REVIEW

Kawasaki Disease: Pathology, Risks, and Management

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Abstract: Kawasaki disease (KD), first reported as an acute febrile mucocutaneous lymph node syndrome, is a self-limiting vasculitis of unknown etiology. The most important aspect of KD is the prevention of coronary artery lesion (CAL) because myocardial ischemia or infarction due to CAL might be lethal. In addition to the CAL, patients with KD develop systemic vasculitis, which indicates the presence of vascular endothelial damage. Studies assessing pulse wave velocity or percentage change in flow-mediated dilatation have shown that aortic stiffness is increased in patients with KD history. In contrast, the cardio-ankle vascular index, a novel parameter not affected by blood pressure, has not demonstrated increased aortic stiffness in patients with KD. Although many studies using various parameters have suggested a risk of atherosclerosis in patients with a history of KD, a few others have reported no significant differences between KD patients and controls. Therefore, it will be necessary to thoroughly understand the characteristics of each parameter, before evaluating the results of those studies, to understand systemic vascular dysfunction in these populations, and to manage their vascular health. Although it is controversial whether the risk of atherosclerosis in patients with KD is higher, those with CAL are thought to be at a high risk of atherosclerosis. Therefore, appropriate treatment to prevent CAL in the acute phase and subsequent regular follow-up is important. Here, we review the pathology, risk, and management of vascular disorders, especially systemic vascular disorders, in patients with KD history.

Keywords: vasculitis, aortic stiffness, atherosclerosis, vascular health

Introduction

Kawasaki disease (KD), first reported as an acute febrile mucocutaneous lymph-node syndrome by Tomisaku Kawasaki in 1967, is a self-limited vasculitis of unknown etiology.[1,2] KD usually occurs in infants or young children, causing coronary artery dilatation or aneurysm, and it is the most common cause of acquired cardiac disorder in children. Coronary artery lesion (CAL) develop in approximately 25% of patients with KD who do not receive appropriate treatment.[3]

A nationwide epidemiological survey of KD in Japan began in 1970.[4] More than 15,000 patients have been reported annually in recent years, and the incidence rate (per 100,000 children aged 0–4 years per year) was 330.2 (371.2 in boys, and 287.3 in girls) in 2015, and 309.0 (343.2 in boys, and 273.2 in girls) in 2016. Genetic factors appear to be involved in KD pathogenesis, as suggested by the highest incidence among Asians and Pacific Islanders and in boys versus girls.[5] Siblings of children with KD are at increased risk of developing the disease.[6] Sibling pairs suffering from KD within a short time interval may be due to some environmental triggers, including infectious antigens.[7] The involvement of infective factors or foreign antigens in the development of KD has been considered. Although viral agents can trigger KD, the cause of this syndrome is still unclear. Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had created a global pandemic, and recent studies have shown that several children diagnosed with COVID-19 had developed KD-like symptoms, that is, multisystem inflammatory syndrome in children (MIS-C).[8–11] Therefore, a detailed study of these contributing factors may help elucidate the pathogenesis of KD. On the other hand, from the recent epidemiologic association between KD and common pediatric infectious diseases during the COVID-19 pandemic period, there is a possibility of KD being triggered by unidentified respiratory pathogens that potentially might be acquired from both, within and outside the household.[12]

The most important aspect of acute management of KD is the prevention of CAL. Patients with intravenous immunoglobulin (IVIG)-resistant KD are at an increased risk of developing CAL compared with IVIG responders. Additionally, the severity of coronary artery aneurysm is associated with long-term coronary events in patients with KD.[13,14] Although various additional treatments have been established for IVIG-resistant KD, such as prednisolone,[15] infliximab,[16] cyclosporine,[17] urinary trypsin inhibitors,[18] and plasma exchange,[19] the development of coronary artery abnormalities has not been overcome. Acute-phase vascular damage, which includes rapid destruction of endothelial cells, elastic lamina, and medial smooth muscle cells, results in aneurysm formation.[20,21] Furthermore, in addition to vascular abnormalities in coronary arteries, patients with KD, especially those with CAL, are noted to be present with systemic vasculitis because inflammation occurs in medium-sized muscular arteries throughout the body.[22,23] Here, we review the pathology, risk, and management of vascular disorders in patients with a history of KD. Vascular disorder in KD is often focused on the coronary arteries. However, the risk of systemic vascular damage and subsequent atherosclerosis is crucial and is the focus of this review.

