Kawasaki disease: Studies on etiology, treatment and long-term follow-up
Tacke, C.E.A.

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Chapter 9

CAROTID INTIMA-MEDIA THICKNESS IN PATIENTS WITH A HISTORY OF KAWASAKI DISEASE

C.E. Tacke*
S.M. Dietz*
J. Gort
I.M. Kuipers
E. de Groot
A. Wiegman
B.A. Hutten
T.W. Kuijpers

* Authors contributed equally

Submitted.
ABSTRACT

Background:
Kawasaki disease (KD) is an acute pediatric vasculitis. An important complication of KD is the development of coronary artery aneurysms (CAA). Concerns have been raised regarding the possibility of a predisposition of KD to premature cardiovascular disease later in life. Therefore, the objective of this study was to determine the carotid intima-media thickness (cIMT) as a surrogate marker of cardiovascular risk of patients with a history of KD, in comparison with healthy controls.

Methods and results:
CIMT was measured using B-mode ultrasound in 174 patients with a history of KD and 82 healthy controls in the same age range (7-20 years). Ten patients were excluded because of an incomplete cIMT measurement. Mean cIMT (±SD) was significantly greater in patients with KD than in healthy controls (0.378±0.030 mm versus 0.360±0.027 mm, respectively; \( P \text{ adjusted}<0.001 \)). When the difference in cIMT between patients with KD and controls was plotted against age, the increased cIMT was only apparent at young age in the patients without CAA. In the patients with CAA the increased cIMT was steadily observed at all ages, demonstrating a more severe disease course.

Conclusion:
We observed a significantly greater cIMT in patients with a history of KD compared to healthy controls, especially in patients with CAA. In patients without CAA, the cIMT normalized with age while an increased IMT was observed at all ages in patients with CAA. Our data might indicate that the cIMT differences between KD patients and healthy controls are the results of the acute inflammation of the vessel wall rather than a process of atherosclerosis.
INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology that predominantly occurs in children less than 5 years of age\(^1\). Coronary artery aneurysms (CAA) develop in 15 to 25% of untreated patients and may lead to myocardial ischemia, infarction and sudden death\(^2\). Although treatment with high-dose intravenous immunoglobulins (IVIG) has reduced this risk to less than 10%, KD is the leading cause of acquired heart disease in developed countries\(^3\). The disease is self-limiting and only rarely recurs, but there has been ongoing concern that patients both with and without coronary artery involvement may have a predisposition to endothelial damage and premature atherosclerosis in adulthood\(^4-7\). Since the first case of KD was reported in 1967, patients who have recovered will now be middle-aged or younger, and therefore the follow-up of these patients has not been long enough to establish the natural history of the disease. To determine if KD is a risk factor for the future development of cardiovascular disease, several studies reported on the carotid intima-media thickness (cIMT) of patients with a history of KD. CIMT, as assessed by B-mode ultrasound, is currently the best validated non-invasive surrogate marker for atherosclerosis available\(^8,9\). Multiple studies have shown that cIMT is positively associated with cardiovascular disease\(^10\). An increased cIMT has been reported in former KD patients both with and without CAA in the past\(^11,12\), although these findings have not been confirmed by other studies\(^13,14\).

The objective of the present study was to compare cIMT of patients with a history of KD with healthy controls. We hypothesize that, due to their history of a systemic vasculitis, patients with KD have an increased risk of cardiovascular disease as measured by cIMT.

METHODS

Participants

The study was conducted between August 2006 and September 2013 at the Emma Children’s hospital, a tertiary referral center. Children aged 7 to 20 years with a history of KD were recruited consecutively during follow-up as outpatients. The diagnosis of KD was based on criteria from the American Heart Association\(^15\). Patients diagnosed as having KD within 6 months of the study were excluded to minimize the potential confounding influence of the (sub)acute inflammation. If multiple IMT-measurements were performed, the measurement at the oldest age was included in the study.

