

Dear Editor

We wish to submit the revised version of the manuscript entitled “**Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years – a study from North India**”.

We wish to thank the reviewers for their painstaking efforts and comments. This critique has helped us in improving our manuscript.

We have highlighted the track changes in yellow font. Our responses to the points raised by reviewers are also enclosed.

We hope you will find the revised manuscript in order.

Sincerely,

Prof. Amit Rawat

Reviewer #1: Specific Comments to Authors: This study by Praharaj et al aims to determine if children in the convalescent phase of Kawasaki disease (KD) have alterations in

adipokine levels compared to healthy controls. The study is easy to follow and well written, and the research question is interesting. Due to the rarity of the disease, the studies done on the topic enrich the current literature.

Comment 1: The main limitation of the study is that the population cohort is small, which can be expected because KD is a rare disease. However, I think that the manuscript could be highly improved by adding a larger control group, maybe matched 1:2 or 1:3.

Response: We agree with the reviewer. However, as this study was the MD dissertation of the lead author (DP) there were time constraints and financial constraints for the conduct of the study. The Thesis Committee and Ethics Committee of the institute had prescribed the number of patients that were to be included in study and control groups.

Comment 2: Another suggestion is to adjust the main analyses (i.e. adipokines levels across the two groups) for current age as adipokine levels may vary with age.

Response: Suggestion incorporated in revised manuscript (Table 3).

Comment 3: Minor comment: - Discussion: “adiponectin has 2 isoforms - low molecular weight (LMW)-adiponectin and high molecular weight (HMW)-adiponectin. The former has anti-inflammatory effects, while the latter has pro-inflammatory effects”. It is still unclear if adiponectin isoforms exert different effect, and I suggest to tone down this sentence

Response: Suggestion incorporated in revised manuscript.

Reviewer #2: Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years – a study from North India by Praheraj et al. Dear Editor, The topic of the work is interesting even if there are some points to review.

Comment 1: First of all, English should be revised, there are various grammatical errors and typos.

Response: Suggestion incorporated in revised manuscript.

Comment 2: The abstract is clearly written and the purpose of the work is well reported.

Response: No response required.

Comment 3: Among the keywords, I suggest to insert also “lipid metabolism”.

Response: Suggestion incorporated in revised manuscript.

Comment 4: In the table 1, why is the lipid profile of the controls not reported? Authors may enter this information?

Response: We agree with the reviewer. However, lipids were not assayed in controls as this was not included in the study protocol approved by Thesis Committee and Ethics Committee of our institute.

Comment 5: It should also be seen whether adipocytokines correlate with the lipid profile of patients.

Response: Suggestion incorporated in revised manuscript (Table 3).

Comment 6: Anthropometric characteristics of patients and controls should also be reported, as it is well reported in the literature that adipocytokines levels are also influenced by anthropometric parameters such as BMI or this topic should be mentioned. Mean +/- SD value of BMI has been added in Table 1.

Response: Suggestion incorporated in revised manuscript (Table 1).

Comment 7: In addition, in the discussion section, the authors should better clarify the role that adipocytokines, and in particular adiponectin, have in the immune response and

inflammation, also related to the lipid profile. In this regard, the authors can consult these works “Adiponectin Expression Is Modulated by Long-Term Physical Activity in Adult Patients Affected by Cystic Fibrosis” by Polito et al., and “Supervised physical exercise improves clinical, anthropometric and biochemical parameters in adult cystic fibrosis patients: A 2-year evaluation “by Elce et al, which could be useful for this purpose.

Response: Suggestion incorporated in revised manuscript. The suggested references have been appended.

Science editor:

Comment 1: Scientific quality: The manuscript describes an observational study of the adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years. The topic is within the scope of the WJCP. (1) Classification: Two Grades C;

Response: No response required.

Comment 2: Summary of the Peer-Review Report: This study aims to determine if children in the convalescent phase of Kawasaki disease have alterations in adipokine levels compared

to healthy controls. The study is easy to follow and well written, and the research question is interesting. The questions raised by the reviewers should be answered;

Response: No response required.

Comment 3: Format: There are 3 tables;

Response: No response required.

Comment 4: References: A total of 41 references are cited, including 6 references published in the last 3 years;

Response: No response required.

Comment 5: Self-cited references: There are 14 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and

Response: Suggestion incorporated in revised manuscript.

Comment 6: References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A and Grade B. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form. Written informed consent was not provided. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No

financial support was obtained for the study. The topic has not previously been published in the WJCP.

Response: No response required.

Comment 7: The “Author Contributions” section is missing. Please provide the author contributions;

Response: Suggestion incorporated in the revised the manuscript.

Comment 8: PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

Response: Suggestion incorporated in the revised the manuscript.

Comment 9: The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Response: Suggestion incorporated in the revised the manuscript.

