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Vascular health late after Kawasaki disease: implications for accelerated atherosclerosis

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Kawasaki disease (KD), an acute vasculitis that primarily affects young children, is the most common acquired paediatric cardiovascular disease in developed countries. While sequelae of arterial inflammation in the acute phase of KD are well documented, its late effects on vascular health are increasingly unveiled. Late vascular dysfunction is characterized by structural alterations and functional impairment in term of arterial stiffening and endothelial dysfunction and shown to involve both coronary and systemic arteries. Further evidence suggests that continuous low grade inflammation and ongoing active remodeling of coronary arterial lesions occur late after acute illness and may play a role in structural and functional alterations of the arteries. Potential importance of genetic modulation on vascular health late after KD is implicated by associations between mannose binding lectin and inflammatory gene polymorphisms with severity of peripheral arterial stiffening and carotid intima-media thickening. The changes in cholesterol and lipoproteins levels late after KD further appear similar to those proposed to be atherogenic. While data on adverse vascular health are less controversial in patients with persistent or regressed coronary arterial aneurysms, data appear conflicting in individuals with no coronary arterial involvements or only transient coronary ectasia. Notwithstanding, concerns have been raised with regard to predisposition of KD in childhood to accelerated atherosclerosis in adulthood. Until further evidence-based data are available, however, it remains important to assess and monitor cardiovascular risk factors and to promote cardiovascular health in children with a history of KD in the long term.

Key words: Kawasaki disease, Blood vessels, Atherosclerosis

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Introduction

Kawasaki disease (KD) is the most common acquired cardiovascular disease in children in developed countries[1]. This acute vasculitis, which affects primarily infants and young children, can have multiorgan involvements[2]. While systemic involvement is generally self-limiting, cardiovascular complications can be life-threatening[3]. Acute inflammatory damage to coronary and systemic arteries in the early phase of the illness has been well described[4]. A recent animal study using a KD mouse model suggested an important pathophysiologic link between coronary arteritis and subsequent acceleration of atherosclerosis, implicating that KD in childhood may potentially predispose to early atherosclerosis in adulthood[5]. Studies in adults with acute coronary syndrome also provided evidence of persistent risk of thrombosis in regressed coronary aneurysms[6]. Indeed, long-term structural alteration and functional disturbance of coronary and systemic arteries are increasingly recognized in adolescents and young adults with a history of KD. The focus of this review is on vascular health and cardiovascular risk profile late after KD, which may have implications on accelerated atherosclerosis in adulthood.

Late coronary arterial abnormalities

1. Structural alteration

Structural alteration of coronary arterial wall after KD has been demonstrated using intravascular ultrasound. Sugimura et al.[7] reported in KD patients examined at about 9 years after the acute illness intimal thickening and calcification at sites of the coronary aneurysms, and thickened but smooth intima at sites of regressed coronary aneurysms. Importantly, intimal thickening has been noted even in angiographically normal coronary arterial segments near to the site of persistent or regressed aneurysm. Similarly, Suzuki et al.[8] have described thickened intima-media complex at sites of persistent and regressed aneurysms and in angiographically normal coronary arterial segments. Using virtual histologic-intravascular ultrasound, Mitani et al.[9] found heterogeneous plaque areas with varying composition of fibrosis, fibrofatty, necrotic core, and dense calcium areas and provided insights into the potential role of atherogenesis in the evolution of coronary arterial lesions late after KD. In a pathological study of patients with history of KD who died after 15 years of age[10], new intima thickening that superimposes on pre-existing intima thickening has been observed in coronary arteries with no previous formation of aneurysms.

While regression of coronary aneurysms is well described in KD[3], new or expanding aneurysms have also been reported late after the acute illness[11-14]. The timing of detection of new aneurysms after KD ranges from 2 to 19 years after the acute phase[14]. The development of new aneurysms has been hypothesized to be related to abnormal arterial structures with superimposed haemodynamic disturbance in the presence of stenotic lesions. While clinical events associated with expanding aneurysms appear uncommon[14], expanding aneurysms may be at risk of rupture[11] and thrombosis.

Quantification of coronary arterial calcification has been used to assess the risk of developing coronary heart disease in asymptomatic adults with atherosclerosis[15]. During long-term follow-up of patients with KD, coronary arterial calcifications have been detected using electron beam computed tomography[16-18]. In a prospective, cohort study of 18 patients with KD at >1 year from the acute disease onset, coronary calcification was found in four of five patients with late echocardiographic abnormalities, but not in the 13 patients with no or resolved coronary arterial involvement[17]. Sudden death occurred in one patient who had the highest calcium score. The role of electron beam computed tomography-detected coronary arterial calcifications in the risk stratification of patients with KD warrants further assessments.

