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Assessment of lipid profile and some risk factors of atherosclerosis in children whose parents had early onset coronary artery disease

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ABSTRACT

***Background/Aim*:** The objective of our study was to analyze the lipid profile and some risk factors of atherosclerosis such as oxidized-low density lipoprotein (ox-LDL), small dense LDL (sd LDL) in the offspring of patients with premature coronary heart disease (CHD).

***Population and Methods*:** Children whose parents had early onset CHD were matched with age and sex pairs. Study and controls were analyzed for lipid levels, apolipoproteins (Apo-A,B,E), ox-LDL, sd LDL and lipoprotein (a) [Lp(a)]. The data were evaluated with SPSS using "Student t and Mann-Whitney U" tests.

***Results*:** The study group children (n: 43) had higher LDL, Lp(a) and ox-LDL levels, ratios of TC/HDL, Apo-B/A, LDL/HDL and ox-LDL/HDL ($p<0.05$) than control group.

***Conclusion*:** These findings suggest that dyslipidemia and increased LDL, Lp(a) and ox-LDL levels are common in the offspring of patients with early onset CHD and account largely for their familial predisposition for CHD.

Key words: *coronary artery disease, lipids, offspring, risk factors, children.*

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INTRODUCTION

Atherosclerosis is defined as a condition starting from early stages of life and resulting in coronary heart disease (CHD) in middle-age and thereafter. First-degree relatives and offspring of patients who have had CHD prior the age of 55 years have higher risk for development of CHD.[1,2] The process is initiated by the capture and oxidation of lipoproteins at locations prone to lesion formation. Low density lipoprotein (LDL) has been proved to be cytotoxic and definitely atherogenic due to the oxidative modification in endothelial cell cultures. Oxidized-LDL (ox-LDL) is the new parameter considered to have a predictive value in the development of atherosclerosis.[2]

LDL has a heterogeneous structure, consisting of two phenotypes of particles sizes. Type A has a larger size and consists of more buoyant LDL particles. Type B has a smaller size and consists of small dense LDL (sdLDL) particles; sdLDL shows strong atherogenic properties due to increased penetration on arterial wall, decreased binding tendency for LDL receptors, a long half-life in plasma and probably increased sensitivity to oxidative changes. Numerous cross-sectional studies have shown significant associations between LDL particle size and specially sdLDL levels and CHD.[3] In many studies, the predictive role of apolipoproteins (decreased Apo-A, Apo-E and increased Apo-B levels) and lipoprotein-a [Lp(a)], in development of CHD is superior to that of serum lipids.[4,5] The objective of our study was to analyze the lipid profile and some risk factors of atherosclerosis such as ox-LDL, sdLDL, Lp(a) in the offspring of patients with premature CHD.

POPULATION AND METHODS

This prospective study was performed in Pediatric Cardiology Department of Istanbul Medical Faculty between 2010 and 2015 with the permission of Local Ethic Committee. Healthy children, between the age of 6-18 years, who were offspring of subjects suffering from a premature CHD (men <45 years, women <55 years of age) constituted the study group. The control group consisted of age and sex matched healthy subjects without any family history of premature CHD. All groups were selected from outpatient clinic due to detection of an innocent

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murmur. Children who had cardiac deformity, hypertension, chronic disease such as diabetes mellitus, hepatic and renal failure, malnutrition, genetic and endocrinologic disease which affect growth and cardiac development were excluded from the study. Written informed consent was obtained from parents, whose children participated in the study.

The CHD risk factors, body mass index (BMI), systolic and diastolic blood pressure (BP) were compared between groups. The biochemical parameters were assessed using blood samples taken in fasting state; total cholesterol (TC), triglyceride (TG), HDL, Lp(a), Apo A and Apo-B were analyzed using Integra-800 (Roche) according to the Friedewald formula. Apo E levels were studied with a nepholometric method with BN ProSpec System (Dade Behring) autoanalyzer. Modified heparin-magnesium settling method was used for sdLDL analysis. Ox-LDL level measurements were conducted using ELISA (oLAB kit, Biomedica).

The comparisons among groups were made by student t and Mann-Whitney U tests. Statistical significance was considered as $p < 0.05$.

