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Observational Study

Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years: A study from North India

Dibya Lochan Praharaj, Amit Rawat, Anju Gupta, Kanika Arora, Rakesh Kumar Pilania, Sagar Bhattad, Surjit Singh

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Abstract

BACKGROUND

Kawasaki disease (KD) is an acute self-limited vasculitis with a predilection for coronary arteries. Children with KD may have altered lipid metabolism and abnormal lipid profiles that may last for prolonged periods. However, there is a paucity of literature on the role of adipocytokines in KD.

AIM

To estimate the levels of adipocytokines (adiponectin, leptin and resistin) during the convalescent phase of KD.

METHODS

Twenty children, who had KD at least three years earlier, were enrolled in this study. In addition, 20 healthy controls were also enrolled. Clinical and laboratory profiles of patients were obtained from hospital records. Serum adiponectin, leptin and resistin levels were estimated by enzyme-linked immunosorbent assay.

RESULTS

Mean age of the patients in the study group was 10.15 ± 3 years and the male:female ratio was 1.5:1. Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were decreased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) ($P = 0.04$). Median serum leptin levels in cases and controls were 1.83 ng/mL; (IQR: 1.13, 3.80), and 1.10 ng/mL; (IQR: 0.41, 2.88), respectively ($P = 0.09$). Median serum adiponectin levels were similar in both cases (12.20 μ g/mL; [IQR: 9.76, 17.97]) and controls (13.95 μ g/mL; [IQR: 11.17, 22.58]); ($P = 0.18$). There was no significant difference in all 3 adipocytokines between children with (4/20) and without coronary artery abnormalities (16/20).

CONCLUSION

Serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls. Raised resistin and leptin levels may partially explain lipid perturbations observed during the convalescent phase of KD.

Key Words: Adipocytokines; Adiponectin; Resistin; Leptin; Lipid metabolism; Kawasaki disease; Convalescent phase

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Core Tip: The present study suggests that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of Kawasaki disease (KD). Serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls.

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INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis and the most common cause of acquired heart disease in children in most developed countries[1]. There are data to support that the incidence of KD is also rising in the developing world, including India[1]. Coronary artery abnormalities (CAAs) have been noted in 15%-25% of untreated children and treatment with intravenous immunoglobulin (IVIg) reduces this risk to 3%-5%[2]. Children with KD are known to have lipid abnormalities in the acute phase that may persist long after the initial episode of the disease[3-8]. It is known that serum lipid profiles may remain deranged for prolonged periods after the acute stage of the illness and this may contribute to the premature and accelerated atherosclerosis seen in patients with KD[9,10].

Adipocytokines play a significant role in lipid metabolism, inflammation and diseases associated with accelerated atherosclerosis[11-13]. Moreover, their levels may impact lipid abnormalities[11-14]. As some of the lipid abnormalities associated with KD persist during the convalescent phase, we hypothesized that the adipocytokine perturbations seen during the acute phase of KD, may also persist during follow-up. There is a paucity of literature on this subject[15-19], and the results are difficult to interpret. We, and others, have previously shown that children with KD in India have a different clinical phenotype compared to those reported in the developed world[20]. We have also shown that lipid abnormalities are seen in up to 25.9% of children with KD at a mean follow-up of 5 years[6,7]. We, therefore, conducted this study to determine whether adipocytokines are responsible for some of these lipid abnormalities.

MATERIALS AND METHODS

Patients and methods

The present study was a cross-sectional descriptive study conducted in the Paediatric Rheumatology Clinic, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh. Our institute is a federally funded not-for-profit tertiary care centre catering to the population of North-West India. We follow the largest cohort of KD in India. Twenty consecutive cases of KD with at least 3 years of follow-up, and 20 healthy controls were enrolled in the present study. Children with acute KD and convalescent cases with less than 3 years of follow-up were excluded. The diagnosis of KD was based on the American Heart Association guidelines[21]. During the acute phase, children had received standard treatment *i.e.* IVIg 2 g/kg along with aspirin (initially in higher doses [30-50 mg/kg/d], followed by antiplatelet doses [3-5 mg/kg/d]). Written informed consent was obtained from the parents/guardians at study enrolment. Clinical records were reviewed. The study protocol was approved by the Institute Thesis Committee and Institute Ethics Committee. This

manuscript has been approved by the Departmental Review Board.