2. Coronary arterial stiffening

Endothelium-independent coronary dilation in patients with KD has been assessed by intracoronary infusion of agents that directly relax arterial smooth muscle. Sugimura et al.[19] and Iemura et al.[20] reported impairment of coronary vasodilatory response to intracoronary injection of isosorbide dinitrate at sites of persistent and regressed aneurysms. Similarly, impaired coronary vasoreactivity to intracoronary nitroglycerin at sites of regressed aneurysms has been shown[8]. In the latter study, decreased nitroglycerin reactivity has also been observed in segments without evidence of aneurysmal dilation. These data suggest that stiffening of the coronary artery occurs after KD, which may be related to smooth muscle dysfunction and pathological changes secondary to coronary arteritis.

3. Coronary endothelial dysfunction

In normal coronary arteries, local infusion of acetylcholine induces the release of nitric oxide from an intact endothelium to cause vasodilation and forms the basis of endothelial functional assessment[21]. On the other hand, paradoxical constriction of atherosclerotic coronary arteries may result from direct muscarinic action of acetylcholine on vascular smooth muscle. In patients with KD studied late after the acute illness, acetylcholine-induced constriction of coronary arteries with persistent and regressed aneurysms has been found[20,22,23].

Cold pressor test performed in conjunction with positron emission tomography can also be used to assess coronary endothelial function. In coronary arteries with normally functioning endothelium, β-adrenergic activation due to cold stress increases coronary flow and induces vasodilation secondary to shear stress-induced release of nitric oxide from endothelial cells. On the other hand, the significantly lower myocardial blood flow found in patients with regressed aneurysms late after KD suggests coronary endothelial dysfunction[24].

Although the exact mechanism of coronary endothelial dysfunction years after the acute illness remains to be elucidated, ongoing active vascular remodeling and chronic inflammatory processes as discussed below may be possible explanations. Existing data suggest endothelial dysfunction at sites of persistent and regressed aneurysms, but it remains controversial whether angiographically normal coronary arteries are similarly involved[22,23].

4. Reduced myocardial flow reserve

Myocardial flow reserve as assessed by positron emission tomography[24] and induction of hyperaemia by dipyridamole[25] or adenosine triphosphate[26] has been examined in patients with KD. In patients with regressed coronary aneurysms[26] and even in those without documented coronary arterial lesions[24,25], myocardial flow reserve has been shown to be reduced. The global rather than regional blood flow abnormalities suggest diffuse reduction of dilation capacity of the microcirculation.

Indeed, these findings agree with the diffuse nature of the vasculitic process as demonstrated by pathological[27] and intravascular ultrasonography[8] examinations. Although the clinical implications of these findings during childhood are unclear, reduced myocardial flow reserve is undoubtedly of significance in the event of superimposed coronary artery disease during adulthood. Using three-dimensional speckle tracking echocardiography, Yu et al.[28] recently showed impairment of left ventricular strain in patients with and even in those without coronary aneurysms after the acute illness.

Late systemic arterial abnormalities

1. Increased carotid intima-media thickness

Carotid intima-media thickness has been regarded as a surrogate marker of atherosclerosis in adults[29]. In children with coronary aneurysms complicating KD, Noto et al.[30] reported carotid intima-media thickening. Some small scale and nonage matched studies[31,32], however, reported no differences in carotid intima-media thickness between patients and controls and among patients with varying involvement of coronary arteries. Subsequent studies that included age-matched controls or age-adjusted standard deviation scores of intima-media thickness revealed carotid intima-media thickening not only in patients with coronary aneurysms, but also in those without coronary artery lesions[33,34]. A recent study of North American children and young adults, however, showed normal vascular health indices including carotid intima-media thickness in KD patients whose maximum coronary arterial dimensions had always been normal or only mildly ecstatic[35]. However, the mean left carotid intima media thickness tended to differ across different KD subgroups, being highest in patients with giant coronary arterial aneurysms. Whether the conflicting data are related to differences in ethnic backgrounds of study cohorts require further clarifications.

There have been discussions on whether thickening of the intima-media complex represents early atherosclerosis changes or a distinct KD vasculopathy related to luminal myofibroblastic proliferation[36]. The recent finding of a higher grey scale median of the carotid intima-media complex in patients with KD suggests that sclerotic vascular remodeling after KD may be distinct from the atherosclerotic remodeling, which has a lower grey scale median often observed in familial hypercholesterolaemia[37].

