovascular risk in a statistically significant manner (whole model: LDL-C: t = 0.355, p = 0.724; Lp(a): t = 0.791, p = 0.431; Interaction: t = −0.798, p = 0.427) (Fig. 3).

Omnibus-Chi-Square test was significant for family history of CVD between groups (Table 1), and we therefore performed post-hoc Bonferroni corrected Chi-Square comparisons. Family history of pCVD was significantly more frequently present in LDL-/Lp(a)+ and LDL+/Lp(a)+ compared to Lp(a)-/LDL+ (p = 0.003, p < 0.001, respectively). No statistically significant differences were found between LDL-/Lp(a)+ and LDL+/Lp(a)+/(p = 0.642).

3.1. Power calculation

We performed a post-hoc power calculation (ANOVA, omnibus) assuming an α-error probability of 0.05. This revealed an effect size for ANOVA of f = 0.0349, corresponding to a power level of 0.0602 (both rounded to 4 decimals), thus suggesting that our study was severely underpowered to detect real differences between groups. Thus, we performed an additional a-priori sample size calculation based on the assumption of the effect size detected in our sample to be true. To achieve a power level of 0.8 (assuming an α-error probability of 0.05) a sample size of n = 7899 would be required.

4. Discussion

Several major limitations of our study need to be pointed out. First, we performed a retrospective analysis with an inherent risk for unaccountable bias due to unrecorded factors. Secondly, our

Table 1
Patient characteristics by group and of the entire study population.

Parameter	Group				
	LDL-/Lp(a)+	LDL+/Lp(a)-	LDL+/Lp(a)+	whole cohort	p value (omnibus test)
Gender (n; male, female)	*N = 28*	*N = 46*	*N = 39*	*N = 113*	
	11,17	*20,26*	*22,17*	*53,60*	
Age (years)	10.96 (4.04)	9.58 (3.57)	10.71 (3.34)	10.31 (3.64)	0.201
Height z score	0.36 (1.11)	0.34 (1.21	0.38 (1.08)	0.36 (1.14)	0.831
BMI z score	0.41 (1.39)	0.45 (1.33)	0.31 (1.24)	0.38 (1.34)	0.374
SBP z score	0.09 (0.69)	0.07 (0.71)	0.07 (0.79)	0.07 (0.74)	0.701
DBP z score	0.04 (0.76)	0.11 (0.69)	0.08 (0.81)	0.07 (0.75)	0.784
TC (mg/dL)	179.61 (26.27)	253.43 (56.70	261.42 (68.65)	237.68 (64.72)	<0.001
LDL-C (mg/dL)	102.95 (18.37)	180.65 (50.80)	163.37 (60.92)	163.37 (60.92)	<0.001
HDL-C (mg/dL)	58.23 (15.41)	50.54 (14.07)	48.32 (12.17)	51.72 (14.24)	0.068
TAG (mg/dL)	79.70 (39.84)	106.37 (59.37)	112.96 (58.53)	101.94 (55.96)	0.054
ApoA1 (mg/dL)	136.25 (27.54)	138.07 (27.51)	135.09 (26.03)	135.09 (26.03)	0.798
ApoB (mg/dL)	77.79 (16.43)	115.30 (30.49)	124.26 (26.69)	108.96 (32.84)	<0.001
Lp(a) (mg/dL)	105.53 (55.54)	14.53 (7.57)	94.75 (49.14)	64.50 (57.89)	<0.001
IMT average (mm)	0.464 (0.024)	0.359 (0.031)	0.361 (0.025)	0.391 (0.027)	0.285
IMT Z score	3.01 (0.84)	2.94 (1.02)	2.93 (0.93)	2.98 (0.93)	0.646
hsCRP (mg/dL)	0.223 (0.536)	0.131 (0.111)	0.200 (0.303)	0.177 (0.328)	0.840
Family history of premature CVD positive (%)	40.3	68.7	78.8	62.8	<0.001
FH variant detected (%)	6.3	53.7	61.5	39.5	n/a

Abbreviations: ApoB: apolipoprotein B, BMI: body mass index, DBP: diastolic blood pressure, HDL-C: high density lipoprotein-cholesterol, hsCRP: high sensitivity C-reactive protein, LDL-C: low density lipoprotein-cholesterol, Lp(a): lipoprotein (A), SBP: systolic lood pressure, SD: standard deviation, TAG: Triglycerides. All values except sex are presented as mean (SD); sex is presented as absolute numbers.

