First Report on the Lipid Profile Late after Kawasaki Disease in Iranian Children

Seyyed-Naserredin Mostafavi[1,2], Elham Barzegar[3], Nayereh Siyah Manssori[4], Roya Kelishadi[5]

[1]Department of Pediatrics, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Pediatrics, Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Pediatric Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of pediatric surgery Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Department of Pediatrics, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence to:
Prof. Roya Kelishadi,
Department of Pediatrics, Child Growth and Development Research Center,
Isfahan University of Medical Sciences,
Isfahan, Iran.
E-mail: kelishadi@med.mui.ac.ir

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Original Article

ABSTRACT

Background: Concerns have been raised about the possibility of a predisposition of Kawasaki disease (KD) to abnormal lipid profile after an acute phase of disease, which can predispose them to premature atherosclerosis later in life. We determined the lipid profile of children late after KD, and compared it with controls.

Methods: This historical cohort was conducted on 32 subjects: 16 children with history of uncomplicated KD (age 11.8 ± 3.3 years, interval from the initial episode 7.1 years), and 16 healthy age-matched of their sibling or cousins. Fasting serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) levels were compared between groups. In addition, blood pressure and body mass index (BMI) were measured and compared.

Results: Six out of 16 KD patients and 7 out of 16 controls had abnormal lipid values. No significant difference was found in mean values of systolic blood pressures, diastolic blood pressures, BMI, TG, TC, HDL-C, and LDL-C between cases and controls.

Conclusions: We conclude that although Iranian KD children probably had no different lipid profile compared with controls, but due to finding dyslipidemia in more than one-third of KD subjects, we suggest that periodic control of lipid values in these patients is of crucial importance.

Keywords: Atherosclerosis, children, Iran, Kawasaki disease, lipid profile

INTRODUCTION

Kawasaki disease (KD) is a common vasculitis of childhood with significant cardiovascular consequences as aneurismal formation, ectasia, and fibrosis in coronary arteries.[1] Recent studies revealed that low grade vascular inflammation can persist for a long period of time after clinical improvement of acute KD.[2-4] Progressive impairment in predictors and indicators of atherosclerosis as decreased flow mediated dilatation of the brachial artery, and increased intima media thickness of carotid artery are attributed to this long-term endothelial inflammation.[2,5,6]

Dyslipidemia during childhood is important.[7] A growing body of evidence, although controversial, proposed that prolonged pro-atherogenic change in serum lipid profile, that is, decreased high-density lipoprotein cholesterol (HDL-C), increased triglycerides (TG), and/or increased low-density lipoprotein cholesterol (LDL-C) may occur in children after KD.[1,3,4,8-10] This can put KD patients at increased risk for premature atherosclerosis.

Nationwide studies in Iran revealed that dyslipidemia, notably low HDL-C and elevated TG are prevalent in Iranian children and adolescents[11,12] even in those with normal weight.[13]

Given the conflicting results about serum lipid levels after KD[1,3,4,8-10] and high prevalence of dyslipidemia in Iranian children,[11-13] and by considering ethnic differences in the lipid profile of children and adolescents,[14] in the current study, we examined lipid profile of Iranian KD patients at least 4 years after resolution of acute KD.

METHODS

This historical cohort was conducted in 2012 in Isfahan, Iran. The Institutional Ethics Committee of Isfahan University of Medical Sciences (IUMS) approved the study. Oral assent was obtained from participants, and written informed consent was obtained from their parents.

Study population

Patients with a history of admission in AlZahra Hospital, Isfahan, Iran, which is the only tertiary care referral hospital for the pediatric age group affiliated to IUMS, were recruited for assessment of cardiovascular risk factors. All patients had confirmed diagnosis of KD in 4-10 years prior to the current study. The diagnosis of KD was made based on the criteria of the American Heart Association.[1] The following information was obtained from the patient's medical files: Age at the diagnosis of KD, drugs administered, coronary complications, and interval from the disease onset to the current study.

Age-matched sibling or cousins of KD patients, who had no history of KD and any chronic disease, were invited to participate as the control group.