Histopathology of Vasculitis

The inflammatory phase of coronary arterial vasculitis in acute KD usually lasts for approximately six weeks.[24] The earliest histological change in coronary arteritis is infiltration of inflammatory cells in the tunica adventitia and tunica intima that occurs approximately one week after the onset of KD. Subsequently, inflammatory cells infiltrate the tunica media, leading to the inflammation of all layers of the coronary arterial wall. Due to significant damage to arterial components, such as the internal elastic lamina and tunica media, the artery begins to dilate approximately 10–12 days after the onset of KD. The inflammatory cell infiltration continues for about two weeks and then gradually fades, leaving scars that heal after ~40 days of the disease. Even after the inflammatory cells disappear, the inflammatory scar persists for a long time. Especially in patients with coronary aneurysms, various findings of arteritis may be observed, such as stenotic lesions or extensive calcification of the aneurysm wall. Regressed or transiently dilated aneurysm lesions have been found to have residual scarring due to vasculitis in the chronic phase.[25]

In the acute phase of clinical course, coronary arteries are mainly injured, but it is considered that other systemic blood vessels have also been injured by inflammation. Whole-body examination for KD to evaluate systemic vasculitis revealed that vascular lesions, such as dilatation or aneurysm develop at various sites throughout the body, especially in the subclavian, brachial, axillary, and iliac arteries.[26–29] The course of KD vasculitis is thought to be synchronous throughout the body.[22] The incidence of systemic arterial aneurysm has been reported to be 0.8–2.0%, and it is seen in KD patients with CAL who underwent angiography three months after the onset. Although these reports are based on data obtained prior to year 2000, these incidence rates cannot be easily contrasted over time.[30,31] Improved treatment strategies for the acute phase of KD might be able to reduce the incidence of systemic arterial aneurysms; however, a recent report has shown a similar incidence (2.0% of KD patients).[29] Additionally, many case reports have revealed that systemic arterial aneurysms are almost always associated with giant coronary arterial aneurysms,[22,26–29] and detailed evaluation should be considered in these patients.

Atherosclerosis and Vascular Stiffness
Adverse Cardiovascular Events

Early documented post-KD patients are now old enough to progress to atherosclerosis. Endothelial injury and dysfunction in vessel walls are key to the development of atherosclerosis. Endothelial injury and endothelial dysfunction induce inflammatory reactions. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified low-density lipoprotein cholesterol levels. Endothelial dysfunction after vasculitis in KD might be one of the factors promoting the development of atherosclerosis.[32]

It is well known that vascular stiffness increases in the atherosclerotic vasculature. As mentioned above, patients with KD have systemic vasculitis because inflammation occurs in medium-sized muscular arteries throughout the body.[22,23] Thus, patients with KD are considered to be at an increased risk of general atherosclerosis.[33,34] Although vessel lesions caused by KD are observed at various sites throughout the body, such as the aorta, brachial artery, and renal artery,[22,35] investigations of the association between atherosclerosis and KD are still controversial.

Atherosclerosis
Atherosclerosis and KD
The relationship between the atherosclerotic lesions in large elastic arteries and the development of myocardial infarction in adult patients has long been established,[36] and increased aortic stiffness has been reported to be associated with coronary atherosclerosis.[37] Given the noted association between atherosclerosis of elastic arteries and coronary artery lesions, it is easy to understand that patients with a history of KD, who develop CAL, are at risk for developing atherosclerosis. On the other hand, because patients without CAL are not at risk for early onset of atherosclerosis, most physicians have not conducted long-term follow-up. Although there is insufficient evidence for the early progression of atherosclerosis in patients with a history of the development of CAL, as described above, possible pathophysiologic conditions that promote atherosclerosis are thought to exist in KD.

Endothelial Dysfunction
In the etiopathogenesis, atherosclerosis is an inflammatory disorder. Bioactive substances such as platelet-derived growth factor are released into the vessel wall in response to endothelial cell damage, forming the initial lesion of atherosclerosis.[32] In the normal vascular wall, endothelial cells that act as barriers for the sub-endothelium are in direct contact with plasma and blood cell components, and transmit these signals to the tunica media. Specifically, endothelial cells release several vasoactive substances, such as nitric oxide (NO) and endothelin, and are involved in vascular wall contraction or relaxation, adhesion of inflammatory cells to the vascular wall, vascular permeability, and regulation of coagulation and fibrinolytic systems.

NO, a vasodilator synthesized by endothelial NO synthase (eNOS) and inducible NO synthase (iNOS), has diverse roles in the pathophysiology of cardiovascular system. Neutrophils, monocytes, and endothelial cells express iNOS at different stages of acute KD. Expression of iNOS in neutrophils is restricted to the very early stage, suggesting that NO synthesized by iNOS in neutrophils has an important role in triggering early endothelial dysfunction in acute KD.[38]

Oxidative stresses, such as reactive oxygen species (ROS), free radicals derived from ROS, and lipid peroxide, play an important role in the pathology of inflammation-based KD by damaging endothelial cells, followed by decreased NO production and inflammation in the vascular wall.[39] In KD patients with CAL, oxidative stress was increased as compared to KD patients without CAL or normal control, and was associated with carotid intima-media thickening and stiffening.[40] The effect of oxidative stress on the wall of the vessels may remain for a long time and contribute to the development of atherosclerosis.[39]

