Altered Lipid Profile After Kawasaki Syndrome

Jane W. Newburger, MD, MPH; Jane C. Burns, MD; Alexa S. Beiser, PhD; and Joseph Loscalzo, MD, PhD

Background. Delineation of lipid values in children after Kawasaki syndrome is important because of the predilection of this disease for the coronary arteries.

Methods and Results. We measured plasma concentrations of total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides using enzymatic methods in 105 patients with a history of Kawasaki syndrome. Measurements were obtained during six time periods: 10 days or less, 11–31 days, 1–3 months, 3–12 months, 1–3 years, and more than 3 years. Total cholesterol was depressed in the first interval (122.0±19.8 mg/dl, mean±SD), but the mean values were normal in all periods after clinical recovery (overall mean, 149.0±24.0 mg/dl). High density lipoprotein cholesterol was also depressed in the first interval (15.2±9.9 mg/dl); although high density lipoprotein cholesterol increased significantly with duration since disease onset (p<0.001), it remained significantly lower than expected (p<0.001), even in the latest interval (47.2±10.9 mg/dl). Nonfasting triglyceride levels were high (162.5±63.4 mg/dl) in the first interval and then diminished steadily with time, but this relation did not achieve statistical significance. We compared adjusted lipid levels (z scores) of 46 Kawasaki patients after clinical recovery with those of their parents; patients had similar total cholesterol levels but significantly lower high density lipoprotein cholesterol levels (p=0.021 for mothers, p=0.001 for fathers). Mean high density lipoprotein cholesterol after clinical recovery tended to be lower in patients with persistent coronary abnormalities than in those without such lesions (p=0.085).

Conclusions. Kawasaki syndrome is associated with important abnormalities in lipid metabolism. Continued long-term surveillance of this population is necessary to monitor lipid levels and their relation to future development of coronary atherosclerosis. (Circulation 1991;84:625–631)

Kawasaki syndrome is an acute vasculitis of unknown cause that predominantly occurs in infancy and early childhood. Coronary artery aneurysms or ectasia develop in approximately 15–25% of affected children.1–3 Recently, therapy during the acute phase with intravenous γ-globulin has been demonstrated to achieve a fivefold reduction in the prevalence of coronary artery lesions.4–7 Although coronary artery abnormalities are detectable by echocardiography occur in a minority of patients, the known histopathology of early Kawasaki syndrome8–12 suggests a more frequent occurrence of subclinical inflammation in the coronary arteries and in other medium-sized muscular arteries. Acute Kawasaki syndrome is also a diffuse vasculitis involving the noncoronary arterioles, venules, and capillaries. Although the inflammatory responses involving the endothelium in the acute phase have been well characterized,13 the extent and persistence of endothelial abnormalities after Kawasaki syndrome are unknown.

The purpose of the present study was to investigate the lipid profiles of children with a history of Kawasaki syndrome. Delineation of the lipid profile is particularly vital in these patients because of the predilection of Kawasaki syndrome for coronary artery involvement. Furthermore, we wanted to explore whether there are any abnormalities in lipid profile that linger after the usual signs and symptoms of the acute illness have resolved.

From the Departments of Cardiology and Pediatrics, The Children’s Hospital (J.W.N., J.B.); the Department of Medicine, Brigham and Women’s Hospital (J.L.); the Departments of Pediatrics and Medicine, Harvard Medical School; and the Epidemiology and Biostatistics Section, Boston University School of Public Health (A.S.B.), Boston, Mass.

Supported by grants HL-34545 (J.W.N.) and HL-40411 (J.L.) from the National Institutes of Health (NIH). J.L. is the recipient of a Research Career Development Award from the NIH (HL-02273).

Address for reprints: Dr. Jane W. Newburger, Department of Cardiology, The Children’s Hospital, 300 Longwood Avenue, Boston, MA 02115.

Received September 19, 1989; revision accepted March 19, 1991.
Methods

Subjects

Subjects included 105 children with a history of Kawasaki syndrome who were prospectively evaluated at The Children’s Hospital, Boston, between January 1986 and June 1988. All children met the criteria for Kawasaki syndrome as previously defined. In addition, we measured the lipid profiles of the parents of 46 Kawasaki patients (mothers of 41 children and fathers of 28 children).