Evaluation of different adipocytokines

Collection of blood sample: Two milliliters of peripheral venous blood was collected from cases and controls in plain vials under aseptic conditions. Serum was extracted and collected in cryovials and immediately stored at -80°C. Hemolyzed and turbid samples were discarded.

Estimation of serum resistin: Serum resistin level was estimated using the AssayMax Human Resistin enzyme-linked immunosorbent assay (ELISA) kit designed for determining human resistin in plasma, serum, urine, saliva and cell culture samples as per the manufacturer's recommendations. Sensitivity of the assay was 0.2 ng/mL; intra-assay coefficient of variability (CV) was 4.5% and inter-assay CV was 7.0%. Absorbance was measured at 450 nm on a microplate ELISA reader (Infinite PRO 2000 TECAN Austria).

Estimation of serum adiponectin: Serum adiponectin level was estimated using the AssayMax Human Adiponectin ELISA kit designed for measuring human adiponectin in plasma, serum, urine, saliva and cell culture samples. Sensitivity of the assay was 0.7 ng/mL, intra-assay CV was 4.3% and inter-assay CV was 7.2%.

Estimation of serum leptin: Serum leptin level was similarly estimated using the DRG Human Leptin ELISA kit designed for determining human leptin in plasma and serum samples. Sensitivity of the assay was 1.0 ng/mL, intra-assay CV was 6%-7% and inter-assay CV was 8.5%-11.5%.

All 3 adipocytokines were measured in convalescent cases of KD and in healthy controls. Serum lipids were also estimated in 18 children in the study group during follow-up. Reference values for lipids in healthy Indian children were obtained from the study by Marwaha *et al*[22].

Statistical analysis

Data were collected on a pre-designed proforma and transferred to a Microsoft Office Excel sheet. Preliminary analysis was conducted by descriptive statistics, expressed as means (SD), medians (range) and proportions (centiles). A comparison of the study and control group with regard to levels of individual adipocytokines (*i.e.* leptin, resistin, and adiponectin) was performed using the Mann-Whitney test wherever data had skewed distribution and the Student's *t* test was used for normal distribution. Analysis was carried out using the Statistical Package for Social Sciences Version 20.0 for Windows.

RESULTS

Observation and results

The mean age of patients with KD and controls was 10.1 and 9.1 years, respectively. The male:female ratio in patients with KD was 1.5:1. Mean duration of follow-up in the cases was 5.5 years. No case of IVIg resistance was documented in this cohort. Four children (20%) had CAAs at first admission that resolved on follow-up of 6-8 wk. Eighteen of 20 cases had lipid estimations during follow-up. Lipid abnormalities noted in these children are shown in Table 1. No association was observed between the occurrence of CAAs and the presence of lipid abnormalities.

Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were increased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) ($P = 0.04$). Median serum leptin levels in cases and controls were 1.83 ng/mL; (IQR: 1.13, 3.80), and 1.10 ng/mL; (IQR: 0.41, 2.88), respectively ($P = 0.09$). Median serum adiponectin levels were similar in both cases (12.20 µg/mL; [IQR: 9.76, 17.97]) and controls (13.95 µg/mL; [IQR: 11.17, 22.58]); ($P = 0.18$) (Table 2). There was no significant difference in all 3 adipocytokines between children with CAAs (4/20) and without CAAs (16/20). We performed a correlation analysis of different lipid profiles with adipocytokines (Table 3). No significant correlation was observed between adipocytokines and lipid values. Body mass index (BMI) has also been shown to have a significant positive correlation with leptin levels. No significant correlation between BMI and resistin or adiponectin was observed.

