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### Title

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### Permalink

<https://escholarship.org/uc/item/8h47565g>

### Journal

Journal of Pediatrics, 165(4)

### ISSN

0022-3476

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### Publication Date

2014-10-01

### DOI

10.1016/j.jpeds.2014.06.017

Peer reviewed

# Lipoprotein Particle Concentrations in Children and Adults following Kawasaki Disease

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**Objective** To test the hypothesis that children and adults with a history of Kawasaki disease (KD) are more likely to have abnormal lipoprotein particle profiles that could place them at increased risk for developing atherosclerosis later in life.

**Study design** Fasting serum samples were obtained from 192 children and 63 adults with history of KD and 90 age-similar healthy controls. Lipoprotein particle concentrations and sizes were measured by nuclear magnetic resonance spectroscopy (LipoScience Inc, Raleigh, North Carolina), and serum was assayed for total cholesterol (TC), triglycerides, and high-density lipoprotein (HDL) cholesterol (HDL-C). Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula. Data were analyzed in a least-square means model, with adjustment for age and sex and with the use of Holm correction for multiple comparisons.

**Results** Compared with respective control groups, both adult and pediatric subjects with KD had significantly lower mean very low-density lipoprotein-chylomicron particles, intermediate-density lipoproteins, triglycerides, and TC concentrations. Pediatric subjects with KD had significantly lower LDL particle and LDL cholesterol concentrations and lower mean TC/HDL-C ratio ( $P < .001$ ). In contrast, the adult subjects with KD had significantly lower HDL particle, small HDL particle, and HDL-C concentrations ( $P < .001$ ), but HDL-C was within normal range.

**Conclusions** Nuclear magnetic resonance lipoprotein particle analysis suggests that pediatric and adult subjects with KD, regardless of their aneurysm status, are no more likely than age-similar, healthy controls to have lipid patterns associated with increased risk of atherosclerosis. (*J Pediatr* 2014; ■: ■ - ■).

Since the first published report in 1967, Kawasaki disease (KD) has become the leading cause of acquired pediatric heart disease in developed countries.<sup>1,2</sup> Coronary artery aneurysms develop in 25% of untreated patients, placing them at increased risk for cardiovascular complications, including myocardial ischemia and infarction.<sup>3-6</sup> The current guidelines of the American Heart Association recommend lipid profile screening for those who have recovered from KD because of concerns that these patients may be at increased risk of accelerated atherosclerosis.<sup>7</sup> Determination of lipoprotein profiles is one component of risk stratification for the development of atherosclerosis, a process that may be superimposed upon existing arterial wall damage, termed KD vasculopathy.

The protective role of high-density lipoprotein (HDL) and pathogenic role of low-density lipoprotein (LDL), especially the small-dense LDL, in atherosclerosis and coronary artery disease are well-established. However, the traditional lipid panel may not provide the most robust measurement of lipoprotein-attributable risk.<sup>8</sup> Nuclear magnetic resonance (NMR) spectroscopy directly quantifies the number of LDL and HDL particles (LDL-Ps and HDL-Ps) and their size distribution and may yield a more accurate assessment of atherosclerotic risk.<sup>9-13</sup> Results of multivariable analyses from several studies in adults have supported the hypothesis that it is the number of lipoprotein particles, not lipoprotein particle size or concentration of cholesterol, that is most strongly associated with atherosclerotic risk.<sup>14-16</sup> Studies of lipid profiles in small cohorts of acute and convalescent patients with KD have yielded conflicting results.<sup>17-21</sup> Using NMR lipoprotein particle counts, we sought to assess whether pediatric and young adults with KD are more likely to have atherogenic lipid profiles compared with healthy control subjects.

CAA	Coronary artery abnormality	LDL-P	Low-density lipoprotein particle
HDL	High-density lipoprotein	NMR	Nuclear magnetic resonance
HDL-C	High-density lipoprotein cholesterol	TC	Total cholesterol
HDL-P	High-density lipoprotein particle	TG	Triglyceride
KD	Kawasaki disease	VLDL	Very low-density lipoprotein
LDL	Low-density lipoprotein	VLDL-C-P	Very low-density lipoprotein-chylomicron particle
LDL-C	Low-density lipoprotein cholesterol		

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Supported by the American Heart Association, National Affiliate (09SDG2010231 to L.D.), the National Institutes of Health, Heart, Lung, and Blood Institute (RO1-HL69413 to J.B.), and the Gordon and Marilyn Macklin Foundation (to J.B. and L.D.). The authors declare no conflicts of interest.