2. Systemic arterial endothelial dysfunction

High-resolution ultrasound assessment of reactive hyperaemia of the brachial artery in response to sphygmomanometer cuff occlusion has been used to assess systemic arterial endothelial function based similarly on the principle of endothelium-dependent release of nitric oxide in response to shear stress[38]. Using this technique, Dhillon et al.[39] demonstrated significant reduction of brachial arterial flow-mediated dilation in KD patients, even in those without detectable coronary artery involvement, at a median of 11 years after the acute disease. In adults with a history of KD, flow-mediated dilation has similarly been found to be impaired[40]. Other investigators have, however, reported endothelial dysfunction only in patients with persistent coronary artery lesions[31], being worse in those with coronary arterial aneurysms[32]. Others have, on the other hand, reported on normal brachial arterial flow-mediated dilation in patients with KD[41,42]. The conflicting data in the literature and their possible reconciliation is discussed later in this review. Nonetheless, given the pathological processes during acute illness of endothelial necrosis and leukocyte infiltration of medium-sized arteries[43,44], the late functional abnormalities of the brachial artery endothelium may be a long-term consequence of diffuse systematic inflammation.

3. Systemic arterial stiffening

Increased cross-sectional stiffness of carotid artery has been found in patients with KD with and without coronary aneurysms late after the acute illness[30,33,45]. The magnitude of carotid arterial stiffening was further shown to be related to serum high-sensitivity C-reactive protein concentrations[45] and carotid intima-media thickness[33] but not alternations in lipid profile[30]. Increased regional stiffness of the aorta and brachioradial and brachial-ankle arterial segments, as evidenced by increased pulse wave velocity, has further been shown in patients with KD[46-49].

Arterial stiffness is directly related to characteristic impedance of the arterial bed, the pulsatile component of the afterload presented to the left ventricle. Indeed, invasive studies have shown significantly increased characteristic impedance and reduced total peripheral arterial compliance in patients with KD[50], suggesting that both central and peripheral arterial wall stiffness is increased after KD. Importantly, this abnormal profile was found regardless of persistence of coronary arterial lesions. Structural alteration and endothelial dysfunction probably contribute to stiffening of the arterial tree in patients with KD late after the acute illness. Reparative process in the convalescent and chronic phase of the illness is characterized by intimal thickening, fibrous scar formation, and smooth muscle proliferation[51-55], which may lead to an increase in vascular wall stiffness. Endothelial dysfunction may act by increasing vasomotor tone[56,57]. Stiffening of the arterial wall may increase intraluminal stress due to an increase in pulse pressure[58] and predispose to vascular damage and atherosclerosis. The possibility of establishing a feedback loop in patients with KD has been hypothesized[33]. Indeed, carotid intima media thickness in KD patients has been shown to correlate with carotid arterial stiffness, after adjustment for potential confounding influence of age, sex, systemic blood pressure, and

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serum cholesterol levels[33].

4. Genotype and arterial sequelae

An association between mannose binding lectin gene mutation and coronary arterial complications has been reported in infants with KD[59]. Studies have furthermore shown modulating effects of mannose binding lectin genotypes on peripheral conduit arterial stiffness late after KD[60]. Patients with intermediate- or low-level mannose binding lectin expression genotypes were found to have stiffer peripheral conduit arteries than those with high-level expression genotypes. The mechanism of the modulating effects of mannose binding lectin genotypes remains speculative. Given that mannose binding protein binds to mannose and N-acetyl glucosamine residues on the surface of many microbial antigens and plays a role in complement activation and opsonization of microorganisms, a low serum mannose binding lectin level may be associated with delayed clearance of the triggering infectious agent, hence resulting in more significant acute arterial inflammation and late dysfunction. Indeed, inflammatory gene polymorphisms have been shown to influence vascular health of patients with KD late after the acute illness[61]. Specifically, *C-reactive protein* +1444 C>T and *tumour necrosis factor*-α-308 G>A polymorphisms are shown to be associated with increased carotid arterial stiffness and intima media thickness in the long-term.