Subjects with a family history of hyperlipidemia, or those using medications influencing on lipid values, as steroids, thiazides, and propranolol were excluded from the study. In addition, children with any chronic disease as diabetes mellitus, hepatic disorder, renal disease, or thyroid abnormalities, were excluded by appropriate history, physical examinations, and conducting laboratory tests, including fasting blood sugar, alanine aminotransferase, serum albumin, serum creatinine, and thyroid stimulating hormone levels.

Participants and one of their parents were invited to our clinic; children were asked to come after a 12-14 h overnight fasting. A team of expert physicians and nurses conducted the physical examination under standard protocols and by using calibrated instruments. Body weight and height were measured in a light cloth and without shoes in duplicate for more accuracy. Body mass index (BMI) was computed as weight (kg) divided by height squared (m^2). After at least 15 min of rest, systolic and diastolic blood pressures (SBP, DBP) were measured in the seated position and from the right arm. Each child was examined by two separate experienced physicians and the average of the two exams was recorded as real blood pressure.[15]

Afterward, 4-5 mL venous blood sampling was collected from each participant and was analyzed in the laboratory of AlZahra hospital, which is under quality control of the National Reference Laboratory (a collaborating center of the World Health Organization in Tehran).

Laboratory assays

Triglycerides and total cholesterol (TC) levels were measured using an enzymatic colorimetric assay (Pars Azmoon kit, Tehran, Iran) by an automatic serum auto analyzer (Hitachi 902; Boehringer Manneheim, Germany). LDL-C and HDL-C levels were measured directly by immuno-turbidometric assay (Pars Azmoon kit; Tehran, Iran). Samples were tested in batches to minimize inter-assay differences. Cut-offs proposed by the National Cholesterol Education Program on blood cholesterol in American children and adolescents were used to define normal values. TC > 170 mg/dL, LDL-C > 110 mg/dL, HDL-C < 35 mg/dL, and TG levels > 150 mg/dL were considered as abnormal lipid profile.[16]

Statistical methods

Data were analyzed using SPSS for Windows software version 20 (SPSS Inc., Chicago, IL, USA). Results of age, SBP, DBP, BMI, and mean

lipid profile were expressed as the mean ± standard deviation. For gender and abnormal lipid profile, the number of participants was reported. Comparisons between the age, BMI, blood pressure, and mean lipid profile in two groups were performed by Student's *t*-test. For gender variable and number of subjects with abnormal lipid profiles the Chi-square test was applied. For all analyses, $P < 0.05$ was considered to be statistically significant.

RESULTS

Sixteen KD patients and 16 control subject were enrolled in the study. In the KD group, the mean age at the diagnosis of KD was 5.4 (6.2 ± 3.3) years and the interval time between the acute phase of the disease and the current study was 7.1 (6.5 ± 2.5) years. All KD patients had received intravenous immunoglobulin and aspirin in early phases of the disease and none had coronary complication at any stages. Demographic, clinical, and laboratory findings of the cases and controls are summarized in Table 1. The groups were comparable in regard of age, gender, and BMI. No significant difference was found in mean values of SBP, DBP, TG, TC, HDL-C, and LDL-C of the two groups studied.

Table 1: Demographic, clinical and lipid profile characteristics of KD and control groups

Demographic characteristic	Group (*n*=16)		*P* value
	KD	Control	
Age (years)	11.8±3.3	12.0±4.8	0.9
Gender (male/female)	6/10	9/7	0.29
BMI (kg/m^2)	19.0±4.6	19.9±7.0	0.69
Clinical assessment			
SBP (mmHg)	108.1±13.1	108.4±20.0	0.96
DBP (mmHg)	73.4±11.2	69.4±14.1	0.38
Lipid profile			
Mean TG	127.4±54.3	102.1±38.6	0.14
TG>150 mg/dL	4	1	0.33
Mean TC	162.0±24.3	164.9±20.9	0.72
TC>170 mg/dL	6	7	0.72
Mean LDL-C	92.6±18.6	96.5±18.9	0.57
LDL-C>110 mg/dL	3	5	0.41
Mean HDL-C	43.9±7.2	48.0±8.7	0.16
HDL<35 mg/dL	1	1	1.00

KD=Kawasaki disease, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, TG=Triglyceride, TC=Total cholesterol, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol

Six out of 16 KD patients and 7 out of 16 controls had abnormal lipid values. In KD group all of these patients had elevated cholesterol levels. One had also elevated TG, LDL-C, and decreased HDL-C levels. Two others had elevated TG and LDL-C, but normal HDL-C levels. One had only high TG in addition to increased TC level. The number of individuals with dyslipidemia was not significantly different between the case and control groups.