RESULTS

Forty-three children, whose parents had early onset CHD (study group) were matched with age and sex pairs (controls, n= 43). There was no statistically significant difference between groups with regard to weight, height, BMI, and systolic and diastolic BP (*Table 1*). Lipid profiles were compared between groups and the results of the comparison are presented in *Table 2*. No statistically significant difference regarding TC, TG, VLDL and sdLDL was detected. LDL, Lp(a), Ox-LDL levels were found to be higher in the study group compared to the control group ($p < 0.05$) (*Table 2*). There was no significant difference regarding TG/HDL ratio and LDL/Apo-B ratio between the two groups. The inter-group comparison revealed significant differences regarding LDL/HDL ratio, TC/HDL ratio, Apo-B/Apo-A ratio, and ox-LDL/HDL ratio (*Table 2*).

DISCUSSION

The present study represents the first study that investigates the lipid risk factors for CHD in the offspring of patients with premature CHD in Turkish population. Our data showed significant increased levels of LDL, ox-LDL and Lp(a) in this population. Given the age of the cases, an important reason for this predisposition can be attributed to genetic factors.[1,2]

Endothelial dysfunction is a very early step in atherosclerosis, which is one of the most common pathological manifestations of vascular disease. The interaction between lipoproteins and endothelial cells plays a crucial role in the generation and development of atherosclerosis. Ox-LDL promotes the pathogenesis and development of atherosclerosis and the proliferation, migration and phenotype alteration of vascular smooth muscle cells into foam cells are critical changes in atherosclerosis. It might play a novel role in the pathology.[3] Johnston et al.[6] concluded that ox-LDL levels and ox-LDL/HDL ratio are the superior and more

Table 1. *Characteristics of study and control groups*

	Study group n= 43	Control group n= 43	*p*
Age (years)	13.3 ± 3.6 (5.0-18.2, 14.0)	13.3 ± 3.6 (5.0-18.2, 14.0)	-
Weight (kg)	50.2 ± 15.9 (17.0-86.2, 49.0)	50.7 ± 17.4 (15.4-85.2, 51.0)	0.41
Height (meter)	1.5 ± 0.2 (1.06-1.79, 1.59)	1.5 ± 0.2 (1.03-1.79, 1.59)	0.48
BMI (kg/m^2)	21.0 ± 4.1 (13.5-30.8, 21.2)	20.6 ± 4.1 (12.8-30.5, 21.6)	0.91
Systolic blood pressure (mmHg)	115.3 ± 12.2 (89-146, 114)	115.8 ± 10.0 (89-138, 120)	0.53
Diastolic blood pressure (mmHg)	69.4 ± 8.6 (54-84, 70)	70.1 ± 8.1 (54-85, 75)	0.67

Data were given as mean ± standard deviation (minimum-maximum, median), BMI: Body mass index.

accurate measure compared to classic routine lipid profiles. However, majority of these studies were conducted among adult population and the studies about atherogenic risk factor among children are still limited. Similar to our study; Kelishadi et al.[7] demonstrated elevated ox-LDL metabolites in children with a family history of early-onset CHD. Our study also revealed higher ox-LDL/HDL ratios in the study group. Considering these results, it is concluded that LDL is more sensitive to oxidation in children with a family history of early-onset CHD. If further studies support our findings, preventive approaches and anti-oxidants will gain importance, particularly in children of the families at high risk. Furthermore, ox-LDL/HDL ratios might be given a priority for detection of subjects at risk rather than using the other familiar classic risk factors of CHD.

The ratios between lipid and lipoprotein parameters regarding the CHD risk are also important in the studies.[4,8] The results of our study agree with the study conducted by Widhalm et al.[9] and Rallidis et al.[10] These studies showed a higher level of TC/HDL and LDL/HDL when these ratios were compared between groups.

The predictive role of apolipoproteins in development of CHD is superior to that of