Chronic low-grade inflammation

While widespread inflammatory damage of the coronary and other medium-sized muscular arteries occurs during the acute phase of KD, there is increasing evidence that vasculitis may continue in a low-grade fashion in the long-term[62-64]. In fatal cases of KD with despite apparent resolution of vascular inflammation and the absence of early detectable coronary artery abnormalities, the histological findings of infiltration of lymphocytes and plasma cells in the arterial wall suggest smoldering vasculitis[62,63]. Persistence of low-grade chronic inflammation is further evidenced by increased serum high-sensitivity-C-reactive protein concentrations in children and adolescents with a history of KD complicated by coronary aneurysm formation, whether persistent or regressed[45,65]. The recent demonstration of persistent inflammation *in vivo* in a 40-year-old man with giant coronary aneurysm by positron emission tomography supports the concept of continuous smouldering vasculitis[66].

Inflammatory processes play a pivotal role in atherogenesis[67]. The inflammatory response to vascular injury involves recruitment and activation of monocytes through activation of monocyte chemoattractant protein-1[67], which exerts its action by interacting with the chemokine receptor CCR2 on the surface of monocytes[68]. Cheung et al.[69] demonstrated significant induction of monocyte chemoattractant protein-1 and CCR2 expression in THP-1 macrophages in vitro by the serum of children with a history of KD. C-reactive protein has been shown to upregulate CCR-2 expression in human monocytes[70]. Persistent elevation of baseline CRP level after KD[45,65] may therefore play a role in chronic stimulation of the MCP-1/CCR2 pathway. Indeed, the magnitude of gene induction was found to correlate with serum high sensitivity-C-reactive protein level[69]. *In vitro* studies have further confirmed increased expression of monocyte chemoattractant protein-1 in coronary aneurysmal tissue from patients undergoing coronary artery bypass grafting[70,71]. Taken together, these findings suggest that chronic low-grade inflammation is associated with and may perhaps predispose to long-term structural and functional changes of arteries in patients with KD.

There is further evidence of ongoing active remodeling of coronary artery lesions even late after KD. In patients who died at 2 to 12 years after onset of KD, extensive expression of vascular growth factors including transforming growth factor β_1, platelet-derived growth factor A, and basic fibroblast growth factor was found within and surrounding smooth muscle cells at stenotic and recanalized sites[72]. Limited histological evidence suggests a similar increase in the expression of vascular growth factors even in clinically normal coronary arteries after KD[73].

Dyslipidaemia

Lipid abnormalities, specifically decreased total cholesterol, high-density lipoprotein (HDL)-cholesterol, and apoA-I levels, have been found in the acute phase of KD[74-77]. Newburger et al.[74] further reported persistently reduced HDL cholesterol levels even at 3 years after the initial illness. Cheung et al.[46] further showed that at a mean of 7.1 years after the acute illness, patients with KD and coronary aneurysms had lower HDL cholesterol and apolipoprotein A-I levels and higher apolipoprotein B levels, while in patients without aneurysms, the apolipoprotein B levels are also higher than controls. As severity of vasculitis in the acute phase may be reflected by development of coronary complications[78], the findings of this latter study suggest that the magnitude of acute inflammation may have important relationships with late lipid abnormalities.

The alterations in cholesterol and lipoprotein profiles late after KD are similar to those predisposed to atherogenesis. Endothelial dysfunction documented late after resolution of the acute illness[39] may diminish lipoprotein lipase activity with reduced generation of HDL cholesterol[74]. Furthermore, inhibition of lipoprotein lipase may decrease apoA-I level by increasing its catabolism[79]. In adults with chronic inflammation due to rheumatoid arthritis,

increased LDL cholesterol levels have been reported[80]. Given the evidence of low-grade chronic inflammation late after the acute illness, changes in lipid profile may be a reflection of such process.

Controversies

Notwithstanding the identification of vascular risk factors late after KD, evidence to the contrary exists in the literature. A number of explanations to reconcile conflicting data, especially in individuals of no coronary arterial involvements, has been proposed[81]. The relatively small sample size of different studies, the variable means to assess arterial stiffness and endothelial function, coexistence of other cardiovascular risk factors, and possible ethnic differences may have accounted for the different findings and conclusions.

While alteration of arterial structure and function in patients with persistent or regressed coronary artery aneurysms is less controversial, the major question of whether vascular health late after the acute illness in individuals with no or only transient coronary arterial involvement will be similar to that of healthy subjects remains unanswered. The cardiovascular outcomes of the early Japanese cohorts who reach middle and older age would hopefully shed light on the answers to this issue[82]. In the latest update based on follow-up until 2009, for patients with cardiac sequelae due to KD, the mortality rate was significantly higher than that of the general population. On the other hand, the mortality rates of both male and female patients who did not have cardiac sequelae did not show any increase. Nonetheless, only about 6% of the entire cohort has reached age 30 to date.

