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Original Article

Prevalence and predictors of coronary artery disease in adults with Kawasaki disease

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Abstract *Background:* Accelerated coronary atherosclerosis in patients with Kawasaki disease, in conjunction with coronary artery aneurysm and stenosis that characterise this disease, are potential risk factors for developing coronary artery disease in young adults. We aimed to determine the prevalence and predictors of coronary artery disease in adult patients with Kawasaki disease. *Methods:* All patients aged 18–55 years of age diagnosed with Kawasaki disease were sampled from Nationwide Inpatient Sample database using International Classification of Diseases 9th revision (ICD 9 code 446.1) from 2009 to 2010. Demographics, prevalence of coronary artery disease, and other traditional risk factors in adult patients with Kawasaki disease were analysed using ICD 9 codes. *Results:* The prevalence of Kawasaki disease among adults was 0.0005% (n = 215) of all in-hospital admissions in United States. The mean age was 27.3 years with women (27.6 years) older than men (27.1 years). Traditional risk factors were hypertension (21%), hyperlipidaemia (15.6%), diabetes (11.5%), tobacco use (8.8%), and obesity (8.8%), with no significant difference between men and women. Coronary artery disease (32.4%), however, was more prevalent in men (44.7%) than in women (12.1%; p = 0.03). In multivariate regression analysis, after adjusting for demographics and traditional risk factors, hypertension (OR = 13.2, p = 0.03) was an independent risk factor of coronary artery disease. *Conclusion:* There was increased preponderance of coronary artery disease in men with Kawasaki disease. On multivariate analysis, hypertension was found to be the only independent predictor of coronary artery disease in this population after adjusting for other risk factors.

Keywords: Kawasaki disease; coronary artery disease; hypertension; prevention; adults

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KAWASAKI DISEASE, OR MUCOCUTANEOUS lymph-node syndrome, first described by Tomisaku Kawasaki in 1967, is a vasculitis of the small- and medium-sized arteries.[1] Kawasaki disease is characterised by persistent fever for at least 5 days, accompanied by other clinical features such as erythematous rash, bilateral non-exudative conjunctivitis, erythema of the lips, tongue, and oropharynx, and cervical lymphadenopathy.[2] Other less common clinical features include diarrhoea, hepatitis, pancreatitis, jaundice, aseptic meningitis, anterior uveitis, arthralgia, or arthritis. In the United States, Kawasaki disease is the leading cause of acquired heart disease in children.[3]

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The most common long-term complication of Kawasaki disease is coronary artery vasculitis, leading to coronary artery aneurysm or ectasia in 15–25% of untreated patients.[4,5] The overall size of the coronary artery aneurysm has been proven as an important prognostic factor.[2,6] Other cardiac complications of Kawasaki disease include arrhythmias, myopericarditis, pericardial effusion, and/or sudden cardiac death. As children with Kawasaki disease grow older, it is thought that they are at increased risk for developing myocardial ischaemia, heart failure, and other adverse events.[5,7] Persistent remodelling,[8] intimal proliferation, and calcification[9,10] often result in stenosis adjacent to the aneurysm or occlusion of the coronaries, resulting in ischaemic heart disease.[4]

Administration of intravenous immunoglobulin and high-dose aspirin has been considered as the most effective therapeutic regimen in reducing the likelihood of coronary artery complications in patients with Kawasaki disease.[11,12] Of the patients, 10–20%, however, are unresponsive to intravenous immunoglobulin,[13] and this is associated with an increased risk for coronary artery complications.[14,15] The American Heart Association recommends a single dose of intravenous immunoglobulin (2 g/kg) to be infused over 12 hours[2] and 80–100 mg/kg/day of aspirin in four divided doses,[2] followed by 3–5 mg/kg/day for at least 6–8 weeks. For patients with coronary artery aneurysm, low-dose aspirin is recommended to be continued indefinitely. With prompt diagnosis and early treatment (intravenous immunoglobulin and/or aspirin) coupled with recent advances in long-term management, most patients diagnosed with Kawasaki disease are now adult survivors. However, arterial wall inflammation during acute illness leading to accelerated atherosclerosis and long-term cardiovascular sequelae is not well studied and remains controversial. As little is known regarding the prevalence of Kawasaki disease in adults, the purpose of this study was to determine the prevalence and predictors of coronary artery disease in adult patients with a history of Kawasaki disease.

