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Correlation of Serum Ferritin and Adenosine Deaminase with Body Mass Index in Children: A cross-sectional study

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ABSTRACT

Objectives: The objectives of the study were to correlate the levels of two markers of inflammation, serum Ferritin and adenosine deaminase (ADA), with anthropometric measurements in children.

Materials and Methods: This cross-sectional study was performed in a total of 60 apparently healthy children (30 in each group), aged 6–14 years whose anthropometric measurements were taken and grouped as normal and obese as per body mass index (BMI), and their serum levels of ADA, Ferritin and Lipids were analyzed.

Results: Serum Ferritin, ADA, total cholesterol, and low-density lipoprotein cholesterol levels were significantly higher in the obese compared to normal children. The systolic blood pressure (SBP) was significantly higher in obese children, though the diastolic BP was similar across the groups. There was a strong positive correlation of the SBP, serum Ferritin and ADA with BMI. Ferritin showed a statistically significant positive correlation with waist circumference, hip circumference, waist-hip ratio (WHR), and triceps skinfold thickness. ADA, too, positively correlated with all anthropometric values, though it was statistically significant only with the SBP and WHR.

Conclusion: Serum Ferritin and ADA, which are markers of inflammation, were elevated in obese children compared to normal children. These biochemical markers may predict non-communicable diseases than cumbersome markers like anthropometric indices in the future.

Keywords: Obesity, Inflammation, Non-communicable diseases, Body mass index, Body weight, Lipids

INTRODUCTION

Obesity plays a pivotal role in the etiology of numerous non-communicable diseases (NCD's). The worldwide prevalence of obesity has tripled in the last few decades, with children in the age group of 5–19 years contributing an overwhelming number of 340 million.[1] Childhood weight gain leads to adulthood obesity, and in turn, increases the risk of adult NCD's. Low to medium income countries like India have a unique problem of "double burden" wherein, on one hand, we have poverty and under-nutrition,[2] and on the other, obesity.[3]

A large number of pro-inflammatory intermediaries are released by adipocytes and immune cells, causing low grade inflammation. These inflammatory mediators are involved in chronic systemic inflammation, insulin resistance, and atherosclerosis which leads to NCD's such as type 2 diabetes, cardiovascular disease, hypertension, polycystic ovarian syndrome, certain

cancers, and even severe asthma.[4] Adipose tissue synthesizes adenosine in response to inflammation to work as an anti-inflammatory metabolite. Adenosine deaminase (ADA), an enzyme of purine metabolism, converts adenosine to inosine. ADA plays a role in patients with metabolic syndromes such as obesity, insulin resistance, fasting hyperglycemia, dyslipidemia, and hypertension.[5] Evidence on serum ADA levels and ADA gene polymorphism in patients with insulin resistance and diabetes suggest its high levels in subjects with obesity as well.[5] Obesity being a subclinical mild inflammatory condition, there is evidence correlating C-reactive protein with body mass index (BMI), but there are conflicting reports amongst adults correlating BMI with iron status,[6,7] serum Ferritin[8-11] and hemoglobin.[12]

Keeping these in mind, the present study was designed to correlate serum ADA and Ferritin levels with BMI and other anthropometric measurements in children. In addition, the components of metabolic syndrome (i.e. lipid profile and age-matched blood pressure [BP]) were evaluated with these biochemical parameters.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Departments of Paediatrics and Biochemistry at a tertiary care teaching hospital in Eastern India from April 2019 to September 2019. Ethical approval was obtained from the Institute Ethics Committee vide letter number IEC/AIIMS BBSR/STS/2019-20/01. The study population included children of 6–14 years of age attending the outpatient department. The inclusion criteria were: apparently healthy children who had come for assessment of refractive errors or were attending the vaccination clinic without any known chronic diseases or ailments. These children and their parents were explained the details of the study. Written informed consent was obtained from the parents, and assent obtained from children >7 years of age. History was elicited, and a physical examination performed, which ruled out an acute illness within the past month or an identifiable chronic disease. Those with a history of chronic diseases, for example, allergies such as childhood asthma, chronic lung disease, celiac disease, nephrotic syndrome, chronic kidney disease, history of jaundice suggesting a liver disease, psychiatric illness, hemoglobinopathies, bleeding disorders, malignancies, epilepsy, juvenile diabetes mellitus, long-term medication use, treatment for anemia with hematinics, an infection causing a febrile illness in the previous month, or anemia on clinical examination were excluded from the study as these conditions could indirectly affect serum levels of Ferritin and ADA.