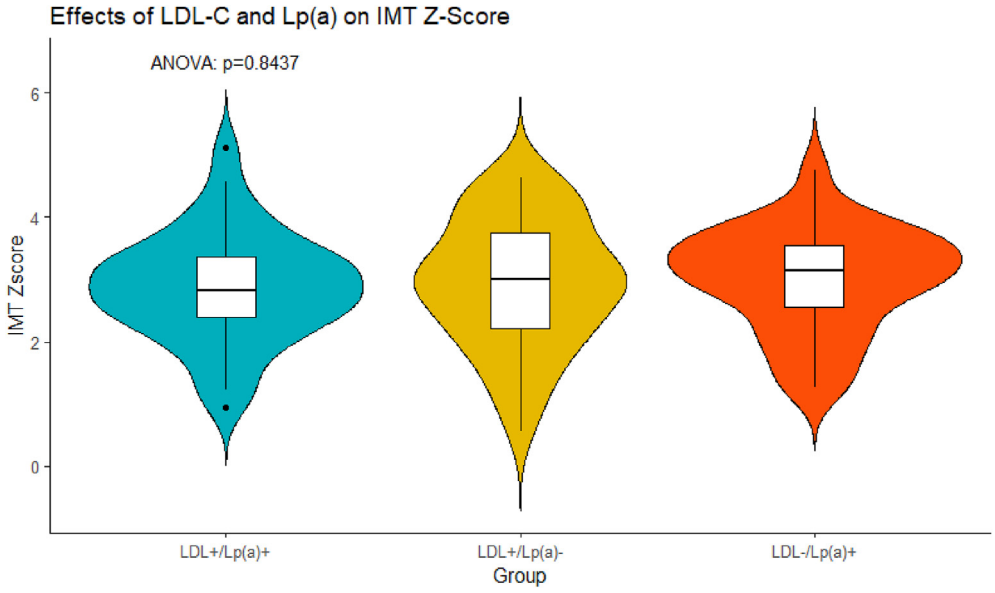

Fig. 1. Violin plot of IMT Zscore by group. There were no significant differences between groups and the data is in good agreement with the null hypothesis (95% CI for bootstrapped F-statistics: 5%: 0.0037, 95%: 3.9420 (df 1, 112.

sample size is relatively small and thus the existence of an interactive effect of LDL-C and Lp(a) on IMT and hs-CRP cannot be excluded as our study does not possess sufficient statistical power to do so. However, as the differences in means in our sample as well as the estimated effect size are extremely small, it seems improbable that clinically relevant differences exist. Assuming the effect size reported in our study to be true, future studies in this population would require a sample size of approximately 7900 children to detect possible differences with sufficient statistical power. Finally, due to the retrospective nature of our study we were unable to include healthy controls and thus normalised to reference values published from a neighbouring central European country [20]. While these historic healthy controls seem highly comparable to our own patient collective, the use of historic controls nevertheless limits the quality of our data. Furthermore, we are unable to provide accurate analysis of the family history of hypercholesterolemia since records for many subjects were incomplete.

Our results indicate that Lp(a) elevation and LDL-C do not possess an interaction regarding their effect on intima media thickness as an early marker of atherosclerosis that is detectable in paediatric- and adolescent age. These results are of particular interest, as literature from the adult population shows an association of increased Lp(a) with familial hypercholesterolaemia and additionally an increased prevalence of elevated Lp(a) in FH-patients with coronary vascular disease (reviewed by Hamasaki et Kotani) [23].

