RESEARCH PAPER

Adiponectin, Interleukin-6 and High-sensitivity C-reactive Protein Levels in Overweight/Obese Indian children

Vandana Jain, Ajay Kumar, Anuja Agarwala, *Naval Vikram and #Lakshmy Ramakrishnan

*From Departments of Pediatrics, *Medicine and #Cardiac Biochemistry, All India Institute of Medical Sciences, New Delhi, India.*

Correspondence to: Dr Vandana Jain, Professor, Division of Pediatric Endocrinology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India. drvandanajain@gmail.com
Received: July 08, 2016;
Initial Review: December 09, 2016;
Accepted: June 13, 2017.

Objective: The aim of our study was to assess serum Adiponectin, Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) levels and their correlation with conventional risk factors for cardiovascular disease and diabetes in overweight/obese Indian children. **Methods**: Body mass index (BMI), waist circumference, blood pressure, fasting serum adiponectin, IL-6, hsCRP, blood glucose, triglycerides, and total and high density lipoprotein cholesterol were measured in children aged 7-15 years with BMI >85th centile. **Results**: 84 overweight/obese children (48 boys) with mean (SD) age 10.2 (1.9) years were enrolled. Mean (SD) adiponectin, hsCRP and median (IQR) IL-6 levels were 6.0 (3.1) µg/mL, 3.4 (2.4) mg/L and 12.7 (5.0-90.0) pg/mL, respectively. Low adiponectin, high hsCRP and high IL-6 were noted in 16.5%, 49.4% and 54.4% participants, respectively. Adiponectin was inversely correlated with waist circumference, and IL-6 positively with BMI and blood glucose. **Conclusion**: Inflammatory mediators, hsCRP and IL-6 were elevated in half of the overweight children. Adiponectin and IL-6 correlated well with traditional risk markers.

Keywords: *Cytokines, Inflammation, Metabolic syndrome.*

Published online: July 11, 2017. PII:S097475591600076

Over the last decade, several studies have indicated that inflammatory markers and adipocytokines mediate the evolution of the cardiovascular and metabolic complications of obesity. Low-grade chronic inflammation in association with obesity plays a major role in the pathogenesis of atherosclerosis and insulin resistance [1,2]. Adipose-tissue macrophages and adipocytes secrete interleukin-6 (IL-6), an inflammatory mediator postulated to affect lipid and glucose metabolism through several mechanisms [2].

C-reactive protein (CRP) is another inflammatory biomarker, associated with impaired insulin sensitivity and the development of cardiometabolic syndrome [3]. It is considered to play an important role in vascular remodeling and plaque deposition [4]. High-sensitivity CRP (hsCRP) test measures low levels of CRP. Values above 3 mg/L are indicative of high risk for cardiovascular disease [4]. Adiponectin is a collagen-like plasma protein secreted exclusively by adipocytes. This protein has anti-inflammatory, anti-atherogenic, and potent insulin-sensitizing effects, which may be partially mediated by suppression of TNF-α and IL-6 [3]. Low levels of adiponectin have been associated with metabolic syndrome, insulin resistance and type 2 diabetes [3,5].

Majority of the studies on these adipocytokines and inflammatory markers have been done in adults. The aim of our study was to assess serum IL-6, hsCRP and Adiponectin levels and their correlation with conventional risk factors for cardiovascular disease and diabetes in overweight/obese Indian children.

Methods

This cross-sectional study was conducted at All India Institute of Medical Sciences, New Delhi after obtaining ethical approval from the Institute ethics committee. Children between 7-15 years, with BMI >85th centile according to Indian reference curves were enrolled from Pediatric outpatient department. Children with genetic, syndromic, endocrine or medication-related obesity were excluded. Informed consent was obtained from the parents, and assent from the children.

Weight, height, waist circumference and blood pressure (BP) were measured. BMI was calculated and pubertal staging was done. Fasting blood sample was collected for adiponectin, IL-6, hsCRP, glucose, total cholesterol, HDL cholesterol and triglycerides. Adiponectin, IL-6 and hsCRP were measured using quantitative colorimetric sandwich ELISA kits. Glucose was measured in the fresh sample by glucose oxidase method, total and HDL cholesterol and triglycerides

were measured by Randox kits (Randox Ltd, Antrim, UK). LDL cholesterol was estimated using Friedewald's formula as total cholesterol – HDL cholesterol – (triglyceride/ 5) mg/dL.

The following cut-offs were considered abnormal: Adiponectin <3 µg/mL [7], hsCRP >3 mg/L [5], IL-6 >10 pg/mL [8], fasting blood glucose ≥100 mg/dL, Total cholesterol ≥200 mg/dL, LDL cholesterol ≥130 mg/dL, HDL cholesterol <40 mg/dL and Triglyceride>150 mg/dL [9]. Abdominal obesity was considered present if waist circumference was above 95th percentile for age or >90 cm in boys/ >80 cm in girls [9].

