Carotid Intima-medial Thickness and Glucose Homeostasis in Indian Obese Children and Adolescents

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Abstract

Objective: To evaluate for subclinical atherosclerosis and its risk factors in Indian obese children. **Materials and Methods:** A cross-sectional, case–control study was conducted to recruit 80 children aged 6–17 years with constitutional obesity as cases and 23 age- and gender-matched controls with normal body mass index (BMI). Anthropometric and clinical evaluation was followed by biochemical analysis and body fat estimation by dual-energy X-ray absorptiometry in cases. Similar evaluation was performed for controls except laboratory parameters. Carotid intima-media thickness (CIMT) was measured with B-mode ultrasonography in both cases and controls to evaluate subclinical atherosclerosis. **Results:** The mean age of cases was 12.8 ± 3 years, with mean BMI of 29.2 ± 4.8 kg/m². The mean CIMT was significantly higher in cases than controls (0.54 ± 0.13 vs. 0.42 ± 0.08; $P < 0.001$ across all ages). CIMT was significantly higher in participants who were hypertensive than nonhypertensive (0.6 ± 0.11 vs. 0.53 ± 0.11 mm; $P = 0.04$). CIMT showed a positive correlation with BMI ($r = 0.23$, $P = 0.02$), percentage body fat and fat mass index ($r = 0.28$ and 0.3 respectively; $P < 0.001$), but not with waist: hip ratio. CIMT showed significant positive correlation with blood glucose at 60 min ($r = 0.22$; $P = 0.04$), serum insulin at 60 min ($r = 0.28$; $P = 0.01$) while negative correlation with whole body insulin sensitivity ($r = -0.27$; $P = 0.01$). **Conclusion:** CIMT correlated significantly to blood pressure, insulin sensitivity, and body fat in Indian obese children.

Keywords: Adiposity, body mass index, carotid intima-media thickness, insulin resistance, lipid

INTRODUCTION

The incidence of childhood obesity has increased globally with a nearly two-fold increase in its prevalence.[1] The reported prevalence of overweight and obesity varies from 10%–19% to 3%–6%, respectively, in India,[1] with recent increase in the prevalence of obesity which was reported at 9.3%.[2,3]

Childhood obesity confers long-term effects on health and predisposes to obesity in adulthood. Adiposity predisposes to chronic inflammation, insulin resistance (IR), and dyslipidemia. Obese participants are prone to develop neointimal proliferation and increased ventricular wall thickness predisposing to cardiovascular (CV) morbidity.[4] Half of the Central Europe's overweight and obese children showed adverse CV risk factors at mean age of 12.6 years, exponentially increasing their risk of CV disease (CVD) in later life.[5]

Carotid intima-media thickness (CIMT) has emerged as an early, noninvasive, feasible, and cost-effective method for evaluating atherosclerosis in adults.[6] Among children, CIMT was significantly raised in obese participants than nonobese controls in Western literature.[7,8] However, there are limited studies which have evaluated carotid arteries for CV risk in obese Indian children and adolescents.

South Asians like Indians exhibit tendency toward central adiposity which increases their vulnerability for CVD.[2,9] They are prone to IR which increases their likelihood of developing metabolic syndrome and diabetes mellitus.[2] There is a paucity of data to correlate subclinical atherosclerosis to metabolic functions in Indian obese children. This study was therefore, undertaken to study CIMT as a marker of early atherosclerosis in obese Indian adolescents and correlate it with various clinical and biochemical parameters.

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MATERIALS AND METHODS

This study was conducted as a case–control study in the Endocrinology Department of large tertiary level hospital in Northern India. This study was approved by the Institutional Ethics Committee. Written informed consent was taken from parents with verbal assent from participants older than 7 years.

The study participants comprised children with constitutional obesity in the age group 6–17 years recruited from outdoor endocrinology department. Any participant who was diabetic or taking metformin or any weight reducing drugs was excluded, as were also participants with known chronic systemic or endocrine illness. Similarly, participants with features of hypothalamic involvement were also excluded from the study.

Weight of all the children was measured with the same weighing machine and corrected to the nearest 0.5 kg in minimal clothing without footwear. Height was measured with wall mounted Holtain's Stadiometer (Holtain Inc., Crymych, Pembs. UK) with the measurement corrected to the nearest 3 mm. The body mass index (BMI) was calculated as weight (kg) divided by square of height in meter. Obesity was defined as per criteria of the International Obesity Task Force.[10] Age- and sex-matched apparently healthy children and adolescents (recruited from families of hospital staff), with BMI in normal range, were recruited as controls. One control of corresponding gender and age (±1 year) was selected for all cases of same age. The BMI of mother and father of the study participants were also recorded. The pubertal staging of both cases and controls was recorded as per Tanner's method.[11]

Children and adolescents in control group were subjected to only CIMT measurement while cases underwent detailed clinical, laboratory, and radiological evaluation. Waist circumference (WC) was measured at the end of normal expiration at the midpoint between the iliac crest and the lower edge of ribs in the midaxillary line with the patient standing erect with abdomen relaxed while hip circumference was measured at the point of maximum circumference over the buttocks and waist: hip ratio (WHR) was calculated. Blood pressure (BP) was measured in the supine position and interpreted against the Indian standards in all participants.[12] Total percentage body fat was measured by dual-energy X-ray absorptiometry (DXA; Hologic QDR 4500A, Hologic Inc., Bedford, MA, USA). The fat mass index (FMI) was calculated as total fat mass divided by square of height in meters.

