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Clinical Research Article

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Lipoprotein(a) Concentrations Correlate With LDL-C in Children With Type 1 and 2 Diabetes

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Abbreviations: ApoB, apolipoprotein B; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; RR, relative risk; T1D, type 1 diabetes; TC, total cholesterol; VAP, Vertical Auto Profile; VLDL-C, very low density lipoprotein cholesterol.

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Abstract

Context: Elevated levels of lipoprotein(a) (Lp[a]) is an independent risk factor for atherosclerotic cardiovascular disease especially in patients with diabetes. Adult levels of Lp(a) are thought to be is expressed by the second year of life.
Objective: We hypothesized that Lp(a) would be influenced by low density lipoprotein cholesterol (LDL-C), race, and HbA1C.
Methods: Retrospective electronic medical record review of children and adolescents with type 1 diabetes (T1D) (n = 607) and type 2 diabetes (T2D) (n = 93).
Results: Total of 700 subjects, ages 12-19 years with T1D (n = 607) and T2D (n = 93), 49% were male, mean age was 13.2 ± 3.08 years, and the median Lp(a) was 8.00 mg/dL, IQR 5.00-12.00. The Black subjects had an increased relative risk (RR) of higher Lp(a) compared with White subjects (RR 1.25, $P < .0001$). Among patients with T1D, Black people had an increased relative risk of higher Lp(a) than White people (RR 1.23, $P = .0002$). In T2D, Black subjects have 43% higher risk of having elevated Lp(a) than White subjects (RR 1.43, $P = .268$). In T1D, a 5 mg/dL increase in LDL-C results in 2% increase in Lp(a) ($P < .0001$). In T2D, a 5 mg/dL increase of LDL-C results in an increase of Lp(a) by 3%. LDL-C and BMI are independently associated with Lp(a) (RR = 1.02, $P < .001$; RR = 0.98, $P < .001$).
Conclusion: Our data suggest that Lp(a) is associated with LDL-C in children with diabetes. Lp(a) is differentially increased at higher concentrations of LDL-C. Black children with diabetes have a significant burden of Lp(a) concentrations compared with White children.

Key Words: Lipoprotein (a), diabetes, children, LDL-C

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Cardiovascular disease (CVD) is a significant cause of mortality in those with diabetes [1-4]. Increased apolipoprotein B (apoB) and low-density lipoprotein cholesterol (LDL-C) have been shown in pediatric patients with diabetes with worsening glycemic control [5, 6]. Little information exists on lipoprotein a (Lp[a]) concentrations in children with diabetes [7].

Lp(a) is a highly atherogenic lipoprotein that attaches to the apoB 100 moiety of LDL-C particle. Lp(a) is concentration is generally fully expressed by the second year in childhood [8]. Lp(a) is highly heritable, with great concordance between parental levels [9]. Current evidence in adults suggests a link between Lp(a) levels and CV morbidity and mortality especially risk for atherosclerotic stenosis, myocardial infarction, aortic valve stenosis [10-14] and stroke [15]. Lp(a) is considered to be an independent CV risk factor by the National Lipid Association and European Atherosclerosis Society [16, 17].

Whether to consider routine Lp(a) screening in youth continues to be an area of debate [18]. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents does not recommend measuring Lp(a) levels as part of routine screening except in youth with an ischemic or hemorrhagic stroke or with a parental history of atherosclerotic CVD not explained by classical risk factors [8, 19]. The National Lipid Association recommendation favors targeted screening for Lp(a) levels in children with clinically suspected or genetically confirmed familial hypercholesterolemia, a family history of first-degree relatives with premature atherosclerotic cardiovascular disease (ASCVD), an unknown cause of ischemic stroke, or a parent or sibling found to have an elevated Lp(a) [20]. The European Atherosclerosis Society recommends universal Lp(a) testing of all adults, at least once during their lifetime [21].

In patients with type 1 diabetes (T1D), those with Lp(a) >120 nmol/L have a higher risk of macrovascular disease with a relative risk of 1.51 [22]. Adults with T1D with better metabolic control (hemoglobin A1C [HbA1c] <6.9%) had lower Lp(a) levels compared to those with higher HbA1c [22]. Studies in adults with type 2 diabetes (T2D) show that high Lp(a) could be associated with higher prevalence of macroangiopathy (15% absolute increase) [23]. Another study in adults with T2D showed that that cardiovascular disease was associated with Lp(a) with a hazard ratio of 1.9 and odds ratio of 2.25 [24-26].