Spearman test was applied to check for correlation between adiponectin, IL-6, hsCRP, BMI, waist circumference and fasting blood glucose. Wilcoxon rank-sum (Mann-Whitney) test was applied to test for difference in adiponectin, IL-6 and hsCRP in children with and without abdominal obesity and impaired fasting glucose.

RESULTS

Eighty-four children (48 boys) with a mean (SD) age of 10.2 (1.9) years were enrolled. Two-thirds of the children were prepubertal, and 87% were obese. The mean (SD) BMI Z-score was 2.7 (0.8). Mean (SD) waist circumference was 82.4 (10.3) cm, with abdominal obesity in 67.3%. Mean (SD) systolic and diastolic BP was 113 (10) and 74 (10) mm Hg, respectively with hypertension present in 15.5%.

The biochemical parameters are summarized in ***Table* I**. Values of lipid profile and fasting blood glucose could not be traced from the central laboratory for some patients. Elevation of inflammatory mediators constituted the commonest abnormality, with IL-6 being elevated in 54.4% and hsCRP in 49.4%. Low HDL was the commonest dyslipidemia, noted in 35.1%. Impaired fasting glucose was seen in 10.7% and low adiponectin levels in 16.5%.

Serum adiponectin was noted to have a significant inverse correlation with waist circumference (r= -0.28, P=0.047). Serum IL-6 had a positive correlation with BMI (r= 0.23, P= 0.09), and blood glucose (r= 0.24, P= 0.08), but was not statistically significant. Median (IQR) serum IL-6 in children with abdominal obesity was 45.2 (6.3-31.2) pg/mL as compared to 6.6 (4.5-22.5) pg/mL in those without abdominal obesity (P=0.047). Median (IQR) serum IL-6 was higher in the children with impaired fasting glucose as compared to those with normal levels (107.0 (22.5-197.5) *vs* 8.5 (5.0-116.0) pg/mL, P=0.06). There was no significant correlation between the serum levels of IL-6, hsCRP and adiponectin. No correlation was observed between hsCRP and BMI, waist circumference or blood glucose.

DISCUSSION

We noted a high prevalence of traditional risk markers of later cardiovascular disease and diabetes in our young study population. Half of our study group had elevated levels of inflammatory mediators IL-6 and hsCRP. To the best of our knowledge, no previous Indian study has reported IL-6 levels in obese children. However, higher levels of hsCRP and lower levels of adiponectin in obese post-pubertal adolescents as compared to lean have been reported by Vikram, *et al*. [9].

A limitation of our study is the lack of lean controls. Another limitation is that as a majority of our study participants were either pre- or early-pubertal, and only 10% were in pubertal stage 3 or above; thus, we could not ascertain the effect of puberty on the levels of IL-6, hsCRP and adiponectin.

In another study by our group (unpublished), serum adiponectin in 29 lean children, (mean (SD) age 11.5 (1.6) y, mean (SD) BMI z-score -0.4 (0.5)) was 8.7 (5.3) µg/mL, which is significantly higher as compared to the level in the overweight/obese children in the present study. In a study in Austrian children with mean (SD) age of 12 (4) years, the mean (SD) hsCRP in the obese group was 4.1(4.8) mg/L [10]; and in another study in

TABLE I SUMMARY OF BIOCHEMICAL PARAMETERS IN OVERWEIGHT/OBESE INDIAN CHILDREN

S.No.	*Parameter*	*Value*
1.	Adiponectin* (µg/mL)	6.0 (3.1)
	<3	13 (16.5)
2.	high-sensitivity C-reactive protein*(mg/L)	3.4 (2.4)
	>3	39 (49.4)
3.	Interleukin-6# (pg/mL)	12.7 (5.0-90.0)
	>10	43 (54.4)
4.	Total cholesterol* (mg/dL)	153.0 (33.0)
	≥200	5 (8.8)
5.	HDL cholesterol* (mg/dL)	43.9 (8.6)
	<40	20 (35.1)
6.	Triglycerides* (mg/dL)	105.6 (39.4)
	>150	7 (12.3)
7.	LDL cholesterol* (mg/dL)	88.0 (33.0)
	≥130	4 (7.0)
8.	Fasting blood glucose* (mg/dL)	85.0 (15.4)
	≥100	6 (10.7)

*Value in No. (%), *mean (SD) or #median (IQR). N = 79 for S.No.1-3, 57 for S.No. 4-7, and 56 for S.No. 8.*

WHAT THIS STUDY ADDS?