Materials and methods

The analysis included all patients aged 18–55 years of age with a diagnosis of Kawasaki disease (ICD-9 code 446.1) from the Nationwide Inpatient Sample (NIS) Database for the years 2009–2010. This is the largest all-payer hospitalisation database that includes all non-federal US hospitals representing up to 8 million hospital stays per year. Each hospitalisation is coded with one primary diagnosis and up to 24 secondary diagnoses associated with that stay. Patient information, regardless of the type of hospital, rural or urban, teaching or non-teaching, is included in the NIS database. Hospital and discharge weights are provided to project national estimates.

Primary outcome was to determine predictors of coronary artery disease in adult patients diagnosed with Kawasaki disease. Demographic and traditional risk factors for coronary artery disease in patients with Kawasaki disease were analysed. Traditional risk factors included in the analysis were diabetes, hypertension, obesity, hyperlipidaemia, and smoking. Other chronic conditions were heart failure, ventricular arrhythmias, and alcohol use. Long-term complications including coronary artery aneurysm and coronary artery disease were studied in patients with Kawasaki disease.

Statistical analysis

Categorical variables were presented as percentage (%), while continuous variables were presented as mean ± SD. Multivariate regression analysis was performed to identify the predictors of coronary artery disease in adult Kawasaki disease patients, after adjusting for patient's demographics and traditional cardiovascular risk factors. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA IC 10.0 (Statacorp, College Station, Texas, United States of America).

Results

Characteristics of the study population

We identified a total of 215 adult patients with Kawasaki disease hospitalised during 2009–2010 (0.0005% of all inpatient admissions), of which 62.33% were men and 37.67% women. The mean age was 27.3 years, with no significant difference between men and women (27.1 years versus 27.6 years; $p = 0.81$). The mean length of hospitalisation was 3.05 ± 0.4 days, and 77% of the population was white. Traditional risk factors prevalent in the study group were hypertension (21%), hyperlipidaemia (15.6%), diabetes (11.5%), tobacco use (8.8%), and obesity (8.8%), with no significant differences noted between men and women. In addition, coronary artery aneurysm was prevalent in 11.16% of the study population, with no statistical significant difference between men and women (14.09% versus 6.31%; $p = 0.44$). Coronary artery disease was seen in 32% of the patients, with a higher prevalence in men (44.7% in men versus 12.1% in women; $p = 0.03$). Interestingly, we found that ST-segment elevation myocardial infarction was prevalent in 8.09% patients, non–ST-segment elevation myocardial infarction in 2.39% patients, and unstable angina in 11.93% patients, with no statistical significant

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Table 1. Baseline demographics of adult patients with Kawasaki disease.

Variables*	Total (n = 215)	Male (n = 134)	Female (n = 81)	p-value**
Age (years)	27.31 (±1.04)	27.12 (±1.39)	27.62 (±1.58)	0.812
Length of stay	3.05 (±0.42)	3.58 (±0.62)	2.19 (±0.37)	0.06
Diabetes mellitus (%)	11.45	18.36	–	0.07
Hypertension (%)	21.09	25.97	13.01	0.33
Hyperlipidaemia (%)	15.61	21.63	5.66	0.16
Coronary artery disease (%)	32.42	44.68	12.13	0.035
ST-segment myocardial infarction (%)	8.09	9.48	5.80	0.66
Non–ST-segment myocardial infarction (%)	2.39	–	6.33	0.20
Unstable angina (%)	11.93	15.31	6.33	0.39
Coronary artery aneurysm (%)	11.16	14.09	6.31	0.44
Smoking (%)	8.88	10.84	5.66	0.56
Atrial fibrillation/atrial flutter (%)	14.86	8.26	25.97	0.14
Obesity (%)	8.8	10.62	5.79	0.58
Pericarditis (%)	4.79	3.46	6.99	0.61
Race (%)				
White	76.67	81.26	67.75	0.36
Black	10.5	7.42	16.48	0.39
Hispanic	5.27	3.6	8.5	0.52
Asian	2.34	3.54	–	0.47

IQR = interquartile range
*Continuous variables are expressed as median (IQR). Categorical variables are expressed as %
**Pearson's χ^2 for categorical; linear regression for continuous variables

difference between men and women. Baseline demographic characteristics of this study population are presented in Table 1.

Outcomes

Of the 215 patients diagnosed with Kawasaki disease admitted to hospital, there was no in-hospital mortality. In unadjusted analysis, age (OR 1.13, 95% CI 1.04–1.25, p = 0.007), diabetes mellitus (OR 12.16, 95% CI 1.09–135.20, p = 0.04), and hypertension (OR 7.91, 95% CI 1.20–52.17, p = 0.03) were independent predictors of coronary artery disease, whereas female sex (OR 0.17, 95% CI 0.03–0.98, p = 0.048) predicted less coronary artery disease risk in adult patients with Kawasaki disease (Table 2). In multivariate logistic regression analysis adjusted for demographic and traditional risk factors, however, hypertension (OR 14.26, 95% CI 1.49–136.45, p = 0.022) was the only predictor of coronary artery disease in adult patients with Kawasaki disease (Table 3).