Recorded Data

We measured plasma concentrations of total cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol. Blood was drawn in EDTA tubes, and plasma was separated within 4 hours at 4°C. Plasma total cholesterol, HDL cholesterol, and triglycerides were measured in a reference laboratory standardized by the Centers for Disease Control using enzymatic methods in accordance with the Lipid Research Clinics Program. Many samples were drawn from subjects in the nonfasting state. Therefore, although total cholesterol and HDL cholesterol measurements were reliable, the triglyceride concentrations demonstrated wide variation, and analyses of LDL and VLDL cholesterol could not be undertaken.

Lipid profiles were obtained on patients during six time intervals from the onset of illness, which was defined as the first day of fever: 1) 10 days or less (n=15), 2) 11–31 days (n=17), 3) 1–3 months (n=60), 4) 3 months to 1 year (n=11), 5) 1–3 years (n=41), and 6) more than 3 years (n=30). Early in the study, we measured total cholesterol at any visit beyond the sixth week of illness. After it became apparent that HDL cholesterol levels were low even after clinical recovery, we systematically measured lipid profiles during the acute phase as well. Total cholesterol, HDL cholesterol, and triglyceride levels were always measured simultaneously. When a child had lipid concentrations measured more than once within an interval, we calculated the mean value for that interval for use in our analyses. Fifty-four patients had a lipid profile performed in only one time period, 35 in two periods, 13 in three periods, and three in four periods.

Coronary artery abnormalities were defined in accordance with the criteria outlined by the Japanese Ministry of Health.

Statistical Methods

Measured lipid values were adjusted for age and sex using z scores based on the Lipid Research Clinics mean±SD values. z scores were calculated as SD units: (patient’s plasma lipid concentration minus age- and race-specific mean) divided by age- and race-specific SD. For children 4 years and younger, for whom population normative data for HDL cholesterol were not available, mean and SEM for HDL cholesterol were assumed to be the same as those for children 5–9 years old. We compared patients with normal subjects using one-sample t tests on z scores. We investigated changes in patient scores over time using repeated measures analysis of variance and Scheffe’s method for post-hoc multiple comparisons. We tested whether adjusted (i.e., z scored) plasma lipid concentrations were different in children and their parents using the paired t test.

Results

Demographic Data

Among the 105 patients with Kawasaki syndrome, 67 (63.8%) were male, 14 (13.3%) had coronary artery abnormalities on at least one echocardiogram, and 58 (55.2%) received intravenous γ-globulin therapy within the first 10 days of illness. Only nine patients (8.6%) were less than 2 years old, and none was less than 1 year old when their first lipid profile was measured. Only one lipid profile was measured in an adolescent (13 years old). The majority of patients (95; 90%) were Caucasian; six were Black (6%), and four were Asian (4%).

Changes in Lipid Profiles Over Time

We examined changes in plasma lipid concentrations as a function of time since onset of Kawasaki syndrome (see Table 1). Plasma total cholesterol concentrations (Figure 1) were depressed (122.0±19.8 mg/dl, mean±SD) during the first 10 days of illness (period 1). Total cholesterol levels during period 1 were significantly lower than during all other periods (p<0.05 by Scheffe’s). Plasma cholesterol concentrations rebounded between 10 and 31 days (163.5±25.3 mg/dl) and were not significantly different from normative values after 3 months.

Plasma concentrations of HDL cholesterol (Figure 2) increased significantly with time since disease onset (p=0.0001 by repeated measures analysis of variance). During the first 10 days of illness, HDL cholesterol was profoundly depressed (15.2±9.9 mg/dl). Mean HDL cholesterol concentration increased sharply (41.5±10.4 mg/dl) by the period of 11–31 days. The highest mean concentration (47.2±10.9 mg/dl) was achieved by the sixth period examined (i.e., more than 3 years after disease onset). Even in this interval, adjusted HDL cholesterol values of Kawasaki patients remained significantly lower than normal (p<0.0001). The relation between HDL cholesterol concentration and time since disease onset was not altered when controlled for patient age.