The exact role of Lp(a) in the pathogenesis of atherosclerosis remains, at least partly, elusive and is recognized to be a complex

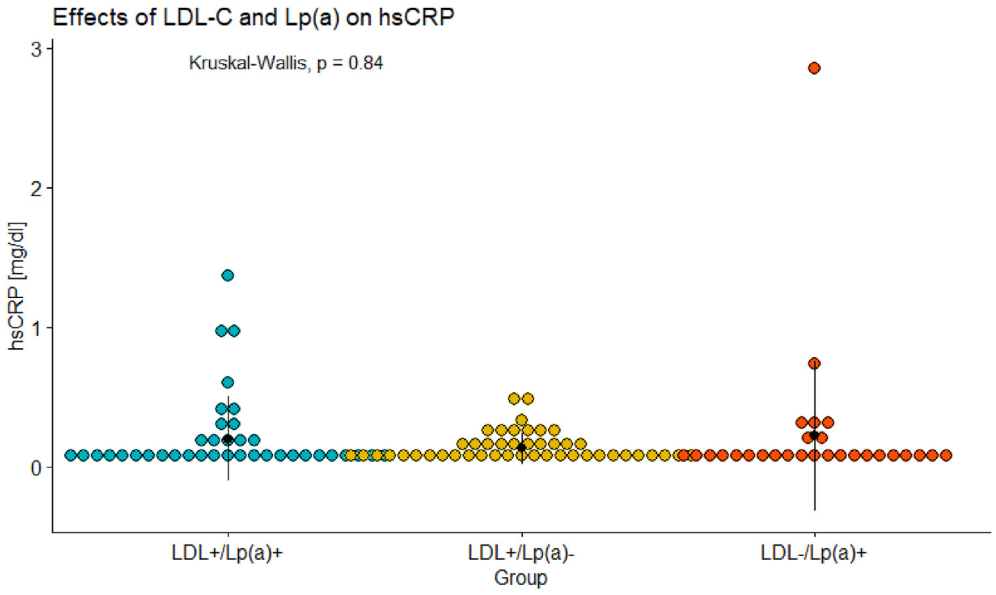

Fig. 2. Scatter plot of circulating hsCRP levels by group (mean ± 1.5 IQR range). No significant differences could be detected.

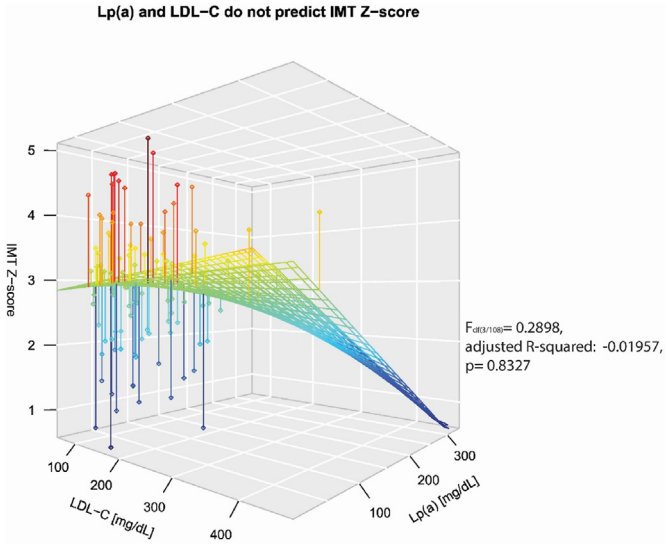

Fig. 3. 3D Scatter plot of correlations between LDL-C, Lp(a) and IMT-Zscore. The multi-coloured plane represents a linear regression model (IMT Zscore ~ LDL-C*Lp(a)).

one. It could be speculated that Lp(a) results in increased risk combined with LDL-C elevation when additional risk factors such as hypertension, obesity, or smoking set in later in life, however, further research through large prospective trials is required to clarify this. Nevertheless, our results highlight that both Lp(a) and LDL-C lead to significantly increased IMT thickness, highlighted by the fact that the population mean reported here exhibits a mean IMT thickness that is more than 2 standard deviations above what had been established as the mean in a population of healthy children [20]. However, recently a prospective study by Karapostolos et al. was able to convincingly demonstrate, that treatment with statins is able to decrease IMT thickness in hyperlipidaemic children irrespective of Lp(a) status. This highlights the need for early identification of children with increased cardiovascular risk and subsequent initiation of treatment. In line with our result, Karapostolos et al. do not report a significant difference in IMT thickness in untreated hyperlipidaemic children with and without Lp(a) elevation [24]. Since most centers do not measure Lp(a) routinely, especially not in pediatric age, there are only few reports on the effect of Lp(a)-plasma-levels on early markers of atherosclerosis. Recently, a multicenter study highlighted the complex nature of the underlying polymorphisms of elevated Lp(a), thus rendering genetic assessment an impractical predictor of CVD in these patients due to the lack of sufficient data [25]. However, there is convincing evidence from adult studies that patients exhibiting Lp(a) elevation combined with increased serum LDL-C levels show increased incidence of cardiovascular events [4].

