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ORIGINAL ARTICLE

Age-Related Acceleration of Endothelial Dysfunction and Subclinical Atherosclerosis in Subjects with Coronary Artery Lesions After Kawasaki Disease

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Abstract The objective of this study was to test the hypothesis that accelerated endothelial dysfunction and the development of premature atherosclerosis are associated with age in subjects with coronary artery lesions after Kawasaki disease (KD). A case-control study was performed at a university hospital that included 35 post-KD subjects across a wide age range (range, 8–42 years) without traditional cardiovascular risk factors and 35 age- and sex-matched healthy control subjects (Cont). Flow-mediated dilatation (FMD) of the brachial artery-induced by reactive hyperemia, intima media thickness (IMT), and elastic modulus (Ep) of the common carotid artery were compared between KD and Cont subjects assessed against age. KD subjects had slightly higher levels of body mass index, lipid profile, and HbA1c than Cont subjects, but the differences were not significant. The mean IMT ($p < 0.001$), age-adjusted percentage normal IMT (%N IMT; $p < 0.0001$), and Ep ($p < 0.001$) were significantly higher in KD than Cont subjects, and the peak FMD% ($p < 0.01$) was significantly lower in KD than Cont subjects. There were significant correlations between FMD% and age ($r = -0.51$ $p < 0.0001$), IMT and age ($r = 0.68$, $p < 0.001$), and Ep and age ($r = 0.58$, $p < 0.01$) in KD but not Cont subjects. When the difference in FMD% between KD and matched Cont subjects (ΔFMD%) was plotted against age, no significant relationship was found, although significant correlations between ΔIMT and age ($r = 0.52$, $p < 0.01$) as well as between ΔEp and age ($r = 0.46$, $p < 0.05$) were observed. When we defined values that were +2.0 SD over the mean control values (i.e., %N IMT ≥ 120% and/or Ep ≥ 50 kPa) as markers of subclinical atherosclerosis, 15 subjects met the criteria. Subjects over the age of 22 years were more likely to have (OR = 16.54, $p = 0.0001$) subclinical atherosclerosis in this cohort. Our results suggest that endothelial dysfunction and the development of premature atherosclerosis were accelerated in adult post-KD compared to Cont subjects.

Keywords Kawasaki disease · Subclinical atherosclerosis · Endothelial dysfunction

Abbreviations

CAL	Coronary artery lesion
CRFs	Cardiovascular risk factors
Ep	Elastic modulus
FMD	Flow-mediated dilatation
IMT	Intima-media thichness
KD	Kawasaki disease

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology in infants and young children. In the acute stage, coronary aneurysm formation may occur, leading to myocardial infarction and death during the convalescent stage [13]. Recent studies revealed that alterations in the lipid profile and generalized endothelial dysfunction persist for a long time after the clinical resolution of KD [2, 17]. There is now accumulating evidence that flow-mediated dilatation (FMD) of the brachial artery induced by reactive hyperemia, a noninvasive marker of endothelial function, is abnormal in post-KD patients [7, 10]. Furthermore, some studies have shown that adverse cardiovascular profiles,

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characterized by proatherogenic alteration of lipid profile [5, 22], increased intima media thickness (IMT) of the carotid artery [4, 6, 19], and arterial stiffness [3, 20], occur in children after KD. In contrast, a recent study revealed that KD patients are at abnormal risk for risk factors for atherosclerosis, but long-term systemic arterial endothelial dysfunction is not present regardless of the degree of coronary artery involvement [14]. Due to conflicting reports, concerns have been raised as to whether KD patients are really at risk for premature atherosclerosis later in adulthood. Although the exact reasons for these conflicting results remain undetermined, differences in study populations, methodology, and latent cardiovascular risk factors (CRFs) including age, pubertal status, and systemic inflammation may play a role [26]. Age is of particular interest because the atherosclerotic process begins in childhood. Additionally, a strong association exists between the adverse lipoprotein levels and the initial stages of atherosclerosis in adolescents and young adults, and advanced atherosclerotic lesions are enhanced with age [15]. We speculated that endothelial dysfunction and the propensity for subclinical atherosclerosis gradually appear during adolescence and then rapidly increase with age, particularly in post-KD patients with persistent coronary artery lesions (CALs), including aneurysm, stenosis, and occlusion, who show diffuse vascular inflammation during the acute phase of KD. To test this hypothesis, we examined the relationship between age and progression of endothelial dysfunction and subclinical atherosclerosis in a case-control study using post-KD patients with CALs and healthy control subjects across a wide age range.