Plasma triglyceride concentrations were extremely high during the first 10 days of illness (162.5±63.4 mg/dl, mean±SD), even when considering that they were obtained with subjects in the nonfasting state. Mean triglyceride concentration declined considerably (119.0±73.9 mg/dl) in the subsequent period (11–31 days). In the sixth period, mean triglyceride concentration was 101.2±47.0 mg/dl; at this time, three of 30 patients (10%) had a plasma triglyceride concentration above the 95th percentile for normal
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1 (≤10 days)</th>
<th>2 (11–31 days)</th>
<th>3 (1–3 months)</th>
<th>4 (3 months to 1 year)</th>
<th>5 (1–3 years)</th>
<th>6 (&gt;3 years)</th>
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<tr>
<td>Age (mean±SD years) (n)</td>
<td>4.3±2.0 (15)</td>
<td>4.2±1.6 (17)</td>
<td>3.7±2.0 (60)</td>
<td>4.2±2.8 (11)</td>
<td>4.5±2.4 (41)</td>
<td>6.6±2.6 (30)</td>
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<tr>
<td>Sex</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male (n)</td>
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<td>13</td>
<td>36</td>
<td>8</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Female (n)</td>
<td>6</td>
<td>4</td>
<td>24</td>
<td>3</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Total cholesterol (mean±SD mg/dl) (n)</td>
<td>122.0±19.8 (14)</td>
<td>163.5±25.3 (17)</td>
<td>148.1±22.9 (60)</td>
<td>152.4±39.1 (11)</td>
<td>150.5±26.3 (41)</td>
<td>153.0±26.3 (30)</td>
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<tr>
<td>High density lipoprotein cholesterol (mean±SD mg/dl) (n)</td>
<td>15.2±9.9 (10)</td>
<td>41.5±10.4 (15)</td>
<td>41.3±11.1 (57)</td>
<td>43.2±15.8 (11)</td>
<td>41.5±10.0 (39)</td>
<td>47.2±10.9 (28)</td>
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<tr>
<td>Triglycerides (mean±SD mg/dl) (n)</td>
<td>162.5±63.4 (15)</td>
<td>119.0±73.9 (16)</td>
<td>114.4±67.3 (60)</td>
<td>86.6±38.6 (10)</td>
<td>113.8±51.0 (40)</td>
<td>101.2±47.0 (30)</td>
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<tr>
<td>Serum alanine amino transferase (mean±SD μm/ml) (n)</td>
<td>41.8±23.7 (12)</td>
<td>22.5±5.5 (11)</td>
<td>20.3±3.3 (43)</td>
<td>...</td>
<td>23.6±4.1 (10)</td>
<td>20.8±5.4 (4)</td>
</tr>
<tr>
<td>Bilirubin (mean±SD mg/dl) (n)</td>
<td>0.6±0.4 (10)</td>
<td>0.3±0.1 (4)</td>
<td>0.4±0.2 (35)</td>
<td>...</td>
<td>0.3±0.1 (2)</td>
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<td>3</td>
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<td>Asian</td>
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<td>1</td>
<td>3</td>
<td>0</td>
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</table>

Nonfasting triglyceride values. Although plasma triglyceride concentrations tended to decline with time, this relation did not achieve statistical significance, in part because of the large variances among these nonfasting samples.

The ratio of total cholesterol to HDL cholesterol was also related to time from disease onset. This ratio was extremely high during the first 10 days of illness (11.6±6.2). By the next period, 11–31 days, the mean ratio had decreased significantly ($p<0.01$ by Scheffe's) to 4.2±1.2. Subsequently, the ratio continued to decrease gradually to 3.3±0.9 during the sixth period.

We explored whether the onset of puberty in male patients could account for the persistent depression of HDL cholesterol levels. The average ages of patients in periods 1–5 were similar, with a higher mean age in period 6. No child was more than 10 years old until period 6, when two boys 11 and 13 years old were included in the sample. Thus, it is unlikely that the persistence of low HDL cholesterol could be attributed to the influence of age.

FIGURE 1. Plot of relation of adjusted total cholesterol to time since onset of Kawasaki syndrome. Solid horizontal line represents expected population mean. Dots and vertical lines depict mean and 95% confidence limits (CL) for adjusted total cholesterol for each time period since disease onset, respectively. Time periods are defined as follows: period 1, ≤10 days; period 2, 11–31 days; period 3, 1–3 months; period 4, 3 months to 1 year; period 5, 1–3 years; and period 6, >3 years.

FIGURE 2. Plot of relation of adjusted high density lipoprotein cholesterol to time since onset of Kawasaki syndrome. Solid horizontal line represents expected population mean. Dots and vertical lines depict mean and 95% confidence limits (CL) for adjusted total cholesterol for each time period since disease onset, respectively. Time periods are defined as follows: period 1, ≤10 days; period 2, 11–31 days; period 3, 1–3 months; period 4, 3 months to 1 year; period 5, 1–3 years; and period 6, >3 years.
The results of lipid profiles were not used to determine the frequency of visits. However, patients with coronary artery aneurysms were evaluated more frequently and tended to have lower HDL cholesterol levels. To investigate the possibility of selection bias, we examined mean HDL cholesterol concentration within each period according to the number of periods in which subjects had lipid profiles measured. There were no significant differences in mean HDL cholesterol within any period between groups of patients with measurements in one, two, three, or four periods.