Non-Invasive Assessment of Vascular Dysfunction
Percentage Change in Flow-Mediated Dilatation: %FMD
Percentage change in flow-mediated dilatation (%FMD) reflects endothelial nitric oxide-dependent vasodilatation. Decreased %FMD reflects endothelial cell dysfunction, and a significant decrease in %FMD is a common feature in adult atherosclerosis.[41] In patients with KD, %FMD has also been reported for the purpose of assessing vascular endothelial damage. Some meta-analyses reported that %FMD was lower in the KD group than in the control group, indicating endothelial damage and risk of atherosclerosis.[42–44] However, a closer look at individual reports reveals that the findings of %FMD in patients with KD are still controversial. Several previous studies have reported that %FMD was significantly lower in patients with a history of KD than in control subjects, showing systemic endothelial dysfunction late after KD onset.[45–48] In addition, some studies have shown lower %FMD, especially in the KD patients with CAL, who were divided into three groups: KD patients with CAL, KD patients without CAL, and control.[49–52] Interestingly, in children with CAL late after KD, there is increased high-sensitivity C-reactive protein in addition to reduced %FMD, indicating the presence of ongoing chronic vascular inflammation and endothelial dysfunction in these patients.[46] On the other hand, studies have reported that systemic endothelial dysfunction detected by %FMD was not present in KD patients, although they did not assess separately the KD patients with and without CAL.[53–55] Additional long-term studies are required to assess the effect of KD on vascular health.

Nitroglycerine Mediated Dilatation: %NMD

In addition to %FMD which assesses vascular endothelial damage and the progression of atherosclerosis, nitroglycerin-induced endothelium-independent vasodilatory response (%NMD) has been used to assess the function of the vascular smooth muscle itself. Some studies assessed %NMD in patients with a history of KD; however, none of the studies found a significant difference between patients after KD and controls even when looking at patients with CAL.[45,47,54]

Peripheral Artery Tonometry

To evaluate endothelial dysfunction, reactive hyperemia peripheral arterial tonometry (RH-PAT), a non-invasive, automatic, quantitative, and reproducible method, is conducted by measuring changes in the digital pulse volume during reactive hyperemia.[56,57] Briefly, we can assess the pulse amplitude in the fingertip at rest, using a PAT device that is placed on the index finger of each hand. In the RH-PAT, the NO-dependent vasodilation rate in response to shear stress is calculated by dividing the ratio of the post-deflation pulse amplitude by the baseline pulse amplitude. Because this result on only one side would be affected by vasoconstriction due to sympathetic excitation, the PAT ratio, divided the dilatation rate of the test hand by that, on the other hand, as a control, is obtained to minimize the effect of the sympathetic nervous system.

There are a few reports on the evaluation of vascular endothelial function using RH-PAT in patients with KD. Studies of children and young adult patients with a history of KD showed no difference in PAT ratio between KD patients and controls, providing reassurance regarding peripheral vascular health in this population.[58,59] On the other hand, another study found a significantly lower PAT ratio in KD patients without CAL, as compared to healthy controls, although it was a small sample size.[60]

Pulse Wave Velocity: PWV

Noninvasive evaluations of vascular elasticity have also been well documented. Pulse wave velocity (PWV) is one of the representative parameters for evaluating arterial stiffness.[61] The PWV can be measured from various arterial sites: the pressure waveforms are usually obtained percutaneously in the common carotid and femoral arteries. The distance covered by the waves was assimilated into the surface distance between the two recording sites, and the time delay measured between the feet of the two waveforms was estimated. Specifically, PWV is calculated as the ratio of the distance to the time delay.[62] Several methods have been developed to measure PWV, such as aortic PWV, brachial-radial PWV, and brachial-ankle PWV. In general, aortic PWV is measured as biophysical properties of the aorta using ultrasonography and two studies showed increased aortic PWV in KD patients.[63,64] There have been five reports on the measurement of brachial-radial PWV in patients with KD history, showing a significant increase in arterial stiffness in the KD group compared with the control group, regardless of whether the patients had CAL or not.[65–69] Two studies measured brachial-ankle PWV and showed increased PWV in KD group.[50,70] One of these studies revealed that vascular stiffness was increased in male KD patients but not in female patients, suggesting that KD-induced vasculitis is sex-dependent.[50]

Aortic PWV is a known predictor of cardiovascular events.[71] In contrast, although we can find studies showing a significant correlation between brachial-ankle PWV and cardiovascular events or risk factors, their sample size does not seem to be large enough. No large prognostic studies looking at the association between brachial-radial PWV, which is less common in use, and cardiovascular events have been performed.[44] Therefore, we should be careful when interpreting the results of PWV.

Cardio-Ankle Vascular Index: CAVI

Cardio-ankle vascular index (CAVI) is also a representative parameter for evaluating arterial stiffness. The stiffness parameter β represents the local stiffness of a blood vessel that depends on the change in vascular diameter, corresponding to arterial pressure variance and is independent of blood pressure. CAVI was developed to evaluate the properties of the whole artery, and essentially represents the stiffness of the aorta, femoral artery, and tibial artery.[72] CAVI is obtained by calculating the stiffness parameter β, which indicates the intrinsic stiffness of blood vessels, independent of blood pressure, using the equation of velocity and volume modulus (Bramwell-Hill's formula).[73] Therefore, CAVI is also theoretically independent of blood pressure. The formula for measuring this index is CAVI = a{(2ρ/ΔP) × ln(Ps/Pd)PWV^2} + b, where Ps and Pd are the systolic and diastolic blood pressures,