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<http://dx.doi.org/10.1016/j.jpeds.2014.06.017>

## Methods

Pediatric subjects included 192 children and adolescents with a history of KD diagnosed and treated at Rady Children's Hospital San Diego, between November 2005 and June 2011. Inclusion criteria were initial diagnosis of KD according to criteria from the American Heart Association and phlebotomy performed at least 11 months after the onset of KD.<sup>7</sup> Serum samples also were obtained from 45 age-similar, healthy control children who were fasting before undergoing minor orthopedic surgical procedures. Adults with KD included 63 young adults enrolled in the San Diego Adult KD Collaborative study. Fasting serum samples were obtained at study enrollment. Adult healthy controls included 45 age-similar healthy volunteers with no history of KD or heart disease. One pediatric subject and 11 adult subjects who were on lipid-lowering medications were excluded. Only 2 subjects with mild mixed hyperlipidemia were on statin therapy for lipid-lowering effects. The remaining 10 subjects were on statin therapy either as standard practice postmyocardial infarction or for the potential anti-inflammatory benefits of statins in the setting of coronary artery abnormalities (CAAs) after acute KD. None of the control subjects were on any lipid-lowering medication. Written informed consent, and assent when appropriate, was obtained from the parents of subjects or the subjects themselves. The protocol was approved by the Institutional Review Board at the University of California San Diego.

Fasting serum samples (stored at  $-80^{\circ}\text{C}$  before testing) were assayed for total cholesterol (TC), triglycerides (TGs), and HDL cholesterol (HDL-C) via the use of standard automated methods on a Vitros 5.1 FS Chemistry System instrument (Ortho Clinical Diagnostics, Rochester, New York). LDL cholesterol (LDL-C) was estimated with the Friedewald formula. Lipoprotein particle profiles were measured by NMR spectroscopy with the LipoProfile-3 algorithm from LipoScience Inc (Raleigh, North Carolina). Very low-density lipoprotein (VLDL)-chylomicron particle (VLDL-C-P), LDL-P, and HDL-P subclasses were quantified by the amplitudes of their spectroscopically distinct lipid methyl group NMR signals. Weighted-average VLDL, LDL, and HDL Particle sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.

Body mass index was calculated from hospital records (pediatric subjects) or by measurements obtained for this study at the time of phlebotomy (adult subjects). Coronary artery status was determined by echocardiography for the pediatric subjects with KD. Subjects were classified as dilated if the internal diameter of the coronary artery normalized for body surface area and expressed as SD units from the mean ( $Z$  score) exceeded 2.5 for the left anterior descending or right coronary arteries assessed by echocardiography during the first 6 weeks after disease onset. Aneurysms were defined as a segment  $\geq 1.5$  times the diameter of the adjacent segment. Adult subjects with KD were evaluated by a combination of

invasive, computed tomography, and magnetic resonance angiography and classified as having normal or aneurysmal coronary arteries.

## Statistical Analyses

Patient characteristics were summarized by group. Medians and IQRs were reported for continuous variables, and frequency counts and percentages were reported for categorical variables. For each of the lipoprotein outcomes, linear regression models were used to compare the differences between subjects with KD and control subjects, as well as between subjects with KD with and without CAAs ( $Z \leq 2.5$ ), after we adjusted for age and sex. Least-square means from the models were reported with 95% CIs, and 2-sided  $P$ -values  $< .05$  were considered statistically significant. Holm multiple testing adjustment procedure was applied. Statistical analyses were performed in R (<http://cran.r-project.org>), version 2.14.0.

## Results

There were no significant differences in the demographic or clinical features of the pediatric and adult groups with KD and their respective controls except for an excess of females in the adult healthy control group (Table I). These differences were taken into account in the analysis model, adjusting for age and sex.