The primary aim of this study was to investigate the relationships between serum concentrations of Lp(a) with low-density lipoprotein cholesterol (LDL-C), race, body mass index (BMI), and HbA1C in children with diabetes. Our secondary aim was to evaluate the factors associated with elevated Lp(a) levels. We hypothesized that Lp(a) would be influenced by LDL-C, race, BMI, and HbA1C in children with diabetes.

Materials and Methods

This was a cross-sectional retrospective chart review of pediatric patients, ages 12-19 years, with T1D and T2D who were managed by the Division of Pediatric Endocrinology and Diabetes at Children's of Alabama, University of Alabama at Birmingham. After institutional review board approval, data were obtained from electronic medical records of patients who were evaluated in the outpatient setting from 2007 to 2013. The International Classification of Diseases 9th revision diagnosis codes of 250.01 and 250.03 were used to identify eligible patients with T1D and 250.00 and 250.02 were used to identify T2D. In addition to standard lipid profile testing, the clinical laboratory at Children's of Alabama also offered Vertical Auto Profile (VAP) testing (through a commercial lab, Atherotech, Birmingham, AL) during the study period which was ordered based on the preference of the attending physician. The details of the study and methods have been published previously [27-29].

The inclusion criteria included availability of a body mass index (BMI) measurement (based on CDC growth charts), the availability of VAP profile, and race reported as Black/White by the caregiver at the time of registration to the clinic. Patients were excluded, if they did not have clear characteristics of T1D or T2D, or if they were on cholesterol-lowering medications, hormone contraceptives, or antihypertensives.

VAP is a rapid and highly sensitive method for the measurement of comprehensive lipoprotein cholesterol profile. The VAP methodology has been described in detail previously [30, 31]. In fact, Lp(a) is an LDL particle with apo(a) attached to it. The VAP algorithm will quantify Lp(a) in such cases.

The method is based upon rapid single vertical spin density gradient ultracentrifugation and simultaneously provides cholesterol concentrations of HDL, LDL, VLDL, intermediate density lipoprotein (IDL), and Lp(a) in a single test.

Statistical Analysis

We performed descriptive analyses (means, SDs, medians, interquartile ranges [IQRs], and frequency distributions [%]) to assess and describe the study subjects. We conducted chi-squared, Fisher exact, Mann–Whitney U, Student's t, or Kruskal–Wallis tests as appropriate for initial univariate analysis when study subjects were compared by T1D and T2D groups. We performed negative binomial regression to identify the risk factors associated

with the non-normal right-skewed outcome Lp(a). To quantify the effects of risk factors associated with Lp(a) we estimated relative risks (RRs) with their 95% CIs. Prior to any multivariate analyses, we performed a stepwise initial variable selection and variables with $P \leq .15$ were initially included in the multivariate models. In addition to building multivariable models by employing variable selection methods we also built multivariable models by sequentially adding 1 covariate at time to explore the independent association of LDL-C with Lp(a). All hypothesis tests were 2-tailed, and we used $P < .05$ to indicate statistical significance. We performed analyses in SAS for windows version 9.4 (Cary, NC).

There were no missing data for the main outcome Lp(a). For the whole cohort multivariable regression analysis with 6 covariates there were 15 (2%) missing data points and multivariable models were based on sample size 685. On average for each covariate there were 3 missing data points, which is negligible for 700 subjects. For the T2D subgroup analysis there were no missing data.

Results

There was a total of 700 subjects, age 12-19 years with T1D (n = 607) and T2D (n = 93), of which 49% were male. Table 1 illustrates the characteristics of patients with diabetes. Majority (96.7%) of those with T2D were overweight or obese while 39% of those with T1D are overweight or obese. Six patients had their lipid panel done within in first 3 months after diagnosis. Table 1 shows descriptive and clinical characteristics of the subjects. On average, the subjects with T1D were younger (12.97 years [9.94-16.0] vs 15.2 years [12.5-20.64]), had lower BMI percentile (76.2 vs 99.0 percentile; $P < .0001$) and had a longer duration of diabetes than subjects with T2D (4.65 years [1.08-8.22]) vs 2.71 years [0.97-4.45]). There were 6 subjects who had their lipid panel done within the first 3 months after diagnosis. Subjects with T1D had higher mean HbA1c than those with T2D (9.14% [5.88-12.4] vs 8.27% [5.67-10.87]).