Conclusions

Structural alteration and functional disturbance of coronary and systemic arteries, chronic low grade inflammation, and dyslipidaemia may exist in children and young adults with a history of KD late after the acute illness, in particular in those with persistent or even regressed coronary aneurysms. Notwithstanding the existence of conflicting data, concerns have been raised with regard to predisposition of KD in childhood to accelerated atherosclerosis in adulthood. Until further evidence-based data are available, it remains important to assess and monitor cardiovascular risk factors and to promote cardiovascular health in children with a history of KD in the long term.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Taubert KA, Rowley AH, Shulman ST. Seven-year national survey of Kawasaki disease and acute rheumatic fever. Pediatr Infect Dis J 1994;13:704-8.
2. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi 1967;16:178-222.
3. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease: a 10- to 21-year follow-up study of 594 patients. Circulation 1996;94:1379-85.
4. Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004;364:533-44.
5. Chen S, Lee Y, Crother TR, Fishbein M, Zhang W, Yilmaz A, et al. Marked acceleration of atherosclerosis after Lactobacillus casei-induced coronary arteritis in a mouse model of Kawasaki disease. Arterioscler Thromb Vasc Biol 2012;32:e60-71.
6. Tsuda E, Abe T, Tamaki W. Acute coronary syndrome in adult patients with coronary artery lesions caused by Kawasaki disease: review of case reports. Cardiol Young 2011;21:74-82.
7. Sugimura T, Kato H, Inoue O, Fukuda T, Sato N, Ishii M, et al. Intravascular ultrasound of coronary arteries in children: assessment of the wall morphology and the lumen after Kawasaki disease. Circulation 1994;89:258-65.
8. Suzuki A, Yamagishi M, Kimura K, Sugiyama H, Arakaki Y, Kamiya T, et al. Functional behavior and morphology of the coronary artery wall in patients with Kawasaki disease assessed by intravascular ultrasound. J Am Coll Cardiol 1996;27:291-6.
9. Mitani Y, Ohashi H, Sawada H, Ikeyama Y, Hayakawa H, Takabayashi S, et al. In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after Kawasaki disease: a virtual histology-intravascular ultrasound study. Circulation 2009;119:2829-36.
10. Takahashi K, Oharaseki T, Naoe S. Pathological study of postcoronary arteritis in adolescents and young adults: with reference to the relationship between sequelae of Kawasaki disease and atherosclerosis. Pediatr Cardiol 2001;22:138-42.
11. Tomita H, Fuse S, Chiba S. Images in cardiology: delayed appearance of coronary aneurysms in Kawasaki disease. Heart 1998;80:425.
12. Yasukawa K, Sonobe T, Yamamoto W. The evolution of newly developed coronary aneurysm in the chronic stage of Kawasaki disease and the usefulness of MRCA. Prog Med 2003;23:1778-83.
13. Kobayashi T, Sone K, Shinohara M, Kosuda T, Kobayashi T. Images in cardiovascular medicine. Giant coronary aneurysm of Kawasaki disease developing during postacute phase. Circulation 1998;98:92-3.
14. Tsuda E, Kamiya T, Ono Y, Kimura K, Echigo S. Dilated coronary arterial lesions in the late period after Kawasaki disease. Heart 2005;91:177-82.
15. O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, et al. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis and