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

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Running title: Adipocytokine profile in children with Kawasaki disease

Word count: 1854

Keywords: Adipocytokines; adiponectin; resistin; leptin; lipid metabolism; Kawasaki disease; convalescent phase

Conflict of interest: The authors declare no “conflicts of interest”

Abstract

Background: Kawasaki disease (KD) is an acute self-limited vasculitis with 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 paucity of literature on role of adipocytokines in KD.

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

Methods: Twenty (20) children who had 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 (ELISA).

Results: Mean age of patients in the study group was 10.15 ± 3 years and male: female ratio was 1.5:1. Median serum resistin values in patients with KD (27.77 ng/mL; [IQR 18.66, 48.90]) was decreased compared to controls (21.20 ng/mL; [IQR 14.80, 27.00]) ($p=0.04$). Median serum leptin values 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 of all 3 adipocytokines between children with CAAs (4/20) and without CAAs (16/20).

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

Introduction

Kawasaki disease (KD) is a medium vessel vasculitis and the most common cause of acquired heart disease in children in most of the developed countries (1). There are data to support that incidence of KD is also rising in the developing world, including India (1). Coronary artery abnormalities (CAAs) are 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 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 probably 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 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 from 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, embarked on this study to see whether adipocytokines are responsible for some of these lipid abnormalities.

Patients and Methods: The present study was a cross-sectional descriptive study conducted in the Paediatric Rheumatology Clinic (PRC), 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 (20) consecutive cases of KD with at least 3 years of follow-up, and 20 healthy controls were enrolled. Children with acute KD and convalescent cases with less than 3 years of follow-up were excluded. Diagnosis of KD was based on guidelines given by American Heart Association (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/day], followed by antiplatelet doses [3-5 mg/kg/day]). Written informed consent was taken from parents/guardians at time of enrolment in the study. Clinical records were reviewed. The study protocol was approved by the Institute Thesis Committee and Institute Ethics Committee. The manuscript has been approved by the Departmental Review Board.

Evaluation of different adipocytokines:

- a. Collection of blood sample:** Two ml of peripheral venous blood sample was collected from cases and controls in plain vials under aseptic precautions. Serum was extracted and collected in cryovials and stored at -80°C without any delay. Hemolyzed and turbid samples were discarded.
- b. Estimation of serum resistin:** Serum resistin level was estimated using the AssayMax Human Resistin ELISA kit designed for determining human resistin in plasma, serum, urine, saliva and cell culture samples as per 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).
- c. 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 assay was 0.7 ng/ml, intra-assay CV was 4.3% and inter-assay CV was 7.2%.
- d. 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 study group during follow-up. Reference values for lipids in healthy Indian children were obtained from a study by Marwaha et al (22).

Statistical Analysis: Data were collected on a pre-designed proforma and transferred to the Microsoft Office Excel sheet. Preliminary analysis was done by descriptive statistics,

expressed as means (SD), medians (range) and proportions (centiles). Comparison of study and control group for levels of individual adipocytokines (i.e. leptin, resistin, and adiponectin) was done using Mann-Whitney test wherever data had skewed distribution and Student's t test was used for normal distribution. Analysis was done using the Statistical Package for Social Sciences (SPSS) Version 20.0 for Windows.

Observation and Results: Mean age of patients with KD and controls was 10.1 and 9.1 years respectively. 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 weeks. Eighteen of 20 cases had lipid estimations during follow-up. Lipid abnormalities noted in these children have been tabulated (**Table 1**). No association was observed between the occurrence of CAAs and presence of lipid abnormalities.

Median serum resistin values in patients with KD (27.77 ng/mL; [IQR 18.66, 48.90]) was decreased compared to controls (21.20 ng/mL; [IQR 14.80, 27.00]) ($p=0.04$). Median serum leptin values 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 $\mu\text{g/mL}$; [IQR 9.76, 17.97]) and controls (13.95 $\mu\text{g/mL}$; [IQR 11.17, 22.58]); ($p=0.18$) (**Table 2**). There was no significant difference of all 3 adipocytokines between children with CAAs (4/20) and without CAAs (16/20). We have performed correlation analysis of different lipid profile with adipocytokines (**Table 3**). No significant correlation was observed between adipocytokines and lipid values. Body mass index has shown significant positive correlation with leptin values. There was no significant correlation of BMI with resistin and adiponectin.

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 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 disease as a result of heightened awareness, remains conjectural. 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 Indian cohorts (20,23,24). Further, periungual desquamation and thrombocytosis seem to appear earlier in children with KD in India (25).

Newburger and colleagues have previously reported that KD was associated with significant abnormalities of lipid metabolism and derangement in serum lipid profiles (3). In the first few days of 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 onset of illness. Lipid abnormalities in KD are in part attributable to concurrent reductions of lipoprotein lipase and hepatic lipase activities (4). Several other authors have also reported similar abnormalities in lipid profile in 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 values of lipids in general population have been studied in Indian children by Marwaha et al and this has been used as a historical reference standard for the present study (22).