Materials and Methods

Subjects

Consecutive KD subjects meeting the following criteria were recruited from our outpatient clinic between August 2005 and August 2006: (1) a diagnosis of KD; (2) CALs documented by previous two-dimensional echocardiography or coronary angiography in the acute phase or the convalescent phase; and (3) an interval from the initial onset of illness $\geq$5 years. Subjects were excluded if they had potentially confounding CRFs for endothelial damage such as diabetes mellitus, hypertension, hypercholesterolemia, hypertriglycemia, smoking history, or a family history of premature coronary artery disease (CAD). Healthy age- and sex-matched subjects recruited from the family and friends of hospital staff served as controls. The study was approved by the Human Research Ethics Committee at our institution, and all subjects or their parents gave informed consent.

Ultrasound Study

All investigations were carried out using a 13-MHz linear array ultrasound device (Aloka SSD-6500; Tokyo) between 8 and 10 a.m. after an overnight fast in a temperature-controlled room (22°C), with the subject in the supine position. A single experienced ultrasonographer (N.N.), blinded to the subject's status, by a randomization code obtained all of the data.

The brachial artery was imaged longitudinally about 5 cm proximal to the antecubital crease. Hyperemia was induced by inflating a blood pressure cuff on the arm to occlude arterial flow (50 mmHg above the measured systolic blood pressure) for 5 min and then rapidly deflating the cuff. Initial pulsed-Doppler recordings were made and then two-dimensional images were then obtained from 30 to 120 s after cuff deflation. The diameter of the brachial artery was measured from anterior to posterior between the media and the adventitia ("m" line) at a fixed distance from an anatomical marker using ultrasonic calipers. The mean diameter was calculated from images obtained during three cardiac cycles synchronized with the R-wave peaks on the electrocardiogram. Peak FMD% was defined as the percentage change of arterial diameter after release of the cuff relative to the baseline vessel diameter (BD). After a 15-min interval to allow restoration of baseline conditions, non-endothelium-dependent brachial artery dilation was assessed with two-dimensional imaging before and 3 to 4 min after administration of sublingual glyceryl trinitrate (GTN) spray (0.3 mg). Peak GTN% was defined as the percentage change of arterial diameter after administration of GTN relative to BD. Endothelial function index (EFI) was defined as FMD% relative to GTN%. Doppler-derived flow measurements were recorded during the first resting scan (baseline) and during the first 15 s of reactive hyperemia. To quantify the vasodilatation response, the increase in blood flow was expressed as the percentage change relative to baseline flow. The total dilatation response, defined as the area under the FMD-versus-time curve from 30 to 120 s after hyperemia (AUC; mm $\times$ s) was assessed. In our laboratory, the coefficients of variation for the measurement of FMD% and GTN% were 2.42 $\pm$ 0.35% and 1.84 $\pm$ 0.25%, respectively.

Longitudinal images of the common carotid artery (CCA) were obtained by routine B-mode ultrasound imaging of subjects in the supine position with their head turned slightly to the left. The IMT of the CCA far wall was measured with electronic calipers of the machine. The mean IMT was calculated for each subject as the average of three consecutive maximal far wall thickness measurements obtained in the CCA 1 to 2 cm proximal to the bulb. M-mode ultrasound examinations were recorded online. The axial resolution of the M-mode system was 0.01 mm.

The maximal end-diastolic (Dd) and peak-systolic (Ds) carotid internal diameter were measured. Three measurements each of Dd and Ds were averaged. The diameter change (ΔD) was calculated as the difference between the systolic and the diastolic averages. Pulse pressure (ΔP) was calculated as systolic minus diastolic pressure. The pressure-elastic module (Ep), as described by Peterson et al. [21], is calculated as (ΔP × Dd)/ΔD. In our laboratory, the coefficients of variance for mean IMT and Ep were 5.0% and 6.9%, respectively [19].

Laboratory Methods

Venous blood samples were taken in the morning after an overnight fast. Serum total cholesterol, triglyceride, and high-density lipoprotein were determined using conventional enzymatic methods. The concentration of low-density lipoprotein was calculated using the Friedewald formula. Glycosylated hemoglobin A1c (HbA1c) was measured by electrophoresis.

Statistical Analysis

Results are expressed as the mean ± standard deviation. Comparisons between the two groups were done with Student's *t*-test or the nonparametric Mann-Whitney *U*-test, as appropriate. Dichotomous variables were analyzed using the chi-square test. Multivariate correlation analyses were done using the stepwise linear regression technique. For all analyses, $p < 0.05$ was accepted as statistically significant.