prognosis of coronary artery disease. Circulation 2000;102:126-40.
16. Ishii M, Ueno T, Ikeda H, Iemura M, Sugimura T, Furui J, et al. Sequential follow-up results of catheter intervention for coronary artery lesions after Kawasaki disease: quantitative coronary artery angiography and intravascular ultrasound imaging study. Circulation 2002;105:3004-10.
17. Dadlani GH, Gingell RL, Orie JD, Roland JM, Najdzionek J, Lipsitz SR, et al. Coronary artery calcifications in the long-term follow-up of Kawasaki disease. Am Heart J 2005;150:1016.
18. Kanamaru H, Sato Y, Takayama T, Ayusawa M, Karasawa K, Sumitomo N, et al. Assessment of coronary artery abnormalities by multislice spiral computed tomography in adolescents and young adults with Kawasaki disease. Am J Cardiol 2005;95:522-5.
19. Sugimura T, Kato H, Inoue O, Takagi J, Fukuda T, Sato N. Vasodilatory response of the coronary arteries after Kawasaki disease: evaluation by intracoronary injection of isosorbide dinitrate. J Pediatr 1992;121(5 Pt 1):684-8.
20. Iemura M, Ishii M, Sugimura T, Akagi T, Kato H. Long term consequences of regressed coronary aneurysms after Kawasaki disease: vascular wall morphology and function. Heart 2000;83:307-11.
21. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046-51.
22. Mitani Y, Okuda Y, Shimpo H, Uchida F, Hamanaka K, Aoki K, et al. Impaired endothelial function in epicardial coronary arteries after Kawasaki disease. Circulation 1997;96:454-61.
23. Yamakawa R, Ishii M, Sugimura T, Akagi T, Eto G, Iemura M, et al. Coronary endothelial dysfunction after Kawasaki disease: evaluation by intracoronary injection of acetylcholine. J Am Coll Cardiol 1998;31:1074-80.
24. Muzik O, Paridon SM, Singh TP, Morrow WR, Dayanikli F, Di Carli MF. Quantification of myocardial blood flow and flow reserve in children with a history of Kawasaki disease and normal coronary arteries using positron emission tomography. J Am Coll Cardiol 1996;28:757-62.
25. Ohmochi Y, Onouchi Z, Oda Y, Hamaoka K. Assessment of effects of intravenous dipyridamole on regional myocardial perfusion in children with Kawasaki disease without angiographic evidence of coronary stenosis using positron emission tomography and H2(15)O. Coron Artery Dis 1995;6:555-9.
26. Furuyama H, Odagawa Y, Katoh C, Iwado Y, Yoshinaga K, Ito Y, et al. Assessment of coronary function in children with a history of Kawasaki disease using (15)O-water positron emission tomography. Circulation 2002;105:2878-84.
27. Fujiwara T, Fujiwara H, Nakano H. Pathological features of coronary arteries in children with Kawasaki disease in which coronary arterial aneurysm was absent at autopsy. Quantitative analysis. Circulation 1988;78:345-50.
28. Yu W, Wong SJ, Cheung YF. Left ventricular mechanics in adolescents and young adults with a history of Kawasaki disease: analysis by three-dimensional speckle tracking echocardiography. Echocardiography 2014;31:483-91.
29. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. Circulation 2000;101:E16-22.
30. Noto N, Okada T, Yamasuge M, Taniguchi K, Karasawa K, Ayusawa M, et al. Noninvasive assessment of the early progression of atherosclerosis in adolescents with Kawasaki disease and coronary artery lesions. Pediatrics 2001;107:1095-9.