Adipose tissue has long been considered as an inert organ and depot for energy storage. However, new advances have unraveled 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 like diabetes mellitus and metabolic syndrome (12). Now it is well recognized that adipocytokines play a pivotal role in immune response and inflammation (13). **Studies have shown that adipokines may be an important biomarker 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 explored adipocytokines in disorders of lipid metabolism and we, therefore, took up this study in the convalescent phase of KD. To the best of our knowledge, there is no published data on adipocytokine levels in children with KD from the Indian subcontinent.

Studies on adipocytokine profile in the follow-up of KD are sparse and have yielded conflicting results (5,9,19) (**Table 3**). Fukunaga et al (19) reported low, medium molecular weight (MMW) and LMW adiponectin levels in convalescent cases of KD compared to controls. In present study, serum resistin values were significantly elevated in patients with

KD during convalescent phase compared to controls. Serum leptin levels appear to be higher in patients with KD, although the difference is not statistically significant. Adiponectin levels were similar in both cases and controls. Cai et al performed meta-analysis to see the association of adiponectin and resistin with patients with KD (29). Authors have shown 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 have also in are consonance with these findings.

Our results suggest that serum adipocytokine levels may impact lipid abnormalities seen 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 in this manuscript (SS), thereby ensuring uniformity in sample recruitment. Further, 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 suggested that the leads provided by our work be taken up for a larger, and preferably multicentric, study.

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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 years	9	
> 5 years	11	
Mean age at enrolment (years)	10.1	9.1
Mean duration of follow-up (years)	5.5	-
Treatment received during acute phase		
- IVIg	20	-
- Aspirin	20	
CAAs	4/20	-
Lipid profile	Mean ± SD	-
LDL	74.73 ± 27.82	
TG	118.72 ± 104.32	

VLDL	16.96 ± 6.72	
HDL	44.93 ± 11.40	
TCh	139.76 ± 27.16	
Body mass index (kg/m²)	16.68 ± 3.25	-
Lipid profile (18/20)		
High TC	2	-
High LDL	2	
Low HDL	6	
Borderline HDL	11	
High TG	4	
High VLDL	0	

Abbreviations: 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 control

	Study group (n=20)	Controls (n=20)	p value
	Median (IQR)	Median (IQR)	
Adiponectin (µg/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

Abbreviations: IQR: Interquartile range

Table 3: Correlation of adipocytokines with different lipid profile, 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)	.030	.90	-.223	.34	-.003	.99
TG (mg/dL)	.076	.75	-.018	.94	.169	.47
VLDL (mg/dL)	-.076	.75	.330	.15	.105	.65
HDL (mg/dL)	-.037	.87	.505	.47	.470	.03
Total cholesterol (mg/dL)	.033	.89	-.379	.09	-.217	.35
BMI (Kg/m ²)	.574	.02	-.334	.20	-.280	.29
Age (years)	.379	.09	-.057	.81	-.128	.59

Abbreviations: LDL: Low density lipoprotein; TG: Triglycerides; VLDL: very low density lipoprotein; HDL: high-density lipoprotein

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

Authors/ Year of publication	Number of cases/controls	Stage of disease	CAA	Resistin	Leptin	Adiponectin
Takeshita et al, 2006, Japan (30)AM	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 acute phase compared to convalescent phase. No difference between convalescent phase and controls.
Nozue et al, 2010, Japan (15)AM	Cases – 44 Controls -17	Acute	0	Increased during acute phase and returned to normal after IVIg administration	Not done	Not done
Fukunaga et al, 2010, Japan (19)AM	Acute phase KD - 9 Convalescent phase KD - 20 Controls - 21	Both acute and convalescent (> 2 years from KD onset) 6.72 ± 3.2 years following KD (for convalescent cases)	NA	Not done	Not done	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 et al, 2012, China (31)AM	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 et al, 2012, China (16)AM	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 et al, 2012, Japan (17)AM	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 et al, 2014, Korea (18)AM	Cases – 40 Febrile controls - 32 Healthy controls - 15	Acute	12	Markedly elevated in acute stage but do not predict development of CAAs	Not done	Not done

Zhang et al, 2018, China (32)AM	Cases - 80 Febrile controls - 20 Healthy controls - 20	Acute phase	24	-	-	Decreased compared to febrile controls. However, no difference with healthy controls.
Zhang et al, 2021, China (33)AM	Cases - 42 Controls - 20	Acute phase (1-10 days) Subacute phase (11-20 days) Convalescent phase (21-30 days)	18	-	-	Serum adiponectin were significantly lower compared to controls.
Present study, 2021, India	KD convalescent phase - 20 Controls - 20	Convalescent > 3 years of follow-up (mean 5.5 years)	4	Elevated in patients with KD compared to controls	Trends towards higher levels of leptin in patients with KD compared to controls	No difference

Abbreviations: 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