respectively, PWV is the pulse wave velocity between the heart and ankle, ΔP is Ps − Pd, ρ is blood density, and a and b are constants.[72] A study reported that there was no significant difference between KD group without CAL and control group. CAVI assessed more central vascular stiffness and did not differ from controls.[74] We have conducted a similar study, but there was no significant difference in CAVI between the control and KD groups with CAL. The CAVI assesses more central vascular stiffness than PVW; therefore, it is speculated that injury to the great vessel may be mild or absent in KD vasculitis. Although some studies, for instance %FMD or PWV, have suggested a risk of atherosclerosis in patients with a history of KD, CAVI, which is a parameter unaffected by blood pressure, they did not demonstrate increased arterial stiffness. CAVI is a relatively new parameter; therefore, further studies are expected to elucidate vascular function in patients with a history of KD.

Carotid Intima-Media Thickness: CIMT

Carotid intima-media thickness (cIMT) is measured by ultrasonography and a validated parameter of cardiovascular risk. A review showed that a hazard ratio of 1.15 for myocardial infarction and 1.18 for stroke with every 0.1 mm increase in cIMT.[75] Although cIMT is validated, it is important to realize that 0.5 mm is measured using a device with an axial resolution of around 0.04–0.05 mm, implicating a large standard deviation by default, hence not suitable for research in small groups.[44]

Based on the results of meta-analysis, a total of 15 studies reported on cIMT in patients after KD. Seven studies reported a significantly increased cIMT, seven studies showed no significant difference, and one study showed a decreased cIMT as compared to controls. However, 13 out of the 15 studies measuring cIMT included less than 50 participants per group, therefore we should be careful in our interpretation of the results.[44]

Summary

As mentioned above, many studies using various parameters have suggested a risk of atherosclerosis in patients with a history of KD. However, few studies have reported no significant differences between KD patients and controls. Therefore, it will be necessary to understand the characteristics of each parameter well before evaluating the results of those studies. In addition, most previous reports have examined pediatric or young adult patients with a history of KD, and there are no reports of an increased incidence of atherosclerotic lesions in adult patients with KD. More than half a century has passed since KD was first reported, and it is expected that the accumulated knowledge of its long-term prognosis will be helpful in the future.

Acute Therapy for KD

Successful management of the acute phase of KD is important for the prevention of CAL. IVIG is a standard therapy for acute KD. The incidence of CAL was reported in 23% to 43% of patients treated with aspirin, as compared to 8% to 15% of patients treated with IVIG plus aspirin, for four consecutive days.[76,77] In addition, the single infusion of 2 g/kg of IVIG, which is the current standard regimen, reduced the incidence of CAL to 4.6%.[78] A systematic review by the Cochrane Collaboration states that CAL development can be reduced by a single dose of 2 g/kg IVIG given before the tenth day after the onset of KD.[79]

Patients with IVIG-resistant KD are at an increased risk of developing CAL compared with IVIG responders. Approximately 10–18% of KD patients were reported to be unresponsive to IVIG therapy.[80–82] A report from China showed that the incidence of CAL in IVIG non-responders was significantly higher than that in IVIG responders (31.3% vs 17.6%), although the incidence could not be known exactly because IVIG non-responders usually underwent additional treatment.[83] Effective treatment to prevent CAL may not only reduce the risk of subsequent coronary arterial complications but also prevent the development of atherosclerotic lesions in systemic vessels. The course of KD vasculitis is thought to be synchronous throughout the body.[22] In particular, systemic arterial aneurysms in KD patients are usually associated with giant coronary arterial aneurysm, therefore, choosing the right treatment at the right time is critical. In Japan, several risk-scoring systems for predicting IVIG non-responders before initial treatment have been reported and are widely used in clinical practice.[84–86] For high-risk patients, refractory to IVIG, administration of prednisolone or cyclosporine is added to standard treatment (IVIG plus aspirin) as first-line therapy, and its efficacy has already been proven by randomized control trials.[15,22] Unfortunately, several reports from other countries revealed that these risk-scoring systems are inadaptable to the prediction of IVIG non-responders in regions other than Japan.[87,88] In

either case, the goal of the treatment in the acute phase of KD is to suppress vascular inflammation, as soon as possible within the first nine to ten days of the illness, to minimize the damage to the coronary artery wall. It is desirable to develop risk-scoring systems that can be used globally, or an original scoring system that can be adapted to each region for the suppression of KD vasculitis.

Patients who do not respond to first-line or second-line treatment should be treated with additional treatments, such as infliximab or plasma exchange, in addition to prednisolone and cyclosporine, without delay. Although these strategies have improved the prognosis of coronary arteries, the occurrence of giant coronary aneurysms is still observed, and further treatment development is desirable.

Management After Acute Therapy

After recovery from acute KD, antiplatelet therapy for a couple of months is recommended, such as 3–5 mg/kg of aspirin because platelet count and coagulation activity increase for 2–3 months after the onset of KD.[89] Aspirin should be used with caution due to allergic eruptions or liver dysfunction. Patients without CAL require no additional medical therapy after the acute phase, with no restrictions on daily life or exercise.