31. Ikemoto Y, Ogino H, Teraguchi M, Kobayashi Y. Evaluation of preclinical atherosclerosis by flow-mediated dilatation of the brachial artery and carotid artery analysis in patients with a history of Kawasaki disease. Pediatr Cardiol 2005;26:782-6.
32. Kadono T, Sugiyama H, Hoshiai M, Osada M, Tan T, Naitoh A, et al. Endothelial function evaluated by flow-mediated dilatation in pediatric vascular disease. Pediatr Cardiol 2005;26:385-90.
33. Cheung YF, Wong SJ, Ho MH. Relationship between carotid intima-media thickness and arterial stiffness in children after Kawasaki disease. Arch Dis Child 2007;92:43-7.
34. Dalla Pozza R, Bechtold S, Urschel S, Kozlik-Feldmann R, Netz H. Subclinical atherosclerosis, but normal autonomic function after Kawasaki disease. J Pediatr 2007;151:239-43.
35. Selamet Tierney ES, Gal D, Gauvreau K, Baker AL, Trevey S, O'Neill SR, et al. Vascular health in Kawasaki disease. J Am Coll Cardiol 2013;62:1114-21.
36. Orenstein JM, Shulman ST, Fox LM, Baker SC, Takahashi M, Bhatti TR, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. PLoS One 2012;7:e38998.
37. Noto N, Okada T, Abe Y, Miyashita M, Kanamaru H, Karasawa K, et al. Characteristics of earlier atherosclerotic involvement in adolescent patients with Kawasaki disease and coronary artery lesions: significance of gray scale median on B-mode ultrasound. Atherosclerosis 2012;222:106-9.
38. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111-5.
39. Dhillon R, Clarkson P, Donald AE, Powe AJ, Nash M, Novelli V, et al. Endothelial dysfunction late after Kawasaki disease. Circulation 1996;94:2103-6.
40. Niboshi A, Hamaoka K, Sakata K, Yamaguchi N. Endothelial dysfunction in adult patients with a history of Kawasaki disease. Eur J Pediatr 2008;167:189-96.
41. Silva AA, Maeno Y, Hashmi A, Smallhorn JF, Silverman ED, McCrindle BW. Cardiovascular risk factors after Kawasaki disease: a case-control study. J Pediatr 2001;138:400-5.
42. McCrindle BW, McIntyre S, Kim C, Lin T, Adeli K. Are patients after Kawasaki disease at increased risk for accelerated atherosclerosis? J Pediatr 2007;151:244-8, 248.e1.
43. Hirose S, Hamashima Y. Morphological observations on the vasculitis in the mucocutaneous lymph node syndrome: a skin biopsy study of 27 patients. Eur J Pediatr 1978;129:17-27.
44. Fujiwara H, Hamashima Y. Pathology of the heart in Kawasaki disease. Pediatrics 1978;61:100-7.
45. Cheung YF, Ho MH, Tam SC, Yung TC. Increased high sensitivity C reactive protein concentrations and increased arterial stiffness in children with a history of Kawasaki disease. Heart 2004;90:1281-5.
46. Cheung YF, Yung TC, Tam SC, Ho MH, Chau AK. Novel and traditional cardiovascular risk factors in children after Kawasaki disease: implications for premature atherosclerosis. J Am Coll Cardiol 2004;43:120-4.
47. Vaujois L, Dallaire F, Maurice RL, Fournier A, Houde C, Therien J, et al. The biophysical properties of the aorta are altered following Kawasaki disease. J Am Soc Echocardiogr 2013;26:1388-96.
48. AlHuzaimi A, Al Mashham Y, Potts JE, De Souza AM, Sandor GG. Echo-Doppler assessment of arterial stiffness in pediatric patients with Kawasaki disease. J Am Soc Echocardiogr 2013;26:1084-9.