The analysis of serum using the NMR LipoProfile test (LipoScience Inc) provided lipoprotein particle concentrations for all groups (Table II), whereas the lipid panel provided cholesterol and TG concentrations. Table III<sup>22,23</sup> separates lipoprotein particles and cholesterol concentrations that are known to be atherogenic and atheroprotective. High concentrations of VLDL, intermediate-density lipoprotein, LDL, and TG concentrations are all known to be associated with atherosclerosis. Both pediatric and adult subjects with KD had significantly lower mean VLDL-C-P, intermediate-density lipoprotein particles, and TG concentrations compared with their respective control groups. Pediatric subjects with KD also had significantly lower mean total LDL-P and LDL-C concentrations ( $P = .001$  and  $P < .001$ , respectively), and a lower mean TC/HDL compared with the healthy pediatric control subjects ( $P < .001$ ). For the pediatric cohort with KD, we compared lipoprotein particle counts with the maximum  $Z$  score of the right and left anterior descending coronary arteries measured by echocardiography during the first 6 weeks after illness onset. For the adult cohort, we compared lipoprotein particle counts between subjects with and without CAA. When we compared the pediatric or adult cohorts via linear regression analysis, we found no significant relationship between lipoprotein particle counts and coronary artery status. Similarly, both pediatric and adult subjects with CAA had similar lipoprotein particle counts that did not differ significantly from the respective healthy control cohort (data not shown).

**Table I.** Demographic and clinical characteristics of study cohorts

Characteristics	Pediatric KD, n = 192	Pediatric healthy controls, n = 45	Adult KD, n = 63	Adult healthy controls, n = 45
Median age, y (IQR; range)	5.4 (3.5-7.9; 1.1-15.3)	4.7 (3.3-6.5; 1.4-15.9)	21.7 (18.4-27.6; 16.0-46.3)	23.3 (22.0-25.8; 16.4-49.0)
Male, n (%)	125 (65)	23 (51)	34 (54)	13 (29)
Interval between KD onset and phlebotomy, years (IQR; range)	1.4 (1.1-4.7; 0.9-12.6)*	N/A	17.6 (14.3-24.3; 1.1-37.4)†	N/A
Coronary artery status of subjects, n (%)				
Normal	134 (70)	N/A	51 (81)	N/A
Dilated	35 (18)		3 (5)	
Aneurysm	23 (12)		9 (14)	
BMI, kg/m <sup>2</sup> , median (IQR; range)	16.5 (15.2-18.6; 12.9-28.7)	16.4 (15.7-18.0; 14.2-38.2)‡	22.2 (20.0-24.6; 15.6-36.8)§	22.3 (20.8-23.9; 19.0-32.5)
Ethnicity, n (%)				
Asian	29 (15)	2 (5)	13 (21)	21 (47)
Black/African American	8 (4)	4 (9)	2 (3)	0 (0)
White	47 (25)	29 (64)	32 (51)	20 (44)
Hispanic	62 (32)	8 (18)	8 (13)	3 (7)
More than one race	38 (20)	2 (4)	7 (11)	1 (2)
Native Hawaiian or other Pacific Islander	2 (1)	0 (0)	0 (0)	0 (0)
Unknown	6 (3)	0 (0)	1 (1)	0 (0)

BMI, body mass index; N/A, not available.

\*n = 188.

†n = 60.

‡n = 27.

§n = 62.

Greater concentrations of total HDL-P are thought to be atheroprotective.<sup>24</sup> Pediatric subjects with KD had significantly greater large HDL-P ( $P < .001$ ) and small HDL-P ( $P = .003$ ) concentrations. The adults with KD had significantly lower mean HDL-P and HDL-C concentrations compared with the adult healthy controls ( $P < .001$ ) (Table II). In contrast to the pediatric subjects, adults with KD displayed significantly lower small HDL-P.

Neither the pediatric nor the adult cohorts with KD had the combination of greater concentrations of small LDL-P and lower concentrations of large HDL-P, the canonical risk profile for atherosclerosis. Compared with control subjects, the pediatric cohort with KD had significantly greater levels of both atherogenic and atheroprotective particles, specifically small LDL-P and large HDL-P ( $P = .002$  and  $P < .001$ , respectively). In contrast, the adult