In contrast, in KD patients with cardiovascular complications, it is important to manage ischemic heart disease to improve symptoms and prevent cardiac events. As mentioned above, in patients with CAL, aspirin and other antiplatelet agents are the mainstay of treatment, and anticoagulants are added mainly in cases of giant coronary artery aneurysms or a history of previous myocardial infarction.[5] Additionally, statins and angiotensin II receptor blocker/angiotensin converting enzyme inhibitors have been suggested to be useful for vascular health.

Statins have been reported to have multifaceted pharmacological effects, such as anti-inflammatory, antioxidant, anticoagulant, and thrombolytic effects, as well as a decrease in serum cholesterol levels.[90,91] Additionally, statins are expected to be effective in improving vascular endothelial function. In fact, it has been reported that patients with KD treated with statins show a decrease in high-sensitivity C-reactive protein and an increase in %FMD, although this study included a small number of cases.[46] In a statement from the American Heart Association, KD patients with CAL need to be treated prophylactically.[5]

Critical stenotic lesions are often observed at the proximal and distal ends of aneurysms or in multiple coronary aneurysms. These findings are due to thickening of the vessel wall by vascular remodeling, due to the action of the renin–angiotensin system. Patients with CAL are likely to have systemic vascular damage; therefore, these treatments are recommended for the prevention of atherosclerosis from the perspective of vascular health.

Patients with KD who develop myocardial ischemia or myocardial infarction due to CAL require percutaneous coronary intervention or coronary artery bypass grafting. Coronary revascularization is required in less than 1% of patients with a history of KD.[92,93] However, CAL caused by KD vasculitis are different from atherosclerotic lesions; therefore, careful attention should be paid to aneurysms or calcified lesions. For patients with KD and CAL, regular monitoring with exercise myocardial scintigraphy, contrast-enhanced computed tomography, or cardiac magnetic resonance imaging is necessary.

Conclusion

Although the etiology of KD remains unknown, effective acute-phase treatments are being developed, and the pathogenesis of vascular complications and long-term prognosis after systemic vasculitis are being elucidated. Many studies using various parameters have suggested a risk of atherosclerosis in patients with a history of KD. On the other hand, a few studies have reported no significant differences between KD patients and controls. Therefore, it will be necessary to understand the characteristics of each parameter thoroughly before evaluating the results of those studies. In addition, most previous reports have examined pediatric or young adult patients with a history of KD; therefore, it is important to consider the long-term prognosis for vascular health in these populations. Further studies and appropriate management based on these studies are needed in the future.

Abbreviations

KD, Kawasaki disease; CAL, coronary artery lesion; IVIG, intravenous immunoglobulin; FMD, flow-mediated dilatation; PWV, pulse wave velocity; CAVI, cardio-ankle vascular index.

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Disclosure

The authors declare no conflicts of interest relevant to this article.