A single trained observer recorded weight and height as per standard guidelines using the same digital weighing scale with a minimum graduation of 10 g and a stadiometer with a minimum graduation of 1 mm. From the above two records, BMI was calculated and plotted on the age and sex-specific Indian Academy of Paediatrics BMI charts for children between 5 and 18 years.[13] The children were divided into the following groups – obese or normal as follows, those with a BMI of >27 adult equivalent matched to the age- and sex-specific growth chart were labeled as obese, and those below 23 adult equivalent but above the 3rd percentile were categorized as normal[13] and were included in the healthy control group.

The triceps skinfold thickness (TST) was measured using Harpenden's skinfold calipers (Baty International, West Sussex, UK) with a measuring range of 0–80 mm, measuring pressure: 10 g/mm^2 (constant over range), accuracy of 99% and minimum graduation of 1 mm. Healthy undamaged, uninfected dry skin with relaxed muscles of the right arm was ensured, an exception for which was if there was a deformity or missing limb wherein the left side was used. The skinfold site was marked using a pen with water-soluble ink after accurately determining the mid-point between the acromion and the olecranon with a tape measure. The skinfold was firmly grasped with the thumb and index finger while gently pulling the skinfold away from the body. The caliper was placed perpendicular to the fold, on the site marked with the dial facing upwards, at approximately 1 cm below the finger and thumb. While maintaining the grasp of the skinfold, the caliper was released so that full tension was placed on the skinfold. The dial was read to the nearest 0.50 mm, 1–2 s after the grip had been fully released. Three measurements were taken, and the mean value calculated.[14] Waist circumference (WC) was measured as the narrowest circumference between the rib cage and the superior border of the iliac crest at the end of expiration. Hip circumference (HC) was measured at the greater trochanters at the widest part of the hips[14] or around the hips at the point of greatest circumference.[15] A ratio of the above two parameters was used to find out the waist-hip ratio (WHR). The BP was measured using an electronic monitoring device after the participants have been rested in a sitting posture for 5 min or more. Three recordings of systolic BP (SBP) and diastolic BP (DBP) were taken on the right arm at 5 min intervals, and the mean was documented.[16]

Fasting blood samples were collected for biochemical testing. Total Cholesterol, Triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured in the autoanalyzer AU 5800 (Beckman Coulter, Inc. USA) using ready to use reagents from the same vendor. The serum ADA levels were estimated by colorimetric method using ready to use reagents from Tulip Diagnostics (P) Ltd, India. Serum Ferritin was estimated using the Chemiluminescence Immunoassay technology in the automated analyzer ADVIA Centaur XP (Siemens Healthcare GmbH, Germany) using their

reagents and calibrators; and quality controls from Randox Laboratories Ltd. were used.

Sample size calculation

A sample size of 60 was determined, with 30 in each arm of the study based on the proposition by Browne.[17]

Statistical analysis

The continuous variables were expressed as mean, standard deviation and analyzed using unpaired *t*-test using XLSTAT for Microsoft Excel. The coefficient of correlation (r) was calculated using Pearson's correlation between BMI with the biochemical parameters and BP and between biochemical parameters with BP, WC, HC, WHR and TST.