Most existing studies conclude that elevated Lp(a) or elevated LDL-cholesterol in childhood leads to early atherosclerotic lesions or even vascular diseases. LDL-cholesterol-elevation in children appears to cause detectable vascular lesions [26], while high Lp(a)-values seem to be associated with cerebral insult [27] as well as arterial [28] and venous thromboembolism [29] in childhood.

It is possible that the cut-off level of 30 mg/dL for Lp(a) used by most studies including ours may no longer be acceptable at this time, as suggested by the HELENA-study [30]. In 2012 the HELENA-study with a study population of more than 1000 healthy European children and adolescents arrived at the conclusion that the 95.Lp(a)-percentile was 63 mg/dL for boys, respectively 71 mg/dL for girls, but not 30 mg/dL as broadly assumed. This would drastically influence the conclusions drawn from studies on the effects of Lp(a)-elevation in adolescent age in European cohorts [30]. However, the regression analysis presented here suggests that Lp(a) does not have an interaction on IMT with LDL-C and thus a different cut-off level would not alter the outcomes of our analysis. Additionally, our model does not indicate the existence of a linear correlation of serum LDL-C with IMT in hyperlipidaemic paediatric subjects, which is in line with previous findings from Kusters et al. [31].

We found that increased Lp(a) in the presence of concomitantly increased LDL-C showed a non-statistically significant trend towards a higher burden of pCVD in the family of affected subjects compared to LDL-C elevation alone in our population. While increased plasma Lp(a) levels are well established as an independent risk factor for pCVD, we here report a relatively low prevalence of pCVD in isolated Lp(a) elevation, which was significantly lower

than that of the group exhibiting isolated LDL-C elevation. However, it is important to highlight that the majority of subjects in the Lp(a)-/LDL + group had been diagnosed with FH and thus, unsurprisingly, exhibit a disproportionately high rate of pCVD in close relatives [32]. Albeit statistically non-significant, the higher prevalence of pCVD in the families of subjects with Lp(a)+/LDL-reported here warrants targeted investigation in the future. Previous studies reported a higher prevalence of pCVD in families of subjects Lp(a) elevation and conversely found high Lp(a) to be an independent risk factor for positive family history in close relatives [11,33–35].

This highlights the crucial clinical relevance of thorough medical anamnesis as the family history may aid in early identification of paediatric subjects at particularly high risk of developing atherosclerotic complications later in life, especially since currently most healthcare systems do not provide universal screening for FH and Lp(a)-elevations in pediatric age [11,33].

5. Conclusion

Since there is sufficient evidence from adults to conclude that high Lp(a) levels are an independent risk factor for cardiovascular events in the presents of increased LDL-C, Our results suggest that IMT measurements in pediatric age may not be suitable to identify subjects at high cardiovascular risk in patients with combined elevations of atherogenic lipoproteins [17,36,37]. These findings highlight the urgent need for further research into the cardiovascular risk Lp(a) poses in order to make informed and individualized treatment decisions.

Ethics approval and consent to participate

The study was carried out in accordance with the latest declaration of Helsinki and was approved by the ethics committee of the Medical University of Vienna (EK 2011/1214).

As this is a retrospective data analysis, the requirement to obtain patient consent was waived by the responsible ethics committee.

Consent for publication

Not applicable.

Availability of data and material

Primary data are available upon reasonable request.

Funding statement

This study was funded internally.

Authors' contributions

OH was responsible for the statistical analysis and the writing of the manuscript. AB helped with creation of the data. SC assisted with interpretation of the results. KW was responsible for the design of the study and data generation.

Declaration of competing interest

No conflicts of interest identified.

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