Table 2. Unadjusted analysis for predictors of coronary artery disease in adult patients with Kawasaki disease.

Variables	Odds ratio (95% CI)	p-value
Age	1.13 (1.04–1.25)	0.007
Female	0.17 (0.03–0.98)	0.05
Diabetes mellitus	12.16 (1.09–135.20)	0.04
Hypertension	7.91 (1.20–52.17)	0.03
Obesity	7.69 (0.65–91.09)	0.10
Coronary artery aneurysm	1.50 (0.20–11.31)	0.68
Race		
White	0.91 (0.17–4.88)	0.91
Black	0.62 (0.05–7.49)	0.70
Hispanic	1.95 (0.10–39.0)	0.66

Table 3. Multimodal logistic regression analysis for predictors of coronary artery disease in adult patients with Kawasaki disease.

Variable	Odds ratio*	p-value
Age	1.16 (0.98–1.36)	0.07
Diabetes	0.92 (0.03–29.31)	0.96
Hyperlipidaemia	0.90 (0.12–6.72)	0.92
Obesity	7.66 (0.25–234.40)	0.24
Female	0.10 (0.01–1.12)	0.06
Hypertension	14.26 (1.49–136.45)	0.02

*Model adjusted for age, sex, diabetes, obesity, hyperlipidaemia, and smoking

Discussion

There has been increase in the incidence of Kawasaki disease[16,17] since the description of the first case. The inflammatory insult as a result of Kawasaki disease in childhood has the potential to affect all components of cardiovascular system. As children with Kawasaki disease age, they may be at increased risk for developing coronary artery aneurysm and, subsequently, coronary artery disease, acute myocardial infarction, and other adverse events.[5]

Currently, very little is known regarding the long-term risk factors of Kawasaki disease vasculopathy.

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To the best of our knowledge, this is the largest study in the United States to determine the prevalence and predictors of coronary artery disease in adults previously affected with Kawasaki disease. Principal findings of our study are as follows: (1) the prevalence of Kawasaki disease in hospitalised adults was 215/39,053,810 (0.0005%) with no in-hospital mortality; (2) the prevalence of coronary artery disease in our population was 32%, with increased prevalence in men as compared with women (45% versus 12%); and (3) hypertension was an independent predictor of coronary artery disease in adult Kawasaki disease patients.

In our analysis, adult patients with Kawasaki disease were predominantly men (62%). The results are consistent with a previous study from Taiwan, where men had a higher prevalence of Kawasaki disease.[18] In our study, the prevalence of coronary artery disease was also high among adult male Kawasaki disease patients as compared with female patients. This parallels the higher incidence of coronary artery disease in adult men as compared with women in general population. It is quite possible that sex-related difference in hormone-mediated glucose and lipid metabolism observed in general population might also contribute to differences in progression of coronary artery disease in patients with Kawasaki disease.[19,20] Tsuda et al[21] demonstrated that smoking was associated with an increased incidence of acute myocardial infarction in adult Kawasaki disease patients. Our study failed to demonstrate any statistical significance (OR 2.02, p = ns), however. This may be explained by a smaller percentage of smokers (9%) in our study as compared with the former (47%).

Pathophysiology of coronary artery disease in Kawasaki disease is different from patients with classic coronary atherosclerosis. Autopsy reports of patients who died as a result of cardiovascular sequelae of Kawasaki disease demonstrated myointimal proliferation, calcified aneurysms, and organised thrombus burden in the coronary vasculature with scanty deposits of lipid-laden macrophages, and cholesterol crystals, which are the hallmarks of atherosclerotic disease.[22]

In the acute inflammatory phase of Kawasaki disease, there is disruption and disassociation of the internal elastic lamina and oedematous dissociation of the tunica media. In the sub-acute phase, the inflamed tunica intima and thinned media/adventitia are replaced by the fibrous connective tissue.[23] The normal coronary vasculature is destroyed by inflammatory cell infiltrate with necrosis of the smooth muscle cell associated with fibrosis and calcification and, in turn, loss of elasticity of the vessel wall, with subsequent increase in the arterial stiffness, thereby demonstrating that this was not the aim of this study. There has been increasing evidence demonstrating that arterial stiffness is an independent risk factor for the development of coronary artery disease.[24] Various indices have also been studied to assess arterial stiffness – aortic pulse-wave velocity and the augmentation index.[25,26] Studies have shown that augmentation index is associated with increased cardiovascular risk and is an independent predictor of adverse cardiovascular events.[27] Tobayama et al[28] demonstrated that adults with a history of Kawasaki disease have increased arterial stiffness as assessed by augmentation index as compared with age- and gender-matched control group.