DISCUSSION

KD is the most common cause of acquired heart disease in children in the developed world[1]. KD is being increasingly reported in several developing countries, including India[23]. Hospital-based studies at our centre have shown that the incidence of KD has risen significantly over the last 2 decades[23]. Whether, this increase represents a true increase in incidence, or an increased ascertainment of the disease as a result of heightened awareness, remains unknown. We, and others, have previously shown that KD in India has a different phenotype inasmuch as a higher proportion of older children are seen in

Table 1 Clinical and laboratory features of the study population

	Study group (n = 20)	Controls (n = 20)
Male:female ratio	1.5:1	1.5:1
Age at diagnosis < 5 yr	9	-
Age at diagnosis >5 yr	11	-
Mean age at enrolment (yr)	10.1	9.1
Mean duration of follow-up (yr)	5.5	-
Treatment received during the acute phase		-
IVIg (mg/dL)	20	
Aspirin (mg/dL)	20	
CAAs (mg/dL)	4/20	-
Lipid profile	mean \pm SD	-
LDL (mg/dL)	74.73 \pm 27.82	
TG (mg/dL)	118.72 \pm 104.32	
VLDL (mg/dL)	16.96 \pm 6.72	
HDL (mg/dL)	44.93 \pm 11.40	
TC (mg/dL)	139.76 \pm 27.16	
Body mass index (kg/m ²)	16.68 \pm 3.25	-
Lipid profile (18/20)		-
High TC (mg/dL)	2	
High LDL (mg/dL)	2	
Low HDL (mg/dL)	6	
Borderline HDL (mg/dL)	11	
High TG (mg/dL)	4	
High VLDL (mg/dL)	0	

IVIg: Intravenous immunoglobulin; KD: Kawasaki disease; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; TG: Triglycerides, CAAs: Coronary artery abnormalities; SD: Standard deviation.

Table 2 Adipocytokine profile in patients with Kawasaki disease and healthy controls

	Study group (n = 20), Median (IQR)	Controls (n = 20), Median (IQR)	P value
Adiponectin (μ g/mL)	12.20 (9.76, 17.97)	13.95 (11.17, 22.58)	0.18
Leptin (ng/mL)	1.83 (1.13, 3.80)	1.10 (0.41, 2.88)	0.09
Resistin (ng/mL)	27.77 (18.66, 48.90)	21.20 (14.80, 27.00)	0.04 ^a

^aP value < 0.05 was taken as significant. IQR: Interquartile range.

Indian cohorts[20,23,24]. Furthermore, periungual desquamation and thrombocytosis seem to appear earlier in children with KD in India[25].

Newburger and colleagues previously reported that KD was associated with significant abnormalities of lipid metabolism and derangement of serum lipid profiles[3]. In the first few d of the illness, mean plasma concentration of total cholesterol and HDL-cholesterol was profoundly depressed, whereas mean triglyceride level was very high. Total cholesterol values rapidly returned to normal and remained stable more than three months after the onset of illness. HDL-cholesterol concentration recovered more slowly after illness onset. Mean HDL-cholesterol level was significantly reduced, even after three years of illness onset. Lipid abnormalities in KD are in part attributable to concurrent reductions in lipoprotein lipase and hepatic lipase activities[4]. Several other authors have also reported

Table 3 Correlation of adipocytokines with different lipoproteins, body mass index and age of the patients with Kawasaki disease

Characteristics	Leptin		Adiponectin		Resistin	
	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value
LDL (mg/dL)	0.030	0.90	-0.223	0.34	-0.003	0.99
TG (mg/dL)	0.076	0.75	-0.018	0.94	0.169	0.47
VLDL (mg/dL)	-0.076	0.75	0.330	0.15	0.105	0.65
HDL (mg/dL)	-0.037	0.87	0.505	0.47	0.470	0.03 ^a
Total cholesterol (mg/dL)	0.033	0.89	-0.379	0.09	-0.217	0.35
BMI (kg/m ²)	0.574	0.02 ^a	-0.334	0.20	-0.280	0.29
Age (yr)	0.379	0.09	-0.057	0.81	-0.128	0.59

^aP value < 0.05 was taken as significant. LDL: Low density lipoprotein; TG: Triglycerides; VLDL: Very low density lipoprotein; HDL: High-density lipoprotein.