Unaffected siblings of children with KD and other healthy subjects (family from the staff of our hospital) without a history of KD were eligible for the control cohort if they were in the same age range, and did not take any cardiovascular medication. All subjects and/or their parents gave informed consent as approved by the institution’s Research Ethics Board.
Study protocol

A medical history was obtained from all participants, and body height, weight and blood pressure were measured. A noninvasive measurement of the carotid IMT was performed as described below. The mean arterial pressure (MAP) was calculated using the following formula: (systolic blood pressure + (2*diastolic blood pressure))/3. Using data of the fifth Dutch growth study performed in 2009 in 20,867 children in The Netherlands, standard deviation scores for body mass index (BMI) were calculated based on the age and gender of each participant (http://groeiweb.pgdata.nl/calculator.asp).

The medical records of the patients with KD were reviewed retrospectively to collect the following clinical details: age at disease onset, time interval between disease onset and time of study, treatment with IVIG, aspirin and/or steroids, and the presence of CAA. The coronary arteries had been evaluated by two-dimensional echocardiography and a CAA was defined as a coronary z score >2.5. In the patients with KD, a venous blood sample was taken after an overnight fast for measurement of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, lipoprotein(a), and apolipoprotein E genotype. LDL cholesterol was calculated using the Friedewald formula.

Carotid IMT

An 85-MHz linear array transducer, interfaced to a Acuson Sequoia 512 instrument ultrasound machine (Siemens AG, Malvern, PA; Erlangen, Germany), was used to make longitudinal images of the carotid arteries. All studies were done according to a standardized scanning protocol for the left and right carotid arteries. B-mode scans of the common, bulb and internal far-wall carotid segments were made. The distal common carotid artery wall was measured over a length of one cm directly proximal to the carotid bifurcation. Two experienced and certified ultrasonographers made all images that were stored as DICOM stills for offline analysis. One image analyst performed the IMT measurements while blinded for the patient’s case status and risk factor levels. The mean combined cIMT was calculated as follows: (mean of the left and right common carotid arties + the mean of the left and right carotid bulb + the mean of the left and right internal carotid far wall segments)/3. For subjects in whom the scan of one of the segments had failed, the measurement of the same segment of the opposite carotid artery was taken as the mean of both carotid arteries. If both left- and right-side values were unavailable, the IMT was considered missing for that segment, and in that case the mean combined cIMT was also considered missing.

Statistical analysis

We evaluated differences in demographic between patients with KD and controls by linear or logistic regression analysis. Differences in cIMT between patients with KD and controls
were evaluated using linear regression analyses. We adjusted for potential confounders by means of stepwise backward elimination.

An equation for difference in cIMT (ΔIMT) was derived by subtracting the equation for patients with KD (if GROUP=1), that is, IMT\text{KD} = \beta_1 \text{AGE} + \beta_2 + \beta_3 \text{AGE}, from the equation for the healthy controls (if GROUP=0), that is, IMT\text{CO} = \beta_1 \text{AGE}. This calculation resulted in ΔIMT = \beta_2 + \beta_3 \text{AGE}. Betas and standard errors were derived from the output of a linear regression analysis for the whole group. Linear and logistic regression analyses were performed using the generalized estimating equation method in the SAS procedure GENMOD to account for correlations within families. The exchangeable correlation structure was used for these models. A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SAS release version 9.2 (SAS Institute, Cary, NC) and SPSS version 20.0 software (SPSS Inc, Chicago, IL).

**RESULTS**

In total, 174 patients with KD and 82 healthy controls were enrolled. The control group consisted of 74 unaffected siblings and 8 family members from the hospital staff. Ten patients were excluded because of missing cIMT segments. Demographic characteristics of the remaining 164 patients with KD and the 82 controls were comparable with respect to mean age (12.1±3.3 versus 12.3±3.4 years; \(P=0.654\)), sex distribution (62% versus 54% males; \(P=0.199\)), mean BMI SD score (0.44±1.1 versus 0.26±1.1; \(P=0.235\)) and MAP (80.3±7.5 versus 81.4±8.8 mmHg; \(P=0.329\)) (Table 1).

Clinical and laboratory data of patients with a history of KD are shown in Table 1. Median age at onset of KD was 3.2 years (interquartile range: 1.2-5.3). Based on their worst-ever coronary artery z-score, 124 (76%) had no coronary enlargements (z-score <2.5 during the (sub)acute phase) and 40 patients had coronary aneurysms (29 with z-score 2.5-10; and 11 with z-score >10). Of all patients, 148 (90%) had been treated with IVIG.