Endothelial function is regarded as a marker of integrative index of cardiovascular risk factors and vasculoprotective factors.[29] Mechanical forces and fluid shear stress elicit a large number of humoral and structural responses in the endothelial cells, and modulate the endothelial cell function and vascular function in both healthy and diseased states.[30] Endothelium-derived nitric oxide is a potent endogenous vasodilator and plays a pivotal role in flow-mediated dilatation.[31] Reactive oxygen species produced as result of haemodynamic stress react with nitric oxide and reduce its vascular bioavailability and enhance cellular damage resulting in endothelial dysfunction.[32,33] The reduced anti-inflammatory effect of dysfunctional endothelial results in creation of raised plaque, plaque destabilisation, and eventually results in progressive atherosclerosis.

Measurement of flow-mediated dilatation – arterial response to reactive hyperaemia – is a non-invasive index to assess endothelial cell function.[34,35] Studies have demonstrated that endothelial cell dysfunction is one of the long-term sequelae of Kawasaki disease and even occurs late after resolution of the acute phase.[36] Noto et al[37] also demonstrated that persistence of vascular endothelial dysfunction in addition to advancing age resulted in accelerated premature atherosclerosis in adults with a history of Kawasaki disease as compared with healthy controls.

We demonstrated that hypertension was an independent predictor of coronary artery disease in adult patients with a history of Kawasaki disease. The association between hypertension and coronary artery disease has been well documented. The Framingham risk model has been widely used to predict a 10-year risk for coronary heart disease in the presence of risk factors.[38] Zhang et al[39] has also demonstrated that uncontrolled hypertension at young age is associated with increased cardiovascular risk as compared with age-matched healthy individuals.

As endothelial dysfunction is one of the earliest manifestations of atherosclerosis,[40] we propose that endothelial dysfunction and arterial stiffness as a

result of vasculitis in Kawasaki disease along with hypertension may result in synergistic effect and, in turn, result in accelerated atherosclerosis and coronary artery disease. We also found that hypertension as an additional risk factor for accelerated premature atherosclerosis and coronary artery disease in patients with Kawasaki disease, which has never been established before. Adult patients with Kawasaki disease should be screened for hypertension at periodic intervals. When appropriate, additional screening strategies such as ambulatory blood pressure monitoring should be considered. Optimal blood pressure control with lifestyle measures and anti-hypertensive agents may be an effective strategy to improve endothelial function and reduce the incidence of coronary artery disease in this population.

The strength of this study is its large sample size and inclusion of patients from all geographical regions in the country. There are several limitations to our study that deserve special mention. We only included hospitalised Kawasaki disease patients, thereby excluding patients admitted to the hospital under observational status, owing to the absence of information recorded in the NIS database, or who were discharged from the emergency room directly. Patients admitted to any federal hospital are excluded from this database. Thus, it is quite possible that the actual estimate of patients with Kawasaki disease was way more than recorded in the database, thereby underestimating the power of the study. Moreover, diagnostic codes are subject to misclassification and there is no way to determine whether secondary diagnosis represented an active problem versus past medical history. In addition, ICD 9 446.1 code does not distinguish between the complete Kawasaki disease and incomplete or atypical forms of Kawasaki disease. We also could not differentiate whether any patient had essential hypertension or hypertension secondary to vasculitis, renovascular disease, etc. Information on prior treatment of Kawasaki disease, if any, is not available from this registry. The retrospective observational design of the study can only demonstrate association, and hence causation between the predictors of coronary artery disease cannot be determined. Relevant information such as echocardiogram, coronary angiogram findings, cardiac biomarkers, and dates is not available from NIS database.

In conclusion, coronary artery disease was widely prevalent in adult patients with Kawasaki disease. Hypertension was found to be the only independent predictor of coronary artery disease in this population. As more patients with Kawasaki disease survive into adulthood, the adult cardiologists need to be familiar with the sub-acute and chronic coronary and non-coronary sequelae of Kawasaki disease. Further prospective studies with long-term follow-up are needed to investigate the extent of cardiovascular disease and appropriate target for blood pressure control in adult patients with Kawasaki disease.

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Conflicts of Interest

None.

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