RESULTS

A total of 124 children were screened and 64 excluded leaving a total of 60 children who were recruited to the study, with 30 in each group. Most exclusions were due to parental consent not being obtained, mainly in the non-obese group. More boys fell in the obese category as compared to girls. The mean age of the children was 10.233 ± 2.542 years in the non-obese group versus 10.433 ± 1.924 years in the obese group. The mean weight of the children was 28.867 ± 7.127 kg in the non-obese versus 53.608 ± 12.923 kg in the obese group, which was statistically significant. All the anthropometric measures considered except height (Weight, BMI, WC, HC, WHR, and TST) were statistically significantly higher in the obese group as compared to the non-obese group [Table 1]. The SBP was significantly higher in obese children, but the DBP was similar in both groups [Table 1]. The mean serum Ferritin in the obese group was 44.937 ± 28.439 ng/L, which was significantly higher than that in the non-obese group of 28.797 ± 14.268 ng/L. The ADA results showed a similar trend as well, with the mean values in the obese (25.298 ± 12.387 U/L) being higher than that in the non obese (18.845 ± 11.936 U/L). This difference also was statistically significant. The mean total cholesterol and LDL cholesterol levels had the following values 160.167 ± 39.975 mg/dl among the obese and 128.600 ± 39.667 mg/dl in the non-obese; 100.267 ± 23.205 mg/dl in the obese; and 84.467 ± 27.256 mg/dl amongst the non-obese, respectively; both these differences were statistically significant. The serum triglyceride levels were higher in the obese (122.867 ± 48.055 mg/dl) compared to the non-obese (108.767 ± 40.642 mg/dl) children, but this difference was not statistically significant. HDL cholesterol, which is used as a cardiovascular risk factor in adults, was similar across the two groups.

There was a strong positive correlation of the SBP, serum Ferritin and ADA with BMI [Table 2]. Statistically significant differences were not obtained for any of the parameters of lipid profile with BMI. The correlation of anthropometric measurements with Ferritin [Table 3] showed a statistically significant positive correlation with WC, HC, WHR, and TST. The positive correlation with BP was not statistically significant. All anthropometric measurements had a positive correlation with ADA [Table 3]. However, there was a statistically significant difference only with the SBP and WHR.

DISCUSSION

There are some theories proposed for chronic inflammation in obesity which is a preventable risk factor for adult-onset NCD's. Adipose tissue warrants a higher amount of oxygen than most other tissues for its normal functioning.[18] With an increase in the adipose tissue mass with obesity, there is an increased distance from its vascular supply, causing hypoxic conditions. As occurs in any tissue undergoing hypoxia, there is a triggered release of Hypoxia-Inducible Factor-1 which counters the lack of oxygen in the tissue at the acute stages.[19,20] As obesity persists chronically, this hypoxia eventually causes tissue fibrosis and a vicious cycle of inflammation.[21,22] Tissue immune cells fuel obesity-related inflammation and oxidative stress in adipose tissue.[23,24]

Our study showed that serum Ferritin, ADA, total cholesterol, and LDL cholesterol levels were significantly higher in the obese compared to normal children, which was similar to a study by Jadhav and Jain done among adults, who observed that serum ADA activity was significantly increased in overweight and obese Indian subjects as compared to controls ($P < 0.0001$).[25] Another Nigerian study too showed a strong association of serum ADA with BMI, lipid parameters, and glucose.[26]

Ferritin is a well-established acute phase reactant, and more specifically, it is associated with abdominal obesity and other indices of body fat distribution.[8] In a meta-analysis of Ferritin and metabolic syndrome,[27] which included 26 studies, it was seen that there is a strong positive correlation of BMI with serum ferritin levels. Similarly, our study showed a statistically significant, positive correlation of ferritin with BMI, WC, HC, WHR and TST. Adipocytokines have been implicated in increasing the synthesis and secretion of the hormone hepcidin, which inhibits intestinal iron absorption and release by tissues, causing an iron deficiency.[28] Furthermore, the low-grade inflammation in obesity, even with iron deficiency, may falsely increase ferritin levels. Another school of thought suggested that iron excess in obesity could be explained by mechanisms of insulin resistance affecting iron homeostasis,[29] causing liver damage, hyperinsulinemia, and dyslipidemia. Although the above studies were in adults and animal models, our study also showed similar results as marked differences in ferritin ($P = 0.007$), total cholesterol ($P = 0.003$), and

Table 1: Comparison of general characteristics anthropometric parameters, BP, and biochemical parameters amongst normal and obese children.