Table 2 presents study sample variables stratified by race. Among the patients with T1D, 477 subjects were White (78%). Among those with T2D, 73 subjects (78.5%)

Table 1. Demographic and clinical characteristics of children with diabetes

Variable	All subjects (n = 700)	T1D (n = 607)	T2D (n = 93)	*P* value
Age (years) at lipid profile	13.27 (3.08)	12.97 (3.03)	15.2 (2.72)	**<.001**
Male (%) (n)	48.86% (342)	51.89% (315)	29.0% (27)	**<.001**
White subjects (%)	71.7%	78.6%	21.5%	
Black subjects (%)	28.3%	20.3%	78.5%	
Duration (years) of diabetes at lipid profile	4.39 (3.54)	4.65 (3.57)	2.71 (1.74)	**<.001**
Weight (kg)	60.26 (23.52)	54.71 (17.22)	96.50 (26.81)	**<.001**
BMI (kg/m^2)	23.68 (6.82)	21.90 (4.37)	35.23 (8.48)	
Mean (SD)		N = 605	N = 93	
BMI percentile	82.0 (58.2, 94.00)	76.00 (54.00, 91.00)	99.00 (96.25, 99.00)	**<.001**
Systolic BP (mmHg)	115.01 (13.46)	113.4 (12.01)	125.41 (17.31	**<.001**
	N = 692	N = 600	N = 92	
Diastolic BP (mmHg)	64.86 (8.24)	64.24 (7.93)	68.89 (9.14)	**<.001**
Mean (SD)	N = 691	N = 599	N = 92	
HbA1C (%)][a,b]	9.02 (3.18)	9.14 (3.26)	8.27 (2.60)	**.015**
Total cholesterol[a] (mg/dL) Mean (SD)	174.4 (38.4)	174.59 (37.63)	173.14 (43.25)	.7351
LDL-C (mg/dL)[a]	98.19 (31.79)	97.33 (30.75)	103.80 (37.59)	.117
HDL-C (mg/dL)[a]	55.84 (14.12)	57.12 (13.84)	47.55 (13.15	**<.001**
TG (mg/dL)	96.50 (68.00, 152.00)	95.00 (67.00,146.00)	113.00 (73.00, 175.00)	.0903
Non-HDL-C[a] (mg/dL)	118.34 (31.79)	117.23 (37.5)	125.59 (41.93)	.0903
TC/HDL-C ratio[a]	3.28 (1.17)	3.20 (1.14)	3.84 (1.19)	**<.001**
ApoB 100 (mg/dL)	82.85 (21.75)	81.85 (20.73)	89.29 (26.90)	**.0121**
	N = 695	N = 602	N = 93	
Lp(a) (mg/dl)[a]	8.00 (5.00, 12.00)	8.00 (5.00, 12.00)	7.00 (5.00, 11.00)	.2890

Continuous variables are reported as mean (SD), median (interquartile range [a]); categorical variables are shown as percent (frequency), n (% total).
Significant differences between groups (bolded) were considered at $P \leq .05$
Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; BP, blood pressure; HbA1C, hemoglobin A1C; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
[a]May not be normally distributed; Wilcoxon rank sum test performed.
[b]Contains suspicious outlier(s)

were Black, while 20 (21.5%) subjects were White. The median Lp(a) was significantly higher in Black people than in White people, 9 (6-14) vs 7 (5-11). HbA1c and BMI were also significantly higher in Black people than in White people (A1c: 9.43 [6.41-12.45] vs 8.52 [4.89-12.15]; BMI:27.60 [18.74-36.36] vs 22.17 [17.07-27.27].

Table 3 demonstrates relative risk of each risk factor for having elevated Lp(a) adjusted for BMI, race, age, gender, and A1c. In the entire cohort, the Black subjects had an increased RR of having higher Lp(a) compared with White subjects (RR 1.25, 1.13-1.38), an estimated 25% higher. Among patients with T1D, Black subjects had an increased relative risk of having higher Lp(a) than Whites (RR 1.23, 1.10-1.38), 21% higher. In subjects with T2D, Black subjects had 47% higher Lp(a) than White subjects (RR 1.44, 1.02-2.01). Estimated risk of having higher Lp(a) was not significantly different by gender, age, and HbA1C. In the whole cohort as well as in children with T1D, a 5 mg/dL increase in LDL-C results in 2% increase in Lp(a) (RR 1.02, 1.01-1.03) Whereas, in children with T2D, a 5 mg/dL increase of LDL-C results in an increase of Lp(a) by 3% (RR 1.03, 1.00-1.05).

Table 4 depicts the crude and adjusted association of variables modifying Lp(a) concentrations. Utilizing a multilinear regression model, BMI ((RR = 0.985, $P < .017$), race (RR = 1.25, $P < .0001$) and LDL-C (RR = 1.02, $P < .0001$) were associated with Lp(a). Lp(a) was strongly associated with LDL-C (adjusted RR = 1.20, $P = <.001$). Race was negatively associated with Lp(a) when comparing White with Black as baseline, which persisted even after adjusting for age, gender, BMI, type of diabetes, and HbA1C. BMI was negatively associated with Lp(a) after adjusting for HbA1C. The glycemic control, age, and gender did not have any significant relationship with Lp(a).