**Carotid IMT**

The mean combined cIMT (±SD) was significantly greater in patients with KD in comparison with healthy controls (0.378±0.030 mm versus 0.360±0.027 mm; \(P<0.0001\), respectively). This remained significant after adjustment for age, sex, and family relations (\(P<0.0001\)). In table 2 the means adjusted for age and gender per subgroup (according to worst-ever CAA status) are shown.

KD in our patient cohort occurred at young age. Thus, age at cIMT measurement was analyzed as a variable. In Figure 2A, the difference in cIMT between all patients with KD and healthy controls (ΔIMT) was plotted against age. This was also performed for the subgroups of patients without CAA (Figure 2B) and with CAA (Figure 2C), based on their worst-ever z-score. In CAA-negative patients, the ΔIMT decreased with age at cIMT measurement and
at older ages there was no significant difference between CAA-negative patients and controls anymore detectable. In contrast, in patients with CAA this difference in cIMT remained present at all ages.

### Table 1. Demographic data of patients with Kawasaki disease and healthy controls, and clinical and laboratory data of the patients

<table>
<thead>
<tr>
<th></th>
<th>Patients n=164</th>
<th>Controls n=82</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.1 ± 3.3</td>
<td>12.3 ± 3.4</td>
<td>0.654</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>102 (62)</td>
<td>44 (54)</td>
<td>0.199</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>154 ± 0.18</td>
<td>155 ± 0.17</td>
<td>0.645</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>46 ± 16</td>
<td>47 ± 19</td>
<td>0.752</td>
</tr>
<tr>
<td>BMI SD score</td>
<td>0.44 ± 1.1</td>
<td>0.26 ± 1.1</td>
<td>0.235</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>80.3 ± 7.5</td>
<td>81.4 ± 8.8</td>
<td>0.329</td>
</tr>
<tr>
<td>Age at disease onset (years)*</td>
<td>3.1 (1.2-5.3)</td>
<td>8.0 (6.0-11.0)</td>
<td></td>
</tr>
<tr>
<td>Interval disease onset to study (years)*</td>
<td>8.0 (6.0-11.0)</td>
<td>8.0 (6.0-11.0)</td>
<td></td>
</tr>
<tr>
<td>Treatment with IVIG, n (%)</td>
<td>148 (90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.07 ± 0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.24 ± 0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.47 ± 0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)*</td>
<td>0.71 (0.51-0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>1.28 ± 0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>0.63 ± 0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/L)*</td>
<td>108 (45-341)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein E4 genotype, n (%)</td>
<td>40 (24.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation unless otherwise noted.

*Median (interquartile range).

Abbreviations: MAP=mean arterial pressure; n=number; BMI=body mass index; SD=standard deviation; IVIG=intravenous immunoglobulin; LDL=low-density lipoprotein; HDL=high-density lipoprotein

### Table 2: Carotid IMT data of controls and subgroups of patients based on their coronary artery status*

<table>
<thead>
<tr>
<th></th>
<th>Total (%)</th>
<th>Mean cIMT**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>82 (100)</td>
<td>0.360 ± 0.003</td>
</tr>
<tr>
<td>No enlargement (z-score &lt;2.5)</td>
<td>124 (75.6)</td>
<td>0.376 ± 0.002</td>
</tr>
<tr>
<td>CAA (z-score 2.5-10)</td>
<td>29 (17.7)</td>
<td>0.372 ± 0.006</td>
</tr>
<tr>
<td>Giant CAA (z-score &gt;10)</td>
<td>11 (6.7)</td>
<td>0.412 ± 0.010</td>
</tr>
</tbody>
</table>

* Based on worst-ever z-score during acute phase of either left coronary artery, right coronary artery or left anterior descending artery.

**IMT=mean adjusted for age and gender.

Abbreviations: CAA=coronary artery aneurysm; IMT=intima-media thickness.
DISCUSSION

This study shows that children with a history of KD have an increased cIMT compared to healthy controls. Plotting the difference in cIMT between patients and controls against age indicated that the observed difference in cIMT decreased with increasing age and disappeared in young adulthood in patients without CAA. In contrast, in children with CAA during acute KD – being either transient or persistent – the difference in cIMT was observed at all ages and remained significantly different from healthy controls at all ages.