**Table II.** NMR lipoprotein particle concentrations and sizes

Lipoprotein subclasses	Pediatric KD, n = 192	Pediatric healthy controls, n = 45	P-value	Adult KD, n = 63	Adult healthy controls, n = 45	P-value
Total VLDL/chylomicron particles, nmol/L	43.4 (39.9-46.9)	51.6 (44.4-58.9)	.046	50.3 (43.2-57.4)	72.1 (63.7-80.6)	<.001
Large VLDL/chylomicron particles, nmol/L	1.4 (0.9-2.0)	3.1 (1.9-4.2)	.01	1.9 (1.4-2.5)	2.1 (1.5-2.8)	.61
Medium VLDL particles, nmol/L	18.3 (16.0-20.5)	14.2 (9.5-18.9)	.12	16.5 (12.9-20.1)	23.4 (19.2-27.7)	.017
Small VLDL particles, nmol/L	23.7 (21.8-25.6)	34.4 (30.4-38.4)	<.001	31.9 (26.9-36.8)	46.5 (40.6-52.4)	<.001
Total LDL-P, nmol/L	935 (894-975)	1098 (1014-1182)	.001	937 (854-1020)	1056 (957-1155)	.075
IDL-P, nmol/L	14 (9-18)	113 (104-123)	<.001	62 (50-75)	89 (74-104)	.009
Large LDL-P, nmol/L	382 (358-406)	610 (560-661)	<.001	498 (453-544)	533 (478-587)	.35
Small LDL-P, total, nmol/L	539 (494-584)	374 (281-467)	.002	376 (293-458)	434 (336-533)	.38
Total HDL-P, $\mu$ mol/L	30.4 (29.8-30.9)	30.5 (29.3-31.8)	.77	34.0 (32.5-35.4)	40.5 (38.8-42.2)	<.001
Large HDL-P, $\mu$ mol/L	9.0 (8.5-9.4)	4.9 (4.0-5.8)	<.001	6.8 (6.0-7.7)	7.7 (6.7-8.7)	.21
Medium HDL-P, $\mu$ mol/L	3.2 (2.7-3.7)	9.6 (8.5-10.7)	<.001	11.7 (10.1-13.3)	12.4 (10.4-14.3)	.61
Small HDL-P, $\mu$ mol/L	18.2 (17.6-18.8)	16.1 (14.8-17.3)	.003	15.4 (14.1-16.8)	20.5 (18.9-22.1)	<.001
VLDL particle size, nm	53.5 (52.1-54.8)*	44.2 (41.2-47.3)†	<.001	47.1 (45.9-48.3)‡	43.5 (42.1-44.9)§	<.001
LDL-P size, nm	21.2 (21.1-21.3)	21.1 (20.9-21.3)	.49	21.1 (21.0-21.2)	20.9 (20.8-21.1)	.10
HDL-P size, nm	9.1 (9.0-9.2)	9.2 (9.1-9.3)	.05	9.2 (9.1-9.3)	9.2 (9.1-9.4)	.68
Total TG, mg/dL	82 (75-89)	105 (90-119)	.008	93 (84-103)	116 (105-127)	.003
Total VLDL/chylomicron TG, mg/dL	54 (47-61)	69 (55-84)	.06	63 (54-72)	81 (70-92)	.012
Total HDL-C, mg/dL	50 (49-52)	48 (45-51)	.13	54 (51-56)	63 (60-66)	<.001
Total LDL-C, mg/dL	85 (82-88)	106 (100-113)	<.001	87 (81-94)	95 (88-103)	.12
TC, mg/dL	148 (145-152)	169 (161-176)	<.001	154 (147-161)	176 (168-185)	<.001
Ratio of TC/HDL-C	3.1 (2.9-3.2)	3.6 (3.4-3.8)	<.001	3.0 (2.8-3.2)	2.9 (2.7-3.2)	.83

IDL-P, intermediate-density lipoprotein particle.

Values are model-estimated means (95% CI). P values are after Holm correction for multiple testing.

\*n = 191.

†n = 39.

‡n = 55.

§n = 43.

**Table III.** Atherogenic and atheroprotective lipoprotein subclasses and cholesterol concentrations adapted from Kuller et al<sup>22</sup> and Carmena et al<sup>23</sup>

Subclass	Pediatric KD compared with pediatric healthy controls	Adult KD compared with adult healthy controls
Atherogenic		
Small LDL-P	↑	NS
Small HDL-P	↑	↓
Total LDL-P	↓	NS
IDL-P	↓	↓
Total VLDL/chylomicrons	↓	↓
LDL-C	↓	NS
Total TGs	↓	↓
Atheroprotective		
Large HDL-P	↑	NS
Total HDL-P	NS	↓
HDL-C	NS	↓

NS, not significant.

cohort with KD was similar to controls for these particle concentrations.