49. Ooyanagi R, Fuse S, Tomita H, Takamuro M, Horita N, Mori M, et al. Pulse wave velocity and ankle brachial index in patients with Kawasaki disease. Pediatr Int 2004;46:398-402.
50. Senzaki H, Chen CH, Ishido H, Masutani S, Matsunaga T, Taketazu M, et al. Arterial hemodynamics in patients after Kawasaki disease. Circulation 2005;111:2119-25.
51. Amano S, Hazama F, Hamashima Y. Pathology of Kawasaki disease: I. Pathology and morphogenesis of the vascular changes. Jpn Circ J 1979;43:633-43.
52. Amano S, Hazama F, Hamashima Y. Pathology of Kawasaki disease: II. Distribution and incidence of the vascular lesions. Jpn Circ J 1979;43:741-8.
53. Masuda H, Shozawa T, Naoe S, Tanaka N. The intercostal artery in Kawasaki disease: a pathologic study of 17 autopsy cases. Arch Pathol Lab Med 1986;110:1136-42.
54. Tanaka N, Naoe S, Masuda H, Ueno T. Pathological study of sequelae of Kawasaki disease (MCLS). With special reference to the heart and coronary arterial lesions. Acta Pathol Jpn 1986;36:1513-27.
55. Foster BJ, Bernard C, Drummond KN. Kawasaki disease complicated by renal artery stenosis. Arch Dis Child 2000;83:253-5.
56. Ramsey MW, Goodfellow J, Jones CJ, Luddington LA, Lewis MJ, Henderson AH. Endothelial control of arterial distensibility is impaired in chronic heart failure. Circulation 1995;92:3212-9.
57. Joannides R, Richard V, Haefeli WE, Benoist A, Linder L, Luscher TF, et al. Role of nitric oxide in the regulation of the mechanical properties of peripheral conduit arteries in humans. Hypertension 1997;30:1465-70.
58. Demer LL. Effect of calcification on in vivo mechanical response of rabbit arteries to balloon dilation. Circulation 1991;83:2083-93.
59. Biezeveld MH, Kuipers IM, Geissler J, Lam J, Ottenkamp JJ, Hack CE, et al. Association of mannose-binding lectin genotype with cardiovascular abnormalities in Kawasaki disease. Lancet 2003;361:1268-70.
60. Cheung YF, Ho MH, Ip WK, Fok SF, Yung TC, Lau YL. Modulating effects of mannose binding lectin genotype on arterial stiffness in children after Kawasaki disease. Pediatr Res 2004;56:591-6.
61. Cheung YF, Huang GY, Chen SB, Liu XQ, Xi L, Liang XC, et al. Inflammatory gene polymorphisms and susceptibility to kawasaki disease and its arterial sequelae. Pediatrics 2008;122:e608-14.
62. Takahashi M. The endothelium in Kawasaki disease: the next frontier. J Pediatr 1998;133:177-9.
63. McConnell ME, Hannon DW, Steed RD, Gilliland MG. Fatal obliterative coronary vasculitis in Kawasaki disease. J Pediatr 1998;133:259-61.
64. Burke AP, Virmani R, Perry LW, Li L, King TM, Smialek J. Fatal Kawasaki disease with coronary arteritis and no coronary aneurysms. Pediatrics 1998;101(1 Pt 1):108-12.
65. Mitani Y, Sawada H, Hayakawa H, Aoki K, Ohashi H, Matsumura M, et al. Elevated levels of high-sensitivity C-reactive protein and serum amyloid-A late after Kawasaki disease: association between inflammation and late coronary sequelae in Kawasaki disease. Circulation 2005;111:38-43.
66. Suda K, Tahara N, Kudo Y, Yoshimoto H, Iemura M, Ueno T, et al. Persistent coronary arterial inflammation in a patient long after the onset of Kawasaki disease. Int J Cardiol 2012;154:193-4.
67. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115-26.
68. Charo IF, Myers SJ, Herman A, Franci C, Connolly AJ, Coughlin SR. Molecular cloning and functional expression of two monocyte chemoattractant protein 1 receptors reveals alternative splicing of the carboxyl-terminal tails. Proc Natl Acad Sci U S A 1994;91:2752-6.
69. Cheung YF, Karmin O, Tam SC, Siow YL. Induction of MCP1, CCR2, and iNOS expression in THP-1 macrophages by serum of children late after Kawasaki disease. Pediatr Res 2005;58:1306-10.
70. Han KH, Hong KH, Park JH, Ko J, Kang DH, Choi KJ, et al. C-reactive protein promotes monocyte chemoattractant protein-1-mediated chemotaxis through upregulating CC chemokine receptor 2 expression in human monocytes. Circulation 2004;109:2566-71.
71. Fukazawa R, Ikegam E, Watanabe M, Hajikano M, Kamisago M, Katsube Y, et al. Coronary artery aneurysm induced by Kawasaki disease in children show features typical senescence. Circ J 2007;71:709-15.
72. Suzuki A, Miyagawa-Tomita S, Komatsu K, Nishikawa T, Sakomura Y, Horie T, et al. Active remodeling of the coronary arterial lesions in the late phase of Kawasaki disease: immunohistochemical study. Circulation 2000;101:2935-41.
73. Suzuki A, Miyagawa-Tomita S, Komatsu K, Nakazawa M, Fukaya T, Baba K, et al. Immunohistochemical study of apparently intact coronary artery in a child after Kawasaki disease. Pediatr Int 2004;46:590-6.
74. Newburger JW, Burns JC, Beiser AS, Loscalzo J. Altered lipid profile after Kawasaki syndrome. Circulation 1991;84:625-31.
75. Cabana VG, Gidding SS, Getz GS, Chapman J, Shulman ST. Serum amyloid A and high density lipoprotein participate in the acute phase response of Kawasaki disease. Pediatr Res 1997;42:651-5.
76. Salo E, Pesonen E, Viikari J. Serum cholesterol levels during and after Kawasaki disease. J Pediatr 1991;119:557-61.
77. Khovidhunkit W, Memon RA, Feingold KR, Grunfeld C. Infection and inflammation-induced proatherogenic changes of lipoproteins. J Infect Dis 2000;181 Suppl 3:S462-72.
78. Koren G, Lavi S, Rose V, Rowe R. Kawasaki disease: review of risk factors for coronary aneurysms. J Pediatr 1986;108:388-92.
79. Goldberg IJ, Blaner WS, Vanni TM, Moukides M, Ramakrishnan R. Role of lipoprotein lipase in the regulation of high density lipoprotein apolipoprotein metabolism. Studies in normal and lipoprotein lipase-inhibited monkeys. J Clin Invest 1990;86:463-73.
80. Lakatos J, Harsagyi A. Serum total, HDL, LDL cholesterol, and triglyceride levels in patients with rheumatoid arthritis. Clin Biochem 1988;21:93-6.
81. Selamet Tierney ES, Newburger JW. Are patients with Kawasaki disease at risk for premature atherosclerosis? J Pediatr 2007;151:225-8.
82. Nakamura Y, Aso E, Yashiro M, Tsuboi S, Kojo T, Aoyama Y, et al. Mortality among Japanese with a history of Kawasaki disease: results at the end of 2009. J Epidemiol 2013;23:429-34.

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