Results

Fifty two post-KD patients with CALs were screened for this study. Seventeen were excluded because of the existence of CRFs (hypercholesterolemia ([total cholesterol ≥ 220 mg/dl] in seven patients, hypertriglyceridemia [triglyceride ≥ 150 mg/dl] in six patients, cigarette smoking in two patients, and a first-degree relative with CAD in two patients). The remaining 35 KD patients (28 males and 7 females, ranging from 8 to 42 years old; mean, 20.5 ± 9.3 years) and 35 age- and sex-matched healthy control subjects were enrolled in this study. The interval from initial onset of KD ranged from 6 to 35 years (mean, 18.6 ± 8.4 years). A significant relationship was observed between age and time since initial onset of illness ($r = 0.977$, $p < 0.0001$). Twenty-six patients had persistent CALs; among them were 17 patients with medium (5- to 8-mm-internal diameter) and 5 patients with giant (>8-mm-internal diameter) left coronary artery aneurysm, 4 patients with giant right coronary artery aneurysm, and 9 patients with bilateral (4 with giant and 5 with medium right coronary artery aneurysm along with medium left coronary artery aneurysm) coronary aneurysms documented by previous two-dimensional echocardiography. On quantitative coronary angiography, significant coronary stenosis (>70% diameter reduction in the major coronary artery) was detected in five patients (four with right coronary artery occlusion and recanalization and one with 70% stenosis of the LAD). The treatment of the acute phase of KD included intravenous γ-globulin for 52% and aspirin for 100%. All KD patients were medicated; 24 patients were taking aspirin only, and 11 patients were taking aspirin and warfarin for prevention of coronary thrombosis. No patients were taking vasoactive medication. All patients were free of symptoms during their routine daily activities. Physical activity was restricted moderately in 3 patients with risk level V and mildly in 15 patients with risk level IV or V.

Table 1 reports the clinical data and results of blood tests. No significant differences were observed in age or blood pressure between the two groups. KD patients showed slightly higher levels of body mass index, lipid profile, and HbA1c than control subjects, but the differences were not significant.

The results of ultrasound studies are reported in Table 2. There were no differences between the two groups in brachial artery BD, blood flow during reactive hyperemia, AUC, GTN%, or EFI. In contrast, there were significant differences in FMD ($p < 0.001$), IMT ($p < 0.001$), and Ep ($p < 0.01$). Because IMT and Ep are regarded as age-dependent parameters [8, 11], we analyzed the correlation among IMT, Ep, and age in control subjects. A significant correlation ($r = 0.61$, $p < 0.001$) between age and IMT was observed, but no significant correlation between age and Ep ($r = 0.118$, $p = 0.574$). Accordingly, the normal

Table 1 Characteristics of study group subjects

	Kawasaki disease ($n = 35$)	Control ($n = 35$)	p
Age, year	20.5 ± 9.3	19.6 ± 7.2	0.79
Body mass index, kg/m^2	22.0 ± 6.7	20.5 ± 5.0	0.42
Blood pressure, mmHg			
Systolic	113.4 ± 11.0	115.3 ± 7.6	0.56
Diastolic	65.3 ± 9.1	67.8 ± 11.2	0.48
Cholesterol, mg/dl			
Total	172.8 ± 34.5	165.0 ± 21.2	0.43
LDL	94.4 ± 23.8	90.2 ± 17.3	0.56
HDL	60.3 ± 12.1	56.4 ± 16.8	0.44
Triglyceride, mg/dl	91.0 ± 46.1	83.8 ± 42.6	0.63
HbA1c, %	4.72 ± 0.35	4.63 ± 0.22	0.37

Note: values are mean ± SD

Table 2 Results of ultrasound studies in the study-group subjects

	Kawasaki disease	Control	*p*
Baseline diameter, mm	3.7 ± 1.0	3.6 ± 0.9	0.74
Increase in blood flow during hyperemia, %	425 ± 229	451 ± 290	0.75
AUC, mm × s	22.7 ± 7.8	25.4 ± 8.8	0.31
Change in diameter, mm	0.36 ± 0.11	0.43 ± 0.13	0.06
Dilatation, %			
Flow-mediated (FMD)	9.1 ± 2.7	13.3 ± 4.8	<0.001
GTN-mediated (GTN)	20.5 ± 6.2	20.6 ± 7.0	0.96
EFI (FMD/GTN)	0.46 ± 0.13	0.52 ± 0.19	0.25
Mean carotid IMT, mm	0.57 ± 0.15	0.46 ± 0.05	<0.001
%N IMT, %	121.1 ± 24.3	100.1 ± 8.4	<0.0001
Elastic property, kPa	44.7 ± 19.0	31.0 ± 8.0	<0.01