similar abnormalities in the lipid profile of children with KD[4,6,26]. We have shown that HDL-cholesterol was low in 6/18 and borderline in 11/18 patients with convalescent KD. Thus, 17/18 patients had abnormal HDL-cholesterol at follow-up. The persistence of low HDL-cholesterol for many years in our cohort suggests a long-lasting effect of KD on endothelial function, perhaps attributable to the diminished activity of lipoprotein lipase. Normal lipid levels in the general population have been studied in Indian children by Marwaha *et al* and these were used as historical reference standards in the present study[22].

Adipose tissue has long been considered an inert organ and a depot for energy storage. However, new advances have revealed that it is also an important endocrine organ that produces numerous adipocytokines[11]. Perturbations in adipocytokines are well known in obesity. These play a fundamental role in obesity-linked disorders such as diabetes mellitus and metabolic syndrome[12]. It is now well recognized that adipocytokines play a pivotal role in immune response and inflammation[13]. Studies have shown that adipokines may be important biomarkers for inflammation in chronic diseases [27,28]. While some adipocytokines can induce pro-inflammatory effects (*e.g.* leptin, resistin, IL-6, TNF- α), others have predominantly anti-inflammatory effects (*e.g.* adiponectin and IL-10)[14]. Therefore, analysis of specific adiponectin isoforms may be necessary to prove these diverse effects. An imbalance between pro-inflammatory and anti-inflammatory adipocytokines leads to persistent inflammation and may contribute to accelerated atherosclerosis. Low adiponectin, high resistin and high leptin levels have been reported to produce this phenomenon.

As children with KD have lipid abnormalities[6,26], it is plausible that a disturbed adipocytokine milieu may contribute to early development of atherosclerosis. This may, in turn, predispose children with KD to acute coronary events at a young age. Adiponectin, resistin and leptin are the most examined adipocytokines in disorders of lipid metabolism and we, therefore, conducted this study in the convalescent phase of KD. To the best of our knowledge, there are no published data on adipocytokine levels in children with KD from the Indian subcontinent.

Studies on adipocytokines profile in the follow-up of KD are sparse and have yielded conflicting results[5,9,19] (Tables 3 and 4). Fukunaga *et al*[19] reported low, medium molecular weight (MMW) and LMW adiponectin levels in convalescent cases of KD compared to controls. In the present study, serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls. Cai *et al*[29] performed a meta-analysis to assess the association of adiponectin and resistin in patients with KD. These authors showed that while serum resistin levels in patients with KD were significantly higher compared with those in controls, adiponectin levels were similar in patients with KD and controls. Our results are also in accordance with these findings.

CONCLUSION

Our results suggest that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of KD. The strength of our study is that it is a single centre study wherein all children were diagnosed and treated by the senior author of this study (SS), thereby ensuring uniformity in sample recruitment. Furthermore, the diagnosis of KD was based on standard criteria (AHA 2004). One of the obvious weaknesses is the small sample size, but this was unavoidable as the study had to be completed in a given time frame for the dissertation of the first author (DP). It is

Table 4 Comparison of published literature on circulating adipocytokines in children with Kawasaki disease