Studies evaluating the cIMT in patients with a history of KD are limited, and the studies that have been performed mainly included small numbers of patients and have produced conflicting results. Some studies reported no difference between KD patients and controls\(^{13, 14, 18, 19}\), whereas others found an increased cIMT in CAA-positive patients\(^{20-22}\). For example, a study by Noto et al reported an increased cIMT in 18 CAA-positive patients compared to 15 controls (0.54±0.08 versus 0.42±0.04; \(P=0.005\))\(^{21}\). Cheung et al confirmed this finding in 32 CAA-positive patients in comparison with 32 controls, but also studied 19 CAA-negative patients and found no difference in this subgroup of patients compared with controls\(^{23}\). The
Part IV     Imaging during long-term follow-up

latter is consistent with the findings of Laurito and colleagues who studied 14 KD patients without persisting CAA. In contrast, another study by Cheung et al did report an increased IMT in 24 CAA-negative patients compared with 22 age-matched controls (0.39±0.04 versus 0.36±0.04; P=0.008)\textsuperscript{11}. Selamet Tierney et al recently reported on 203 former KD patients and 50 healthy controls (mean age around 17 years). In this largest cohort study to date, these authors reported no significant difference between groups of patients without CAA, patients with CAA, patients with giant CAA, and healthy controls\textsuperscript{14}.

In contrast to this recent study, our results show that the differences in cIMT between patients and controls are not only significantly different from healthy controls but also change over time in CAA-negative but not in CAA-positive patients. Our findings might explain the conflicting data of the prior studies by the different patient groups included and variable ages at analysis.

KD is a vasculitis that predominantly occurs in very young children\textsuperscript{24}. The median age at KD onset in our study cohort was 3.2 years. Therefore, the mean time interval from disease onset to participation in this study increases with age. Our study indicates that the significant difference in cIMT between patients and controls decreased with age and at older ages even disappeared completely in the CAA-negative patients.

Carotid IMT is assumed to be a validated method to estimate subclinical atherosclerosis, but no study has yet correlated cIMT to clinical outcomes in patients with KD. The finding in CAA-negative patients suggests that the initially increased cIMT observed in these patients is merely a result of the acute arteritis rather than a process of atherosclerosis. In the patients with CAA the difference in cIMT persist, but it is not clear what pathophysiological process results in the increased cIMT and what it will mean for the prognosis of any individual patient. The American Heart Association recommends life-long follow-up for both children with and without CAA to assess cardiovascular risk. Controversy exists on whether there is a need for this in children who never or only transiently had CAA. The uncertainty about peripheral vascular health feeds a big part of this discussion. Our study results indicate that a life-long follow-up of children without CAA might not be necessary. Nevertheless, more studies have to be performed to define the real risk of cardiovascular disease and to decide about the follow-up of these children.

A major strength of the present study was the large study group and the use of a standardized imaging protocol. Ultrasound measurements of all participants were obtained by two experienced sonographers and one image analyst read all images blinded for case or CAA status. Some methodological aspects of our study merit discussion. First, we have only included one IMT measurement of each patient. Long-term follow-up studies are warranted to assess the course of cIMT over time in the same KD patients. Second, patients were stratified based on their worst-ever z-score. Because the study was performed in a tertiary referral center, pediatric cardiologist in other centers than ours generated many of the early echocardiograms. This might have caused misclassification of patients in the stratification
for CAA subgroups. Third, although patients were included in a consecutive order at the outpatient clinic, the study population contains a high percentage of patients with CAA, as explained by referral bias with the more severe cases at our tertiary center. This may have overemphasized the mean IMT of the total KD group. The recruitment of healthy subjects may also have been subject to some form of selection bias. The willingness to participate in this study as control subject might have been influenced by lifestyle or other factors, which may have over- or underestimated the mean cIMT of the control subjects.

**CONCLUSION**

The cIMT is increased in patients with a history of KD, and was positively associated with disease severity. In patients without CAA an increased cIMT was most pronounced at a young age, which normalized with age. In patients with CAA the arterial wall morphology did not restore to control values with increasing age, therefore long-term follow-up studies are needed to establish the natural history of the disease. Although cIMT is considered to be a surrogate marker for premature atherosclerosis, we postulate that the increased cIMT in our KD patient groups is the result of the acute inflammation of the vessel wall rather than a process of premature atherosclerosis.
REFERENCES


Chapter 9  Carotid IMT after Kawasaki disease