Note: *AUC* area under the curve, *EFI* endothelial function index, *GTN* glycerol trinitrate, *IMT* intima media thickness, *%N IMT*, percentage normal predicted value of IMT. Values are mean ± SD

predicted IMT value (np-IMT) and percentage normal predicted IMT value (%N IMT) were calculated using the following formulas—np-IMT = 0.381 + 0.004 × age, and %N IMT = 100 × measured IMT/np-IMT—and were identical to the values in current studies regarding the age-related normal range of IMT [12, 28]. There was a significant difference between the two groups in %N IMT ($p < 0.0001$).

We also examined the relationships between these ultrasound parameters and age. There was a significant inverse correlation between FMD% and age ($r = -0.51$, $p < 0.0001$) in KD, but not control subjects. When the difference in FMD% between KD subjects and matched control subjects (ΔFMD%) individually was plotted against age, no significant relationship between ΔFMD% and age was found ($r = -0.07$, $p = 0.68$) (Fig. 1). Likewise, there were significant correlations between IMT and age ($r = 0.68$, $p < 0.0001$) and between Ep and age ($r = 0.58$, $p < 0.01$) in KD patients but not in control subjects. Analyses were also performed for ΔIMT and ΔEp. Significant correlations between ΔIMT and age ($r = 0.52$, $p < 0.01$) and between ΔEp and age ($r = 0.46$, $p < 0.01$) were observed (Figs. 2 and 3).

When we set a cutoff point of +2.0 SD from the mean value in the control group, that is, %N IMT ≥ 120% and/or Ep ≥ 50 kPa as markers of subclinical atherosclerosis, 15 subjects met this criteria, and subjects over the age of 22 years were more likely to be subclinical atherosclerosis in this cohort (OR = 16.54, $p = 0.0001$) (Fig. 4).

Discussion

The present study suggests that the propensity for subclinical atherosclerosis increased with age, in post-KD patients with CALs in this cohort. Of note, our study population consisted of relatively elderly subjects, whose mean age and mean elapsed time from initial onset were 20.5 and 18.6 years, respectively. In contrast, the study populations in most previous studies consisted of the subjects with mean ages in the early teens [3–7, 10, 14, 19, 20, 22]. To our knowledge, ours is the first study to demonstrate long-term structural and functional alterations of systemic arteries more than 18 years after KD, in addition to a role of age in the development of subclinical atherosclerosis in post-KD patients with CALs.

Increased IMT thickness and higher carotid artery Ep, which are thought to be initial pathological changes secondary to atherosclerosis [18], were observed in post-KD patients with CALs in this study. Furthermore, age-related increases in IMT were found only in KD patients. Immunohistochemistry of coronary arteries in children with KD without coronary dilatation revealed thickened intima and increased expression of platelet-derived growth factor-α, transforming growth factor-β1, and inducible nitric oxide synthase in intimal smooth muscle cells [24]. Moreover, a pathological study of KD patients older than 15 years of age without coronary aneurysms, who had died of

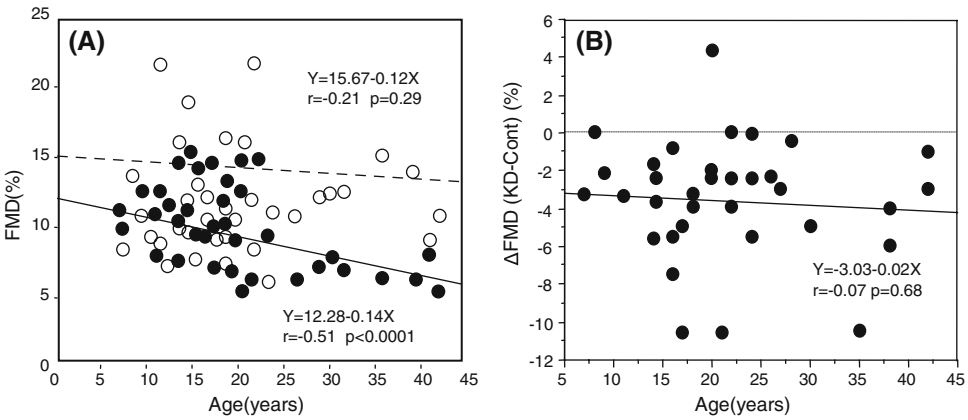

Fig. 1 **a** Scatterplot of %FMD versus age in subjects with KD (●) and control subjects (○). Regression lines: solid, KD patients; dashed, controls. **b** Difference in %FMD (ΔFMD%) and 95% CI between subjects with KD and controls, plotted against age. Mean, solid line