Ref.	Number of cases/controls	Stage of disease	CAA	Resistin	Leptin	Adiponectin
Takeshita <i>et al</i> [30], 2006	Cases-20; Febrile controls-15; Healthy controls-15	Acute phase (day 4-6); Convalescent phase (day 25-39)	NA	-	-	Adiponectin levels were significantly reduced in the acute phase compared to the convalescent phase. No difference between the convalescent phase and controls.
Nozue <i>et al</i> [15], 2010	Cases-44; Controls-17	Acute	0	Increased during the acute phase and returned to normal after IVIg administration	Not assessed	Not assessed
Fukunaga <i>et al</i> [19], 2010	Acute phase KD-9; Convalescent phase KD-20; Controls-21	Both acute and convalescent (> 2 yr from KD onset); 6.72 ± 3.2 yr following KD (for convalescent cases)	NA	Not assessed	Not assessed	Total and HMW adiponectin levels were lower in acute KD compared to controls; MMW and LMW adiponectin levels decreased in convalescent cases compared to controls
Qi <i>et al</i> [31], 2012	Cases-40; Controls-15	Acute; Afebrile; Subacute phase	6	Significantly high in the acute stage of KD and decreased with the course of the disease; No difference between patients with KD in the afebrile and subacute phase compared with the controls		
Liu <i>et al</i> [16], 2012	KD-80; Controls-85	Acute	39	Increased compared to controls. No difference between KD with and without CAAs	No difference	Increased compared to controls. No difference between KD with and without CAAs
Kemmotsu <i>et al</i> [17], 2012	Cases-56; Healthy controls-30; Febrile controls-31	Acute	4	Markedly elevated in acute stage and returned to normal after IVIg administration. Non-responders to IVIg had very high resistin levels	No difference	No difference
Kim <i>et al</i> [18], 2014	Cases-40; Febrile controls-32; Healthy controls-15	Acute	12	Markedly elevated in the acute stage but did not predict development of CAAs	Not assessed	Not assessed
Zhang <i>et al</i> [32], 2018	Cases-80; Febrile controls-20; Healthy controls-20	Acute phase	24			Decreased compared to febrile controls. However, no difference compared with healthy controls
Zhang <i>et al</i> [33], 2021	Cases-42; Controls-20	Acute phase (1-10 d); Subacute phase (11-20 d); Convalescent phase (21-30 d)	18			Serum adiponectin was significantly lower compared to controls
Present study, 2021	KD convalescent phase-20; Controls-20	Convalescent; > 3 yr of follow-up; (mean 5.5 yr)	4	Elevated in patients with KD compared to controls	Trend towards higher levels of leptin in patients with KD compared to controls	No difference

CAAs: Coronary artery abnormalities; HMW: High molecular weight; IVIg: Intravenous immunoglobulin; KD: Kawasaki disease; LMW: Low molecular weight; MMW: Medium molecular weight; NA: Not available.

suggested that the leads provided by our work should be applied in a larger and preferably multicentric study.

ARTICLE HIGHLIGHTS

Research background

Patients with Kawasaki disease (KD) may have abnormal lipid profiles that may last for prolonged periods. The reasons underlying the persistence of lipid abnormalities are unclear in patients with KD.

Research motivation

There is a paucity of literature on the role of adipocytokines and their effect on abnormal lipid metabolism in patients with KD.

Research objectives

To estimate the levels of adipocytokines (adiponectin, leptin and resistin) during the convalescent phase of KD.

Research methods

Serum adiponectin, leptin and resistin levels were estimated by enzyme-linked immunosorbent assay in patients with KD and controls.

Research results

The mean age of patients in the study group was 10.15 ± 3 years. Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were increased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) ($P = 0.04$). Median serum leptin levels and adiponectin levels in cases and controls were similar. There was no significant correlation between adipocytokines and the lipid profile in patients with KD. There was no significant difference in all 3 adipocytokines between children with CAAs and without CAAs.

Research conclusions

Our results suggest that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of KD.

Research perspectives

The leads provided by our work should be applied in a larger and preferably multicentric study to confirm these results.

FOOTNOTES

Author contributions: Praharaj DL, Rawat A, Gupta A and Singh S conceived and designed the research; Praharaj DL, Rawat A, Arora K, and Pilania RK collected data and performed the research; Praharaj DL, Arora K, Pilania RK, and Bhattad S were involved in writing the first draft; Praharaj DL, Rawat A and Arora K performed laboratory tests; Praharaj DL, Rawat A, Arora K, and Pilania RK analyzed the data; Gupta A, Pilania RK, Bhattad S and Singh S were involved in patient management; Praharaj DL, Rawat A, Gupta A, Arora K, Pilania RK, Bhattad S, Singh S reviewed the literature; Rawat A, Pilania RK, and Singh S edited the manuscript, performed critical revision at all stages and final approval of the manuscript; all the authors read and approved the final manuscript.

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