References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi*. 1967;16:178–222. Japanese.
2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics*. 1974;54:271–276. doi:10.1542/peds.54.3.271
3. Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol*. 2016;67:1738–1749. doi:10.1016/j.jacc.2015.12.073
4. Makino N, Nakamura Y, Yashiro M, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016. *Pediatr Int*. 2019;61:397–403. doi:10.1111/ped.13809
5. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-Term management of Kawasaki disease: a Scientific Statement for Health Professionals from the American Heart Association. *Circulation*. 2017;135:e927–e999. doi:10.1161/CIR.0000000000000484
6. Fujita Y, Nakamura Y, Sakata K, et al. Kawasaki disease in families. *Pediatrics*. 1989;84:666–669. doi:10.1542/peds.84.4.666
7. Banday AZ, Bhattacharya D, Pandiarajan V, et al. Kawasaki disease in siblings in close temporal proximity to each other-what are the implications? *Clin Rheumatol*. 2021;40:849–855. doi:10.1007/s10067-020-05328-5
8. Mardi P, Esmaeili M, Iravani P, Abdar ME. Pourrostami K and Qorbani M. Characteristics of children with Kawasaki disease-like sin COVID-19 pandemic: a systematic review. *Front Pediatr*. 2021;9:625377. doi:10.3389/fped.2021.625377
9. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395:1771–1778. doi:10.1016/S0140-6736(20)31103-X
10. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142:429–436. doi:10.1161/CIRCULATIONAHA.120.048360
11. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094. doi:10.1136/bmj.m2094
12. Ae R, Shibata Y, Kosami K, et al. Kawasaki disease and pediatric infectious diseases during the coronavirus disease 2019 pandemic. *J Pediatr*. 2021;239:50–58. doi:10.1016/j.jpeds.2021.07.053
13. Tsuda E, Hamaoka K, Suzuki H, et al. A survey of the 3-decade outcome for patients with giant aneurysms caused by Kawasaki disease. *Am Heart J*. 2014;167:249–258. doi:10.1016/j.ahj.2013.10.025
14. Miura M, Kobayashi T, Kaneko T, et al. Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. *JAMA Pediatr*. 2018;172:e180030. doi:10.1001/jamapediatrics.2018.0030
15. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. 2012;379:1613–1620. doi:10.1016/S0140-6736(11)61930-2
16. Tremoulet AH, Jain S, Jaggi P, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a Phase 3 randomised, double-blind, placebo-controlled trial. *Lancet*. 2014;383:1731–1738. doi:10.1016/S0140-6736(13)62298-9
17. Hamada H, Suzuki H, Onouchi Y, et al. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. *Lancet*. 2019;393:1128–1137. doi:10.1016/S0140-6736(18)32003-8
18. Kanai T, Ishiwata T, Kobayashi T, et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study. *Circulation*. 2011;124:2822–2828. doi:10.1161/CIRCULATIONAHA.111.028423
19. Mori M, Imagawa T, Katakura S, et al. Efficacy of plasma exchange therapy for Kawasaki disease intractable to intravenous gamma-globulin. *Mod Rheumatol*. 2004;14:43–47. doi:10.3109/s10165-003-0264-3
20. Harnden A, Takahashi M, Burgner D. Kawasaki disease. *BMJ*. 2009;338:b1514. doi:10.1136/bmj.b1514
21. Fukazawa R, Ogawa S. Long-term prognosis of patients with Kawasaki disease: at risk for future atherosclerosis? *J Nippon Med Sch*. 2009;76:124–133. doi:10.1272/jnms.76.124
22. Takahashi K, Oharaseki T, Yokouchi Y, Hiruta N, Naoe S. Kawasaki disease as a systemic vasculitis in childhood. *Ann Vasc Dis*. 2010;3:173–181. doi:10.3400/avd.sasvp01003
23. Greco A, De Virgilio A, Rizzo MI, et al. Kawasaki disease: an evolving paradigm. *Autoimmun Rev*. 2015;14:703–709. doi:10.1016/j.autrev.2015.04.002
24. Takahashi K, Oharaseki T, Yokouchi Y. Histopathological aspects of cardiovascular lesions in Kawasaki disease. *Int J Rheum Dis*. 2018;21:31–35. doi:10.1111/1756-185X.13207
25. Harada M, Yokouchi Y, Oharaseki T, et al. Histopathological characteristics of myocarditis in acute-phase Kawasaki disease. *Histopathology*. 2012;61:1156–1167. doi:10.1111/j.1365-2559.2012.04332.x
26. Amano S, Hazama F, Hamashima Y. Pathology of Kawasaki disease: II. Distribution and incidence of the vascular lesions. *Jpn Circ J*. 1979;43:741–748. doi:10.1253/jcj.43.741
27. Amano S, Hazama F, Kubagawa H, Tasaka K, Haebara H, Hamashima Y. General pathology of Kawasaki disease. On the morphological alterations corresponding to the clinical manifestations. *Acta Pathol Jpn*. 1980;30:681–694.
28. Landing BH, Larson EJ. Pathological features of Kawasaki disease (mucocutaneous lymph node syndrome). *Am J Cardiovasc Pathol*. 1987;1:218–229.

29. Zhao QM, Chu C, Wu L, et al. Systemic artery aneurysms and Kawasaki disease. *Pediatrics*. 2019;1:144.

30. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996;94:1379–1385. doi:10.1161/01.CIR.94.6.1379

31. Kato H, Inoue O, Akagi T. Kawasaki disease: cardiac problems and management. *Pediatr Rev*. 1988;9:209–217. doi:10.1542/pir.9.7.209

32. Ross R. Atherosclerosis–an inflammatory disease. *N Engl J Med*. 1999;340:115–126. doi:10.1056/NEJM199901143400207

33. Gupta-Malhotra M, Gruber D, Abraham SS, et al. Atherosclerosis in survivors of Kawasaki disease. *J Pediatr*. 2009;155:572–577. doi:10.1016/j.jpeds.2009.04.054

34. Selamet Tierney ES, Newburger JW. Are patients with Kawasaki disease at risk for premature atherosclerosis? *J Pediatr*. 2007;151:225–228. doi:10.1016/j.jpeds.2007.05.011

35. Orenstein JM, Shulman ST, Fox LM, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. *PLoS One*. 2012;7:e38998. doi:10.1371/journal.pone.0038998

36. Hirai T, Sasayama S, Kawasaki T. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. *Circulation*. 1989;80:78–86. doi:10.1161/01.CIR.80.1.78

37. Duprez DA, Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. *Curr Atheroscler Rep*. 2007;9:139–144. doi:10.1007/s11883-007-0010-y

38. Yu X, Hirono KI, Ichida F, et al. Enhanced iNOS expression in leukocytes and circulating endothelial cells is associated with the progression of coronary artery lesions in acute Kawasaki disease. *Pediatr Res*. 2004;55:688–694. doi:10.1203/01.PDR.0000113464.93042.A4

39. Yahata T, Hamaoka K. Oxidative stress and Kawasaki disease: how is oxidative stress involved from the acute stage to the chronic stage? *Rheumatology*. 2017;1:6–13. doi:10.1093/rheumatology/kew044

40. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340:1111–1115. doi:10.1016/0140-6736(92)93147-F

41. Cheung YF, Woo OK. Oxidative stress in children late after Kawasaki disease: relationship with carotid atherosclerosis and stiffness. *BMC Pediatr*. 2008;8:20. doi:10.1186/1471-2431-8-20