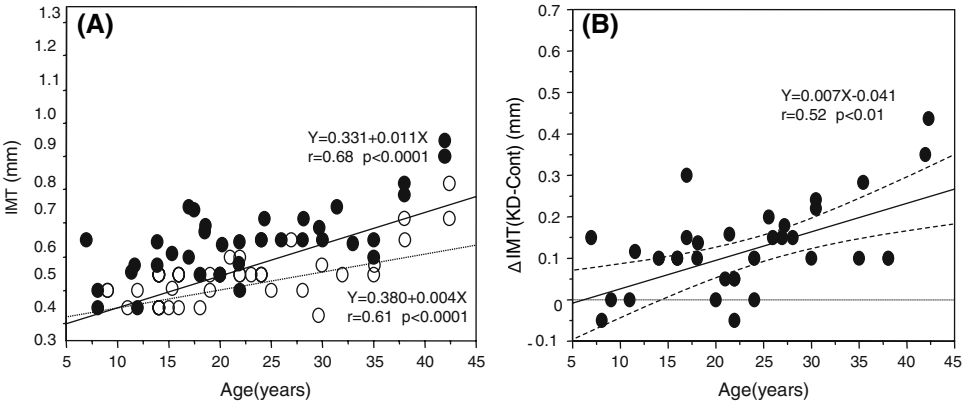

Fig. 2 **a** Scatterplot of IMT versus age for subjects with KD (●) and control subjects (○). Regression lines: solid, KD patients; dashed, controls. **b** Difference in IMT (ΔIMT) and 95% CI between subjects with KD and controls, plotted against age. Mean, solid line; 95% CI, dashed lines

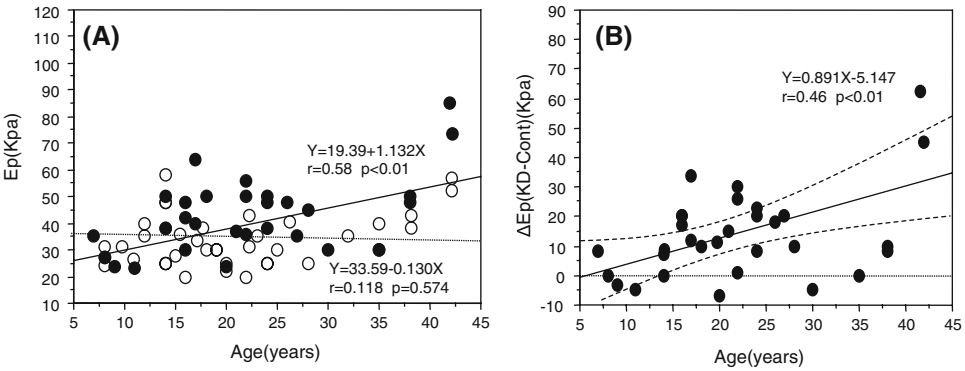

Fig. 3 **a** Scatterplot of Ep versus age for subjects with KD (●) and control subjects (○). Regression lines: solid, KD patients; dashed, controls. **b** Difference in Ep (ΔEp) and 95% CI between subjects with KD and controls, plotted against age. Mean, solid line; 95% CI, dashed lines