Table 2. Study variables stratified by race

	White (n = 497)	Black (n = 196)	*P* value
T1DM % (n)	96% (477)	63% (123)	**<.001**
T2DM, % (n)	4% (20)	37% (73)	
Age (years)[a]	13.03 ± 3.03	13.89 ± 3.17	**.001**
Sex, male	41%	53%	**.009**
BMI (kg/m^2)[a]	22.17 ± 5.10	27.60 ± 8.86	**<.001**
HbA1c (%)[a]	8.52 ± 3.63	9.43 ± 3.02	**.002**
Lp(a) (mg/dl)[a]	7 (5, 11)	9 (6, 14)	**<.001**

Significant differences between groups (bolded) were considered at $P \leq .05$
Abbreviations: BMI, body mass index; TC, total cholesterol; LDL, low-density lipoprotein; apoB, apolipoprotein B; HbA1c, hemoglobin A1c
[a]T tests used to compare between groups. Values expressed as median (interquartile region). Chi-squared test used to compare difference in percentile between 2 groups

Discussion

Even though Lp(a) is thought to be stable throughout life, our data suggest a significant positive association between Lp(a) levels and LDL-C, a modifiable risk factor, in children with diabetes. Thus, Lp(a) concentrations may potentially alter with changes in LDL-C concentration. The primary finding is that increase in LDL-C resulted in increase in Lp(a) in children with diabetes, both T1D and T2, suggesting that elevations in serum LDL-C concentrations may adversely worsen Lp(a) levels. We also found that Lp(a) is significantly higher in Black children and adolescents with diabetes than in their White counterparts, indicating that Black children with diabetes have a significant burden of Lp(a) concentrations compared with White children. Prior studies including several meta-analyses have provided support for an association between Lp(a) and increased risk of CVD [32, 33]. Our finding that Lp(a) and LDL-C are strongly associated suggests an interaction between these lipoproteins and highlights the importance of adequate

Table 3. Relative risk of for having elevated Lp(a) with risk factors

	Whole cohort (n = 700)		Type 1 diabetes		Type 2 diabetes	
	RR	*P* value	RR	*P* value	RR	*P* value
Race[a]	1.25 (1.13-1.39)	**<.0001**	1.23 (1.10-1.38)	**.0002**	1.43 (1.02-2.01)	**.04**
LDL-C[b]	1.02 (1.01-1.03)	**<.0001**	1.02 (1.01-1.03)	**<.001**	1.03 (1.01-1.05)	**.01**
BMI	0.985 (0.977-0.992)	**<.0001**	0.983 (0.971-0.99)	**.003**	0.987 (0.970-1.00)	.114
HbA1c	0.989 (0.974-1.00)	.127	0.989 (0.974-1.00)	.152	0.989 (0.933-1.05)	.711
Age	0.997 (0.982-1.01)	.687	0.997 (0.981-1.01)	.734	1.01 (0.952-1.07)	.765
Gender	0.925 (0.848-1.01)	.0797	0.928 (0.848-1.02)	.104	1.15 (0.631-1.20)	.384

Relative risk of each risk factor regarding Lp(a) adjusted for BMI, race, type of diabetes, and duration of diabetes.
Abbreviations: RR, relative risk; BMI, body mass index; LDL-C, low-density lipoprotein.
[a]Relative risk comparing Black with White. Values expressed as relative risk (confidence interval).
[b]Significant differences between groups (bolded) were considered at $P \leq 0.05$.

Table 4. Crude and adjusted relative risk of variables modifying Lp(a) concentrations

	Crude		Adjusted 1		Adjusted 2		Adjusted 3		Adjusted 4		Adjusted 5	
	RR		RR	*P*	RR	*P*	RR	*P*	RR	*P*	RR	*P*
Race					1.25 (1.13-1.38)	**<.0001**	1.26 (1.14-1.39)	**<.0001**	1.26 (1.13-1.40)	**<.0001**	1.26 (1.13-1.40)	**<.0001**
BMI			0.990 (0.986-1.00)	**.017**	0.987 (0.980-0.994)	**.0001**	0.985 (0.978-0.991)	**<.0001**	0.985 (0.977-0.993)	**.0004**	0.985 (0.977-0.994)	.0006
LDL-C	1.02 (1.01-1.03)	**<.0001**	1.02 (1.01-1.03)	**<.0001**	1.02 (1.01-1.03)	**<.0001**	1.02 (1.01-1.03)	**<.0001**	1.02 (1.01-1.03)	**<.0001**	1.02 (1.01-1.03)	**<.0001**

Multiple regression of LDL-C with Lp(a), adjusted for BMI (Adjusted 1), race (Adjusted 2), HbA1c (Adjusted 3), type of diabetes (adjusted 4), duration of diabetes (Adjusted 5). Significant differences between groups (bolded) were considered at $P \leq .05$

LDL-C control for primary prevention of CVD risk reduction in children with diabetes.