Table 2. *Comparison of lipid parameters in study and control groups*

	Study group n= 43	Control group n= 43	*p*
Total cholesterol (TC)	138.2 ± 27.6 (64.2-97.4, 129.1)	129.9 ± 27.8 (86.2-207.4, 132.1)	NS
Triglyceride (TG)	96.2 ± 58.7 (26.2-281.2, 81.4)	85.9 ± 49.5 (25.2-305.3, 84.4)	NS
HDL	41.6 ± 13.1 (10.4-79.1, 42.3)	46.4 ± 10.8 (24.2-74.3, 44.4)	NS
LDL	77.6 ± 18.9 (36.4-110.1, 70.2)	66.2 ± 20.4 (36.4-125.1, 72.0)	**<0.01**
VLDL	19.2 ± 11.7 (5.0-56.1, 15.2)	17.24 ± 9.9 (5.0-61.1, 16.2)	NS
Lp(a)	12.2 ± 7.4 (4.1-37.2, 9.5)	9.1 ± 5.1 (2.1-22.2, 8.4)	**<0.05**
Ox-LDL	418.4 ± 180.1 (108.1-909.4, 342,0)	302.0 ± 162.9 (100.1-792.4, 308.2)	**<0.01**
sd LDL	11.0 ± 4.7 (1.4-22.7, 10.5)	10.3 ± 4.7 (1.5-24.0, 10.5)	NS
Apo-A	121.1 ± 25.8 (54.0-177.1, 120.4)	129.1 ± 22.2 (70.4-170.2, 126.0)	NS
Apo-B	57.8 ± 13.2 (22.2, 84.2, 58.4)	52.6 ± 13.7 (21.0-83.2, 54.3)	NS
Apo-E	3.3 ± 0.8 (2.4-5.2, 2.7)	4.60 ± 7.2 (2.4-5.1, 3.8)	NS
LDL/HDL	2.1 ± 1.1 (0.8-7.2, 1.8)	1.5 ± 0.5 (0.8-3.1, 1.4)	**<0.01**
TG/HDL	2.9 ± 2.93 (0.4-18.0, 1.8)	2.1 ± 1.9 (0.5-12.0, 1.8)	NS
TC/HDL	3,7 ± 1.6 (1.9-11.8, 3.2)	2.9 ± 0.8 (2.0-5.6, 2.9)	**<0.01**
Apo-B/ Apo-A	0.5 ± 0.2 (0.3-1.2, 0.5)	0.4 ± 0.1 (0.4-1.4, 0.4)	**<0.05**
LDL/Apo-B	1.4 ± 0.2 (1.1-2.6, 1.4)	1.3 ± 0.3 (0.8-2.5, 1.3)	NS
Ox-LDL/HDL	11.3 ± 7.1 (2.5, 44.4, 14.2)	6.9 ± 3.2 (2.0-16.6, 7.2)	**<0.05**

Data were given as mean±SD, (minimum-maximum, median). HDL: High density Lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein. Lp(a): lipoprotein-a. Ox-LDL: oxidative low density lipoprotein. sd LDL: small dense LDL. Apo-A: apoprotein A. Apo-B: apoprotein B. Apo-E: apoprotein E.

serum lipids. Beigel et al.[11] showed that apolipoproteins provide an important parameter in screening coronary risk factors in children. They demonstrated lower Apo-A levels, higher Apo-B levels, and higher Apo-B/A ratios in their subjects. Many investigators now consider Apo-B/A as a significant predictive parameter in determining the groups at risk during the evaluation of cardiovascular risk factors.

Lp(a) is composed by a central LDL-like lipoprotein core particle with Apo-B covalently bound to glycoprotein Apo-A, resulting in the growing of the atherosclerotic plaque.[12,13] We demonstrated higher Lp(a) values in study group. Rallidis[10] and Wilcken et.al.[12] stated that increased Lp(a) was important risk factors of CHD in children with a familial history. Our study also support that Lp(a) values are accepted as a useful marker to predefine the subjects at risk among children with a family history of early-onset CHD.

Numerous retrospective studies have shown significant associations between sdLDL levels and CHD. In subjects with high sdLDL, risk of CHD increases independent from LDL levels. The measurement of this risk factor may be relevant in screening of subjects at risk from childhood.[3] According to Quebec Cardiovascular Studies[14] increased Apo-B values in sdLDL as an important risk factor in development of early-onset CHD. Some recent studies demonstrate findings showing that the cholesterol content of sdLDL has predictive value in determining subjects at risk of CHD. For instance, a study conducted in Japan by Koba et al.[15] in 2006 showed higher sdLDL levels in subjects with CHD compared to the control group. The same study compared sdLDL values between a total of 225 subjects aged 45-75 with CHD and the control group, and showed significant difference. Our studies did not support these findings as the sdLDL levels were similar in both groups, It might be attributed to the younger age of our study group.[3]

The most obvious limitation of this study was its hospital based design and small sample size. Thus, the results must be interpreted with caution. Other limitation was in the evaluation of subjects for diet and exercise behavior. We performed only self-report conversations and did not use diet and exercise questionnaire. Although this study had limitations, it can give valuable data about children whose parents had early onset CHD.

In conclusion, the results of this study suggest the necessity for screening and early detection of dyslipidemia in the offspring of subjects with premature CHD. These children may benefit from dietary measures and daily activities can be instituted as a first step toward a healthy life style for primary prevention of atherosclerosis. ■

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