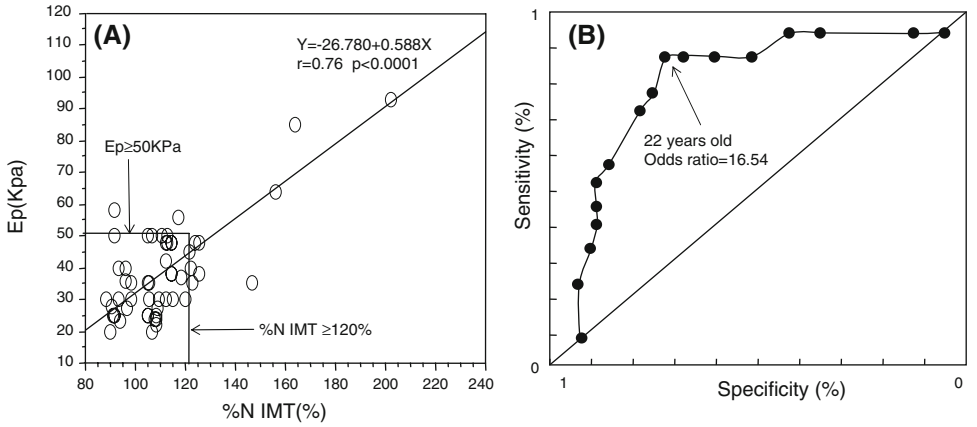

Fig. 4 **a** Relationship between percentage normal predicted value of IMT (%N IMT) and Ep. Regression line for all subjects is represented by a solid line. Arrows represent the cutoff points of %N IMT ≥ 120% and/or Ep ≥ 50 kPa as markers of subclinical atherosclerosis. **b** Receiver-operating characteristic curve for prediction of subclinical atherosclerosis against age in all subjects. Arrow indicates 22 years of age with a high odds ratio (OR = 16.54, $p = 0.0001$)

unrelated causes, demonstrated new intimal thickening in addition to pre-existing intimal thickening that had been caused by arteritis in the acute phase [25]. These findings suggest that even in KD patients without CALs, active remodeling of CALs continues in the forms of intimal proliferation and neoangiogenesis for several years after the onset of KD. Hence, we suspect that the observed increased IMT and higher Ep may have been caused by diffuse vasculitis involving both coronary and noncoronary arteries in the acute phase, in addition to the subsequent post-KD reparative process, which is often observed in patients with Takayasu's arteritis and Behcet's disease [6].

The underlying mechanisms of the age-related increases in IMT and Ep in subjects with KD remain unclear. Age-related changes in vascular free radical production, oxidative stress, and the catabolism of endothelium-derived regulators of vasomotor tone can result in a reduced FMD response and a propensity for subclinical atherosclerosis [9,

27]. Recent studies showed that serum high-sensitivity C-reactive protein (hs-CRP) concentrations are significantly increased in post-KD patients with CALs, and that there is a positive relationship between hs-CRP and carotid artery stiffness [3, 16]. In addition, CRP directly inhibits NO production by endothelial cells and increases the endothelial expression of adhesion molecules. The exposure of endothelial cells to proinflammatory cytokines impairs endothelium-dependent vasorelaxation [1]. These findings suggest that chronic low-grade inflammation late after the acute phase of KD may contribute to functional alterations and the subsequent remodeling process during the convalescent phase of KD. Although we did not examine the expression of these inflammatory markers in the present study, it is possible that persistent low-grade inflammation may be associated with age-related abnormal systemic artery function and structural changes.

In the present study, we found that post-KD patients with CALs had higher normal body mass indexes, lipid profiles, and HbA1c values than control subjects. It is well known that the process of atherosclerosis is enhanced in the presence of CRFs. In epidemiological studies of children, the best correlation with adult cholesterol levels was obtained for cholesterol levels measured during the late teen years, suggesting that subtle adverse lipoprotein profiles obtained at this age could be predictive of future dyslipoproteinemia in young adulthood [23]. Since young adults often become much less active once they leave school and physical activities are generally restricted in KD patients at risk levels IV to V, similar to the risk levels of our patient cohort [18], it is likely that subtle risk factors cluster in individual patients. Hence, we suggest that the clustering of subtle abnormalities in post-KD patients may contribute to further endothelial dysfunction and the propensity for subclinical atherosclerosis, in addition to the predisposed burden of CALs

The present study has limitations. First, we included a relatively small number of post-KD patients with CALs. Moreover, the active recruitment of adolescents and young adult KD patients with or without CALs is a potential limitation because it is introduces the possibility of selection bias. Second, we could not differentiate the IMT data which had been caused by arteritis in KD from those caused by early atherosclerotic change. The assessment of early atherosclerosis is purely hypothetical. Third, we could not exclude individuals with latent CRFs such genetic factors. Because parents of adolescents and young adults with KD are too young to have CAD themselves, it is difficult to determine the actual frequency of CAD in families. Fourth, we have presented a case-control study in a cross-sectional manner. We are unclear as to how cross-sectional data are being used to explain a longitudinal event.

Conclusion

Our results suggest that the propensity for subclinical atherosclerosis was increased in post-KD patients older than teenage with CALs. Thus, longitudinal IMT measurements may provide a valuable tool for identifying candidates for early intervention [15]. Further studies are necessary to determine whether the observed increases in IMT vary between post-KD patients with and those without CALs during adolescence and young adulthood.

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