Comparison of Patients With Their Parents

We compared age- and sex-adjusted plasma total cholesterol and HDL cholesterol levels (i.e., z scores) of 46 patients with those of their parents (Figure 3). For each patient, we calculated mean adjusted lipid concentration by obtaining the average of all measurements obtained after clinical recovery (no less than 6 weeks from illness onset). The children’s adjusted total cholesterol concentrations were not significantly different from those of either parent. However, compared with their parents, children had a much lower mean adjusted HDL cholesterol concentration ($p=0.02$ for mothers, $p=0.001$ for fathers). The adjusted HDL cholesterol in mothers and fathers was not significantly different from that of normal population values. However, we cannot determine conclusively from the available data whether the altered lipid profile among children who have had Kawasaki syndrome are exclusively a result of the disease or whether children with low HDL cholesterol are more susceptible to Kawasaki syndrome.

Influence of Severity of Systemic Inflammation

We examined the correlation of serum lipid concentrations measured at least 6 weeks after illness onset with laboratory parameters of systemic inflammation in the subset of patients in whom these data were prospectively gathered from our center as part of a multicenter clinical trial on treatment of Kawasaki syndrome with intravenous γ-globulin. White blood cell count, absolute band count, and serum concentration of α1-antitrypsin (reflecting the acute phase response) were measured at the time of enrollment (within 10 days of fever onset) and then 4–6 days, 2 weeks, and 7 weeks after enrollment. The small sample size measured during period 1 limited our power to detect correlations of lipid abnormalities with severity of inflammation during the acute phase. None of these laboratory indexes was significantly associated with plasma lipid concentrations after clinical recovery from the disease.

Inflammations of the liver and gall bladder occur frequently in acute Kawasaki syndrome and might influence serum lipid values. We explored whether abnormalities of liver function were correlated with plasma HDL cholesterol concentration. Only during the first three periods was the number of patients with measurements of both lipid levels and liver function sufficient to perform statistical analyses. HDL cholesterol concentration was inversely correlated with serum alanine amino transferase level during period 1 ($p=0.028$) but not during periods 2 or 3. The changes in HDL cholesterol between periods 1 and 2 and between periods 2 and 3 were not significantly associated with the concurrent changes in serum alanine amino transferase level.

The severity of systemic vasculitis in acute Kawasaki syndrome is reflected to some extent in the development of coronary artery lesions. We therefore compared the concentrations of HDL cholesterol in children with or without persistent coronary artery abnormalities as detected by two-dimensional echocardiography. In measurements obtained after clinical recovery, HDL cholesterol concentrations of children with coronary artery abnormalities were lower than those of children without such lesions ($37.2\pm12.7$ versus $44.1\pm9.9$ mg/dl, respectively), but the difference did not achieve statistical significance ($p=0.085$).

Influence of Treatment With γ-Globulin

We compared plasma lipid concentrations of patients who received treatment with high-dose intravenous γ-globulin (1.6 g/kg) and aspirin with those who were treated with aspirin alone (Table 2). The small number of patients in the aspirin group in periods 1 and 2 precluded comparisons between the treatment groups in these periods. Total cholesterol tended to be higher among patients treated with γ-globulin in periods 2–6, but this difference achieved statistical significance only in period 6 ($p<0.001$). This finding could not be attributed to
isolated extreme values in either the aspirin or the γ-globulin group, and its explanation is obscure. Children treated with γ-globulin had higher HDL cholesterol levels during period 3 ($p=0.068$) and period 4 ($p=0.043$), consistent with faster recovery in the γ-globulin group.

**Discussion**

We found that Kawasaki syndrome is associated with significant abnormalities in lipid profile. In the earliest days of illness, mean plasma concentrations of total cholesterol and HDL cholesterol were profoundly depressed, whereas mean triglyceride concentration was very high. Total cholesterol values rapidly returned to normal and remained stable more than 3 months after the onset of illness. HDL cholesterol concentration recovered more slowly after illness onset, and mean HDL cholesterol concentration was significantly lower than expected, even in the period, more than 3 years after illness onset.