When both adults with KD and their control cohorts were compared with subjects in the Framingham and Multi-Ethnic Study of Atherosclerosis studies, their LDL-C and LDL-P values were below the 30th percentile for both studies. Within the adult cohort with KD, the mean LDL-C and LDL-P values fell below the 20th percentile for both the Framingham and Multi-Ethnic Study of Atherosclerosis population comparisons (Table IV).<sup>25,26</sup>

## Discussion

We report NMR lipoprotein particle analysis in subjects with KD. Pediatric and adult subjects with KD displayed a mix of both atherogenic and atheroprotective lipoprotein particle profiles compared with healthy control subjects after

**Table IV.** Population comparisons of lipid and lipoprotein particle concentrations

Percentile	Framingham Offspring, n = 3367 (1367 men; 1732 women)*		MESA, n = 6697 (3154 men; 3543 women)†	
	LDL-C, mg/dL	LDL-P, nmol/L	LDL-C, mg/dL	LDL-P, nmol/L
2	70	720	58	670
5	78	850	69	770
10	88	940	79	870
20	100	1100	91	990
30	111	1220	100	1090
40	120	1330	108	1170
50	130	1440	115	1260
60	139	1540	123	1350
70	149	1670	131	1440
80	160	1820	141	1560
90	176	2020	157	1740
95	191	2210	170	1900

MESA, Multi-Ethnic Study of Atherosclerosis.

\*Specimens collected in 1988-1991 (exam cycle 4). Analysis restricted to subjects with TG <400 mg/dL. Ethnic make-up 99% white.<sup>25</sup>

†Specimens collected in 2000-2002. Analysis restricted to subjects with TG <400 mg/dL. Ethnic make-up 27.4% black, 38.0% white 12.3% Chinese, 22.3% Hispanic.<sup>26</sup>

we controlled for age and sex. The most robust predictors of atherosclerotic risk are thought to be the concentrations of VLDL-C-Ps, TGs, and LDL-P as well as the ratio of TC to HDL-C.<sup>16,27,28</sup> Compared with control subjects, the pediatric KD group had lower mean concentrations of all of these lipids and lipoprotein particles consistent with a lower atherosclerotic risk profile. In contrast, the adult group with KD presented a mixed profile with lower VLDL-C-P and TG but similar LDL-P concentrations and a similar ratio of TC to HDL-C compared with controls.

The acute inflammatory vasculitis of KD produces a spectrum of damage to the coronary arteries and other medium-sized, extraparenchymal muscular arteries throughout the body.<sup>29</sup> Concerns have been raised over the potential for patients with KD to develop accelerated atherosclerosis in these vascular beds.<sup>21,30-34</sup> Evidence cited to support this concern includes greater carotid intima-media thickness, abnormal brachial artery reactivity, and abnormal ankle-brachial indices in some studies. However, in a more recent study that used finger plethysmography (Endo PAT Index; Itamar Medical, Franklin, Massachusetts) as a more accurate tool to assess endothelial cell function, authors found no difference between subjects with KD and controls.<sup>19,35</sup> In addition, autopsy reports of atherosclerotic changes, including lipid-laden macrophages and cholesterol clefts in regions of the vascular wall affected by KD vasculopathy, are rare and do not suggest an increased risk of focal atherosclerotic changes.<sup>36-43</sup> In fact, autopsy reports of sudden death in young adults with a history of KD in childhood have remarked on the relative absence of atherosclerosis.<sup>37</sup> Similarly, the medial necrosis and calcification of the coronary arteries as documented by intravascular ultrasound may be consequences of KD vasculopathy and may not represent early atherosclerosis, as has been widely assumed.<sup>44</sup>

Whether KD vasculopathy alone predisposes individuals to an increased risk of atherosclerosis remains unanswered. Lipid profile screening for patients with KD beyond the acute phase remains prudent, and individual patients with KD with documented hyperlipidemia, such as increased levels of LDL-C, should be managed aggressively. However, on the basis of the data presented here, as a group, neither pediatric nor adult patients with KD have lipoprotein particle counts or lipid profiles associated with increased atherosclerotic risk. ■

The authors thank Deborah A. Winegar, PhD (LipoScience Inc), for guidance and helpful discussion and DeeAnna Scherrer (University of California, San Diego) for technical assistance.

Submitted for publication Feb 27, 2014; last revision received Apr 20, 2014; accepted Jun 6, 2014.

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