Parameter	Non Obese (*n*=30)	Obese (*n*=30)	*P*
Boys	12	20	
Girls	18	10	
Age	10.233±2.542	10.433±1.924	0.732
Weight (Kg)	28.867±7.127	53.608±12.923	<0.001
Height (Centimetres)	136.800±9.286	141.650±10.564	0.064
BMI	15.517±2.581	26.399±4.455	<0.001
WC (cm)	61.558±10.086	87.404±8.072	<0.001
HC (cm)	69.159±10.405	90.253±8.183	<0.001
WHR	0.893±0.052	0.968±0.060	<0.001
Triceps Skin fold Thickness (mm)	10.533±3.598	18.467±4.321	<0.001
DBP	70.233±5.857	71.533±10.395	0.543
SBP	115.133±6.801	120.267±10.58	0.029
S. Ferritin ng/L	28.797±14.268	44.937±28.439	0.007
S. ADA U/L	18.845±11.936	25.298±12.387	0.044
T Cholesterol mg/dL	128.600±39.667	160.167±39.975	0.003
S. LDL mg/dL	84.467±27.256	100.267±23.205	0.019
S. Triglycerides mg/dL	108.767±40.642	122.867±48.055	0.225
S. HDL mg/dL	42.367±13.880	43.133±7.771	0.793

BP: Blood pressure, BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, WHR: Waist/Hip ratio, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ADA: Adenosine deaminase

Table 2: Correlation of BP and biochemical parameters with BMI.

Parameter	Coefficient of correlation with BMI	
	(r)	(*P*)
DBP (mm Hg)	0.188	0.15
SBP (mm Hg)	0.412	0.001
S. Ferritin (ng/L)	0.341	0.008
S. ADA (U/L)	0.299	0.02
T Cholesterol (mg/dL)	0.232	0.074
S. LDL (mg/dL)	0.186	0.154
S. HDL (mg/dL)	0.019	0.884
S. Triglycerides (mg/dL)	0.111	0.72

BP: Blood pressure, BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ADA: Adenosine deaminase

Table 3: Correlation of BP and anthropometric measurements with serum Ferritin and ADA.

Parameter	Coefficient of correlation with			
	S. Ferritin		S. ADA	
	(r)	(*P*)	(r)	(*P*)
DBP (mm Hg)	0.085	0.512	0.236	0.070
SBP (mm Hg)	0.54	0.24	0.324	0.012
WC (cm)	0.375	0.003	0.229	0.079
HC (cm)	0.281	0.029	0.141	0.266
WHR	0.396	0.002	0.301	0.019
Triceps Skin Fold Thickness (mm)	0.302	0.019	0.226	0.083

BP: Blood pressure, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, WC: Waist circumference, HC: Hip circumference, WHR: Waist/Hip ratio, ADA: Adenosine deaminase

LDL cholesterol (P = 0.019) between the two groups, that is, obese and normal children. Our estimated serum Ferritin and ADA in obese and normal children differ by a statistically significant value which can be explained by the above possible reason.

In our study, all anthropometric values positively correlated with ADA, though there was a statistically significant difference only with the SBP and WHR. Though there was a strong positive correlation of the SBP and serum Ferritin amongst adults in an article published by Lee *et al*.[30] who showed an incremental rise of Ferritin with hypertension in males; we could not find any similar studies in children.

CONCLUSION

Serum Ferritin and ADA, which are markers of chronic inflammation, were high in obese children compared to normal children, indicating ongoing cellular inflammation without any overt signs. Future research could be directed to follow-up of a cohort of children longitudinally and correlate their biochemical markers with NCD rather than using more cumbersome markers like anthropometric indices.

What is already known

Over nutrition and obesity causes increasing NCD's.
Anthropometric measures are difficult to measure.
Chronic inflammation is associated with NCD's.

WHAT THIS STUDY ADDS

Biochemical markers such as serum Ferritin and ADA are high in obese children as compared to normal children.

These markers reflect chronic inflammation and may be serially monitored to look at inflammation at the cellular level and may herald NCD's.

These markers may replace anthropometric measures to predict development of NCD's.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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