DISCUSSION

This study showed that more than one-third (6 out of 16) of children with history of uncomplicated KD in an average interval of 7.1 years prior to the study had abnormal lipid profile. The most common abnormal finding in the KD group was high TC followed by increased TG, elevated LDL-C, and decreased HDL-C levels. However, the mean number of individuals with dyslipidemia as well as the mean values of serum lipids, BMI, SBP and DBP was not significantly different in the case and control groups.

To the best of our knowledge, this is the first study to report lipid profile of Iranian children with history of KD. Adverse cardiovascular risk profile manifested as increased BP and abnormal serum lipid levels has been reported in some studies performed long after resolution of acute inflammation of KD in other populations.[1,3,4,8-10]

It is well-documented that increased levels of TC, TG, and LDL-C are of the major risk factors for atherosclerosis.[17]

We found that the mean TC levels in children long after improvement of acute KD was comparable to controls, this finding is in line with previous studies.[3-5,8-10,18,19]

Moreover, in 7 out of the 8 previous investigations, the difference between TG levels has not been significant between KD groups and controls.[3-5,8,9,18,19] Our study showed similar TG level between the case and control groups.

In addition, like other 3 previous studies that showed similar mean LDL-C levels between individuals with history of KD and the control groups,[4,9,18] we did not find any difference between the two groups studied. A study reported higher mean LDL-C level in cases with history of KD than in controls.[10]

The most reported abnormal lipid profile in individuals with a previous history of KD is

decreased serum HDL-C level. Low HDL-C is known as an important predictor of coronary heart disease. Some studies reported that the high HDL-C levels are protective against atherosclerosis.[8] The results of two studies in KD children with coronary complications, which were performed 2-8 years after resolution of acute phase of KD revealed a significant decrease in the level of serum HDL-C compared to controls.[3,9] In one of these studies, the mean of HDL-C in the case and control groups was 44.34 and 42.51 mg/dL respectively.[3] Similarly, another study in children with history of coronary uncomplicated KD in 2.6 years prior to the study time elucidated significant lower values of HDL-C in the patients than in controls.[8] Although the difference between serum values of HDL-C in these studies were statistically significant, but given the close mean serum values of both groups, the clinical significance of this difference is questionable. In contrast to these reports, in three other studies conducted 5-14 years after improvement of acute phase of KD, the mean serum levels of HDL-C in KD patients with normal or abnormal coronary arteries was not significantly different from that of controls.[5,18,19] In our study, we found no significant difference in HDL-C levels between coronary uncomplicated KD patients and controls. Discrepancies between studies may be related to the small number of available KD patients at long-term follow-up, and as a consequence lack of sufficient statistical power, different racial characteristics, or diverse nutritional habits of the subjects. Altogether, it is suggested that in spite of significant differences of TG, LDL-C, and HDL-C levels in KD patients and controls reported in some studies, the magnitude of the differences in these studies were not extreme and may only represent a minimal increase in cardiovascular risk, with uncertain long-term significance.

Study limitations and strengths

A limitation of our study is the small number of participants to preclude strong assertion about lipid values of Iranian KD patients. Some parents of children refused to participate in the study and some were not accessible from phones and addresses in their hospital records. However, comparable number of subjects with other studies in this regard and also concordant results with most other similar studies suggests that our findings could be reliable. The strengths of this study are the novelty in Iranian KD patients and the long-term follow up of patients.

CONCLUSIONS

We conclude that Iranian children with history of KD within 4-10 years of acute illness probably had not abnormal mean lipid profile compared to the normal population. Although due to abnormal endothelial function that predispose KD patients to premature atherosclerosis and according to our results, which showed that more than one-third of children with history of KD had abnormal lipid values, we suggest that periodic control of adverse risk factors of atherosclerosis in KD patients is of crucial importance.

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