- Serum adiponectin has a significant inverse correlation with waist circumference, and serum IL-6 was significantly higher in children with abdominal obesity as compared to those without.

Caucasian pre-pubertal children with mean (SD) age of 8.0 (0.1) years, the median (IQR) hsCRP levels in the obese group were 2.5 (1.4-5.3) mg/L, [11], which were similar to the levels noted in our study. In these two studies, the levels in lean children were significantly lower at 0.9 (1.5) mg/L and 0.5 (0.2-1.7) mg/L, respectively [10,11]. In a Spanish study, mean (SD) serum IL-6 in obese children aged 4-15 years was 7.5 (3.8) pg/mL, similar to our study [12].

We noted an inverse association of adiponectin with waist circumference, indicating that the association between abdominal obesity and insulin resistance may be mediated by lowered adiponectin. Similar observations of inverse association of adiponectin with obesity have been made in Taiwanese and Japanese children [13,14]. We also observed a positive correlation of IL-6 with BMI and fasting blood glucose, as has been reported previously in adults [15].

To conclude, our study showed that inflammatory mediators hsCRP and IL-6 were elevated in half of the obese/overweight children and adiponectin was low in 16.5%. Inverse correlation of adiponectin with waist circumference, and positive correlation of IL-6 with BMI and fasting blood glucose indicated the utility of these parameters as markers of metabolic risk in children.

Contributors: VJ conceptualized and conducted the study and drafted the manuscript. AK helped in conducting the study, AA, NV and RK were co-investigators, AA helped in patient enrolment, NV and RK supervised the biochemical assays. All authors have given their inputs and approved the final manuscript.

Funding: All India Institute of Medical Sciences, New Delhi.
Competing interest: None stated.

REFERENCES

1. Rodríguez-Hernández H1, Simental-Mendía LE, Rodríguez-Ramírez G, Reyes-Romero MA. Obesity and inflammation: Epidemiology, risk factors, and markers of inflammation. Int J Endocrinol. 2013;2013:678159.
2. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? Atherosclerosis 2000;148:209-14.
3. Calle MC, Fernandez ML. Inflammation and type 2 diabetes. Diabetes Metab. 2012;38:183-91.
4. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: A systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151:483-95.
5. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, *et al*. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86: 1930-5.
6. Erhardt E, Foraita R, Pigeot I, Barba G, Veidebaum T, Tornaritis M, *et al*. Reference values for leptin and adiponectin in children below the age of 10 based on the IDEFICS cohort. Int J Obes. 2014;38:S32-8.
7. Sack U, Burkhardt U, Borte M, Schädlich H, Berg K, Emmrich F. Age-dependent levels of select immunological mediators in sera of healthy children. Clin Diagn Lab Immunol. 1998;5:28-32.
8. Fernández JR, Redden DT, Pietrobelli A, Allison DB. International diabetic federation: Criterion of metabolic syndrome in children and adolescents. J Pediatr. 2004;145:439-44.
9. Vikram NK, Misra A, Pandey RM, Dwivedi M, Luthra K. Adiponectin, insulin resistance, and C-reactive protein in postpubertal Asian Indian adolescents. Metabolism. 2004;53:1336-41.
10. Kapiotis S, Holzer G, Schaller G, Haumer M, Widhalm H, Weghuber D, *et al*. A proinflammatory state is detectable in obese children and is accompanied by functional and morphological vascular changes. Arterioscler Thromb Vasc Biol. 2006;26:2541-6.
11. Galcheva SV, Iotova VM, Yotov YT, Bernasconi S, Street ME. Circulating proinflammatory peptides related to abdominal adiposity and cardiometabolic risk factors in healthy prepubertal children. Eur J Endocrinol. 2011;164:553-8.
12. Gileles-Hillel A, Alonso-Álvarez ML, Kheirandish-Gozal L, Peris E, Cordero-Guevara JA, Terán-Santos J, *et al*. Inflammatory markers and obstructive sleep apnea in obese children: The NANOS study. Mediators Inflamm. 2014;2014: 605280.
13. Ochiai H, Shirasawa T, Nishimura R, Nanri H, Ohtsu T, Hoshino H, *et al*. Abdominal obesity and serum adiponectin complexes among population-based elementary school children in Japan: A cross-sectional study. BMC Pediatr. 2014;14:81.
14. Chang CJ, Jian DY, Lin MW, Zhao JZ, Ho LT, Juan CC. Evidence in obese children: Contribution of hyper-lipidemia, obesity-inflammation, and insulin sensitivity. PLoS One. 2015;10:e0125935.
15. Khaodhiar L, Ling PR, Blackburn GL, Bistrian BR. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. J Parenter Enteral Nutr. 2004;28:410-5.