The lipid findings early in the course of Kawasaki syndrome are consistent with those delineated in a variety of acute infections. Both acute bacterial and viral infections are associated with diminished concentrations of low density lipoprotein and HDL cholesterol and with increased concentrations of very low density lipoprotein cholesterol, at least in part attributable to concurrent reductions of lipoprotein lipase and hepatic lipase activities. Altered lipid profile has been demonstrated to be related to the actions of a variety of structurally distinct cytokines (e.g., tumor necrosis factors, interleukins, interferon γ) released during the host response to infection.

The changes in lipoprotein metabolism after acute infections are temporary, although recovery of lipid profile has been reported to be delayed as long as 1 month after disease onset in 80% of patients. The persistence of low HDL cholesterol for many years in our sample suggests a more lasting effect of Kawasaki syndrome on endothelial function, perhaps attributable to diminished activity of lipoprotein lipase. This enzyme resides on the capillary walls of most tissues and functions at the luminal surface of the vascular endothelium. During the acute phase of Kawasaki syndrome, vascular damage is diffuse and involves the endothelium of capillaries, arterioles, and venules. In addition to altered lipid profile, persistence of generalized endothelial cell dysfunction after Kawasaki syndrome has been suggested by the observation that plasma 6-keto-prostaglandin F_{1α} remains generally undetectable for an observation period of 1 year after onset of Kawasaki syndrome.

Low HDL cholesterol is a well-recognized independent risk factor for premature atherosclerotic coronary artery disease. The observation of low plasma HDL cholesterol concentrations after Kawasaki syndrome is particularly important because the vasculitis in this disease has a predilection for the coronary arteries at sites identical to those most often affected in atherosclerosis. In regressed coronary artery aneurysms, fibrous intimal thickening is evident despite normal coronary artery diameter. Children who die in the acute phase of Kawasaki syndrome without coronary artery dilation have microscopic evidence of coronary vasculitis. Furthermore, intimal thickening and fibrosis have been observed in the coronary arteries of children who died due to causes unrelated to Kawasaki syndrome at intervals ranging from 60 days to 2 years after disease onset. These histological abnormalities have raised concerns that after Kawasaki syndrome the coronary arteries may be predisposed to accelerated atherosclerosis.

Our findings with regard to total cholesterol and HDL cholesterol are qualitatively similar to those observed in Japanese children by Okada and colleagues. These authors demonstrated a steady increase in HDL cholesterol concentrations after Kawasaki syndrome, with more severe and persistent depression occurring among those with coronary artery lesions. More than 3 years after disease onset, the distribution of HDL cholesterol values was similar among patients with and without coronary abnormalities and those in a small control group. The persistence of a significantly lower mean adjusted HDL cholesterol during a similar late period in our population might reflect our greater sensitivity to detect such a difference using a large-population normative data base. Our data differ from those recently described in a Hawaiian population in which 24% of children studied after clinical recovery had total cholesterol levels greater than the 95th percentile. The discrepancy in total cholesterol
values between our New England population and the studied children in Hawaii might be related to differences in local population normative values.

We cannot exclude the possibility that changes in habitual activity or diet after clinical recovery influenced plasma lipid concentrations. Furthermore, we cannot eliminate the possibility that low HDL cholesterol concentration anteceded the onset of Kawasaki syndrome and is a risk factor for its development. The patients in our sample were healthy, normal children before the onset of Kawasaki syndrome and appeared to resume their normal lifestyle after clinical recovery.

HDL cholesterol levels improved more rapidly in children treated during the acute phase of Kawasaki syndrome with γ-globulin plus aspirin than in those treated with aspirin alone. The faster recovery of lipid abnormalities in γ-globulin–treated patients suggests an additional benefit of this therapy for Kawasaki syndrome.

Summary

We found alterations in lipid profile in Kawasaki syndrome that appear to persist long after the clinical resolution of the disease. Further basic research is needed to elucidate the mechanisms by which these abnormalities are produced. Continued long-term surveillance will be necessary to monitor lipid concentrations and their relation to development of coronary artery atherosclerosis in this population.

Acknowledgments

We thank Catherine Brosius, RN, MSN, Marilyn McEnhill, RN, MSN, and Grace Shen, PhD, for project coordination; Kathleen M. O’Brien for manuscript preparation; and Harvey L. Meyerson for computer programming.

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Key Words • Kawasaki syndrome • high density lipoprotein • triglycerides • cholesterol
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*Circulation.* 1991;84:625-631
doi: 10.1161/01.CIR.84.2.625
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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