Lp(a) and HbA1c

Our study shows that HbA1c is not associated with Lp(a) levels in children with diabetes, especially in Black children. Several studies have reported that Lp(a) levels were increased in patients with diabetes while by others, a significant relationship was not observed [25, 34-36]. A prior study of 36 pediatric patients with T1D that showed the highest Lp(a) in those with the poorest glycemic control [35]. Lp(a) levels are reportedly also elevated in diabetic nephropathy [34]. Lp(a) levels have also been shown to be inversely associated with insulin levels in subjects with diabetes [37]. An in vitro study reported that insulin suppressed Lp(a) production in primary primate hepatocytes [38]. Results of studies investigating Lp(a) levels in patients with diabetes are inconsistent.

Relationship of Lp(a) With Lipoproteins

We found that LDL-C positively correlates with Lp(a). This study is one of the few studies that has examined the relationship between Lp(a) and LDL-C in children and adolescents with diabetes. It is unknown whether any observed association between Lp(a) and LDL-C is likely to be causal and further investigated. Our study suggests that LDL-C could modulate Lp(a) concentrations. One population where a similar finding has been found is in patients with familial hypercholesterolemia [39]. In the Copenhagen General Population Study, 46 200 individuals had Lp(a) measurements and were genotyped for common familial hypercholesterolemia mutations. It was proposed that a 39% to 58% increased LDL-C was explained by Lp(a) cholesterol contributing to LDL-C. [40].

Race

We found that Lp(a) is significantly associated with race in both T1D and T2D cohort. Black patients appear to have higher Lp(a) concentrations. Black people reportedly have higher Lp(a) levels than White people [12, 41, 42] in the adult literature, which is in concordance with our findings. In our study the association between Lp(a) and race persisted even after adjusting for glycemic control, duration, and type of diabetes. We acknowledge that our sample size for Black subjects were limited (n = 196), which precludes us from drawing definite conclusions. However, given that Black subjects have higher cardiovascular risk than White subjects, racial differences in Lp(a) should be further explored. The race differences in Lp(a) may contribute for an

increased risk of CVD in the Black population. This has been well reported in adults with diabetes and thus anticipated findings in our study.

Strengths and Limitations of the Study

To our knowledge, this is the first study to investigate the association between Lp(a) and LDL-C in children with diabetes. The strengths of our study include that our study subjects are children without significant kidney disease, therefore minimizing the risk of Lp(a) variability. Another strength is that the VAP test quantifies Lp(a) in terms of its cholesterol concentration unlike the commonly used immunoassay methods which quantify Lp(a) particle mass concentration. The immunoassays results can be skewed due to apo(a) protein heterogeneity given multiple isoforms. The VAP Lp(a) method is not affected by Lp(a) heterogeneity because it measures the cholesterol of Lp(a) particle.

Notable limitations of this study include limited sample size of the T2D cohort and the Black cohort and concern for generalizability due to exclusion of other ethnic groups. However, these differences between groups are likely clinically significant as increased Lp(a) has been shown to have increased CV risk. It remains unclear whether Lp(a) causally influence increased CV risk in patients with diabetes. Further study would be needed to understand the mechanism of the increased Lp(a) and its relationship to LDL-C. Given the retrospective and cross-sectional nature of the study, this would not allow for establishment of causality. One other limitation for this study is that this study focuses on a cohort of patients with diabetes. Given this fact, this study design cannot make inferences about differences between a cohort of patients with diabetes compared to healthy controls. Further prospective, case-controlled studies would be needed to establish these differences.

Conclusion

Lp(a) is strongly associated with LDL-C in children with diabetes, indicating a reduction of LDL-C may additionally reduce CV risk by lowering Lp(a) levels. Larger prospective studies are warranted to elucidate the relationship between Lp(a) and potentially modifiable risk factors. It may be important to consider Lp(a) screening in children with diabetes for disease risk management and implement stricter therapeutic goals for LDL-C reduction.

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Additional Information

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