42. Zeng YY, Chen F, Zhang Y, Ji X. Are patients recovering from Kawasaki disease at increased risk for accelerated atherosclerosis? A meta-analysis. *World J Pediatr*. 2021;17:476–483. doi:10.1007/s12519-021-00452-x

43. Zhang H, Xu MG, Xie LJ, Huang M, Shen J, Xiao TT. Meta-analysis of risk factors associated with atherosclerosis in patients with Kawasaki disease. *World J Pediatr*. 2016;12:308–313. doi:10.1007/s12519-016-0023-0

44. Dietz SM, Tacke CE, Hutten BA, et al. Peripheral endothelial (Dys)function, arterial stiffness and carotid intima-media thickness in patients after Kawasaki Disease: a systematic review and meta-analyses. *PLoS One*. 2015;10:e0130913. doi:10.1371/journal.pone.0130913

45. Dhillon R, Clarkson P, Donald AE, et al. Endothelial dysfunction late after Kawasaki disease. *Circulation*. 1996;94:2103–2106. doi:10.1161/01.CIR.94.9.2103

46. Huang SM, Weng KP, Chang JS, Lee WY, Huang SH, Hsieh KS. Effects of statin therapy in children complicated with coronary arterial abnormality late after Kawasaki disease: a pilot study. *Circ J*. 2008;72:1583–1587. doi:10.1253/circj.CJ-08-0121

47. Deng YB, Xiang HJ, Chang Q, et al. Evaluation by high-resolution ultrasonography of endothelial function in brachial artery after Kawasaki disease and the effects of intravenous administration of vitamin C. *Circ J*. 2002;66:908–912. doi:10.1253/circj.66.908

48. Kadono T, Sugiyama H, Hoshiai M, et al. Endothelial function evaluated by flow-mediated dilatation in pediatric vascular disease. *Pediatr Cardiol*. 2005;26:385–390. doi:10.1007/s00246-004-0755-9

49. 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;26:782–786. doi:10.1007/s00246-005-0921-8

50. Niboshi A, Hamaoka K, Sakata K, Yamaguchi N. Endothelial dysfunction in adult patients with a history of Kawasaki disease. *Eur J Pediatr*. 2008;167:189–196. doi:10.1007/s00431-007-0452-9

51. Liu XQ, Huang GY, Liang XV, et al. Endothelial progenitor cells and arterial functions in the late convalescence period of Kawasaki disease. *Acta Paediatr*. 2009;98:1355–1359. doi:10.1111/j.1651-2227.2009.01334.x

52. Ishikawa T, Iwashima S. Endothelial dysfunction in children within 5 years after onset of Kawasaki disease. *J Pediatr*. 2013;163:1117–1121. doi:10.1016/j.jpeds.2013.04.046

53. McCrindle BW, McIntyre S, Kim C, Lin T, Adeli K. Are patients after Kawasaki disease at increased risk for accelerated atherosclerosis? *J Pediatr*. 2007;151:244–248, 248.e1. doi:10.1016/j.jpeds.2007.03.056

54. Silva AA, Maeno Y, Hashmi A, et al. Cardiovascular risk factors after Kawasaki disease: a case-control study. *J Pediatr*. 2001;138:400–405. doi:10.1067/mpd.2001.111430

55. Borzutzky A, Gutierrez M, Talesnik E, et al. High sensitivity C-reactive protein and endothelial function in Chilean patients with history of Kawasaki disease. *Clin Rheumatol*. 2008;27:845–850. doi:10.1007/s10067-007-0808-6

56. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J*. 2003;146:168–174. doi:10.1016/S0002-8703(03)00094-2

57. Hamburg NM, Palmisano J, Larson MG, et al. Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. *Hypertension*. 2011;57:390–396. doi:10.1161/HYPERTENSIONAHA.110.160812

58. Selamet Tierney ES, Gal D, Gauvreau K, et al. Vascular health in Kawasaki disease. *J Am Coll Cardiol*. 2013;62:1114–1121. doi:10.1016/j.jacc.2013.04.090

59. Tobayama H, Takahashi K, Fukunaga H, et al. Analysis of arterial function in adults with a history of Kawasaki disease. *J Cardiol*. 2013;61:330–335. doi:10.1016/j.jjcc.2012.12.007

60. Pinto FF, Laranjo S, Parames F. Long-term evaluation of endothelial function in Kawasaki disease patients. *Cardiol Young*. 2013;23:517–522. doi:10.1017/S1047951112001357

61. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605. doi:10.1093/eurheartj/ehl254

62. Bruno RM, Bianchini E, Faita F, Taddei S, Ghiadoni L. Intima media thickness, pulse wave velocity, and flow mediated dilation. *Cardiovasc Ultrasound*. 2014;12:34. doi:10.1186/1476-7120-12-34

63. Vaujois L, Dallaire F, Maurice RL, et al. The biophysical properties of the aorta are altered following Kawasaki disease. *J Am Soc Echocardiogr*. 2013;26:1388–1396. doi:10.1016/j.echo.2013.08.022

64. 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;26:1084–1089. doi:10.1016/j.echo.2013.05.015

65. Ooyanagi R, Fuse S, Tomita H, et al. Pulse wave velocity and ankle brachial index in patients with Kawasaki disease. *Pediatr Int*. 2004;46:398–402. doi:10.1111/j.1442-200x.2004.01929.x

66. 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;43:120–124. doi:10.1016/j.jacc.2003.08.030

67. Cho HJ, Yang SI, Kim KH, Kim JN, Kil HR. Cardiovascular risk factors of early atherosclerosis in school-aged children after Kawasaki disease. *Korean J Pediatr*. 2014;57:217–221. doi:10.3345/kjp.2014.57.5.217

68. Cheung YF, Ho MH, Ip WK, et al. Modulating effects of mannose binding lectin genotype on arterial stiffness in children after Kawasaki disease. *Pediatr Res*. 2004;56:591–596. doi:10.1203/01.PDR.0000139406.22305.A4

69. Cheung YF, Wong SJ, Ho MH. Relationship between carotid intima-media thickness and arterial stiffness in children after Kawasaki disease. *Arch Dis Child*. 2007;92:43–47. doi:10.1136/adc.2006.096628

70. Lee SJ, Ahn HM, You JH, et al. Carotid intima-media thickness and pulse wave velocity after recovery from Kawasaki disease. *Korean Circ J*. 2009;39:264–269. doi:10.4070/kcj.2009.39.7.264

71. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327. doi:10.1016/j.jacc.2009.10.061

72. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J Atheroscler Thromb*. 2006;13:101–107. doi:10.5551/jat.13.101

73. Branwell JC, Hill AV. Velocity of the Pulse wave in Man. *Proc Roy Soc*. 1922;B:298–306.

74. Nakagawa R, Kuwata S, Kurishima C, et al. Arterial stiffness in patients after Kawasaki disease without coronary artery involvement: assessment by performing brachial ankle pulse wave velocity and cardio-ankle vascular index. *J Cardiol*. 2015;66:130–134. doi:10.1016/j.jjcc.2014.10.003

75. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467. doi:10.1161/CIRCULATIONAHA.106.628875

76. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2:1055–1058. doi:10.1016/S0140-6736(84)91504-6

77. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315:341–347. doi:10.1056/NEJM198608073150601

78. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med*. 1991;324:1633–1639. doi:10.1056/NEJM199106063242305

79. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. 2003;4:CD004000.

80. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics*. 2000;105:E78. doi:10.1542/peds.105.6.e78

81. Fukunishi M, Kikkawa M, Hamana K, et al. Prediction of non-responsiveness to intravenous high-dose gamma-globulin therapy in patients with Kawasaki disease at onset. *J Pediatr*. 2000;137:172–176. doi:10.1067/mpd.2000.104815

82. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, et al. Immunoglobulin failure and retreatment in Kawasaki disease. *Pediatr Cardiol*. 2003;24:145–148. doi:10.1007/s00246-002-0216-2

83. Wei M, Huang M, Chen S, et al. A Multicenter Study of Intravenous Immunoglobulin Non-response in Kawasaki Disease. *Pediatr Cardiol*. 2015;36:1166–1172. doi:10.1007/s00246-015-1138-0

84. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113:2606–2612. doi:10.1161/CIRCULATIONAHA.105.592865

85. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr*. 2006;149:237–240. doi:10.1016/j.jpeds.2006.03.050

86. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr*. 2007;166:131–137. doi:10.1007/s00431-006-0223-z

87. Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr*. 2011;158:831–835e3. doi:10.1016/j.jpeds.2010.10.031

88. Fabi M, Andreozzi L, Corinaldesi E, et al. Inability of Asian risk scoring systems to predict intravenous immunoglobulin resistance and coronary lesions in Kawasaki disease in an Italian cohort. *Eur J Pediatr*. 2019;178:315–322. doi:10.1007/s00431-018-3297-5

89. Yamada K, Fukumoto T, Shinkai A, Shirahata A, Meguro T. The platelet functions in acute febrile mucocutaneous lymph node syndrome and a trial of prevention for thrombosis by antiplatelet agent. *Nihon Ketsueki Gakkai Zasshi*. 1978;41:791–802.

90. Schmidt-Lucke C, Fichtlscherer S, Rössig L, Kämper U, Dimmeler S. Improvement of endothelial damage and regeneration indexes in patients with coronary artery disease after 4 weeks of statin therapy. *Atherosclerosis*. 2010;211:249–254. doi:10.1016/j.atherosclerosis.2010.02.007

91. de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol*. 2002;40:2117–2121. doi:10.1016/S0735-1097(02)02593-7

92. Tsuda E, Kitamura S; Cooperative study group of J. National survey of coronary artery bypass grafting for coronary stenosis caused by Kawasaki disease in Japan. *Circulation*. 2004;110:II61–1166. doi:10.1161/01.CIR.0000138194.61225.10

93. Masuda M; Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery. Thoracic and cardiovascular surgery in Japan during 2015: annual report by The Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg*. 66;2018:581–615. doi:10.1007/s11748-018-0968-0