Biochemical analysis

After overnight fasting of minimum 9 h, participants were called in the morning for oral glucose tolerance test. After baseline sample collection, all participants were given oral glucose (1.75 g/kg body weight, maximum up to 75 g, dissolved in 250 ml of water) and samples were collected at 60 and 120 min after ingestion of glucose. Fluoride vial was used to collect sample for blood glucose. Fasting blood sample was used for measurement of blood glucose, serum insulin, liver function tests, lipid profile, and thyroid stimulating hormone (TSH).

Plasma glucose was measured by glucose oxidase-peroxidase method in HITACHI 912 autoanalyzer using colorimetric method. Plasma insulin was measured with Roche Elecsys 2010 electrochemiluminescent autoanalyzer with an immunoassay format using the sandwich principle. The CV for this method is 2.1%–2.8%. The area under curve was calculated for blood glucose and serum insulin using trapezoidal rule. IR was calculated from a computer-based model called homeostasis assessment model (HOMA).[13] The whole body insulin sensitivity index (whole body ISI) or Matsuda index was calculated by the formula suggested by Matsuda and DeFronzo.[14] Impaired fasting glucose (IFG) was defined as blood glucose values between 100 and 125 mg/dL and impaired glucose tolerance (IGT) was defined at blood glucose between 140 and 199 mg/dL after 2 h of glucose loading.[15]

Liver function test, serum cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and TSH were measured with an automated analyzer whereas low-density lipoprotein-cholesterol (LDL-C) was calculated by Friedewald equation.[16] Based on the lipid profile values, participants were classified according to the classification given by NCEP Expert Panel on Cholesterol Levels.[17] Since NCEP did not provide pediatric cut points for TG or HDL-cholesterol (HDL-C), cutoff for these two parameters was taken from a recently published review.[18]

Radiological

B-mode ultrasonography was used to measure CIMT with 7.5–10 MHz probe (PHILIPS EnVisor Ultrasound). CIMT was measured with the participant in the supine position with neck extended (achieved by placing pillow beneath the shoulders) and the head slightly turned to the opposite side. It was measured at 1 cm proximal to common carotid artery bifurcation on both sides. Measurement of CIMT was done by a single radiologist to reduce the interobserver variability. Images were stored (both cases and controls) and assessed by another radiologist who was blinded to the participant details. CIMT was measured as the distance from the leading edge of the first echogenic line to the second echogenic line. The first echogenic line represents the lumen-intima interface and the second line is produced by the collagen containing upper layer of adventitia.[6] The mean of both sides was used for analysis.

Statistical analysis

The statistical analysis was performed using Stata9 program. For the prevalence of obesity as 5%–6%,[1] the sample size required to detect 10% difference in CIMT in cases and controls with power 90% and Type 1 error as 5%, was calculated as 90 cases (obese patients). Descriptive analysis was carried out to summarize the study population, check for normal distribution, and identify potential confounders and interaction of variables. Comparison of means was done using *t*-test. Mann–Whitney test was used for nonparametric parameters. Correlation (*r*) between variables was assessed using Pearson's

correlation. In case of nonparametric parameters, Spearman's correlation was done. Categorical variables were compared using Chi-square test. HOMA and Matsuda indices showed nonnormal range of distribution. Hence, both of them were converted to log values and then the log values when used in regression analysis.

RESULTS

The flow of the patients during the study is shown in Figure 1. At completion of the study, data from total 80 obese patients and 23 age- and sex-matched controls were used for analysis. The mean age of cases and controls was 12.8 ± 3 years and 12.1 ± 2.5 years, respectively, with a male:female ratio of 1.29 in cases and 1.1 in controls. Of these 80 cases, 25 patients were prepubertal (20 boys and 5 girls) whereas rest were in peri or pubertal stage. The mean BMI of cases was 29.2 ± 4.8 (range - 21.7–46.4) kg/m^2. The BMI of the study participants did not show any significant correlation to maternal or paternal BMI ($P > 0.05$). Twelve cases (15%) were found to be hypertensive whereas 65% cases had acanthosis nigricans.

The details of biochemical parameters in cases are shown in Table 1. In total, 31 patients had abnormalities in glucose metabolism –30% had IFG, 16.3% had IGT, whereas 7.5% had both. Participants with acanthosis had significantly higher levels of fasting as well as 2 h serum insulin while differences in blood glucose levels were not significant (data not shown). Among cases, 34.3% had hypercholesterolemia, 26% elevated LDL-C, 77% had hypertriglyceridemia, and 89.7% had low HDL-C.

The correlation between glycemic kinetics (logarithmic values of both HOMA-IR and Matsuda index) and clinical and biochemical parameters are shown in Table 2. On univariate analysis, age, BMI and FMI were found to be significantly associated with both Matsuda index and HOMA-IR, though none of these remained significantly correlated on multivariate regression.
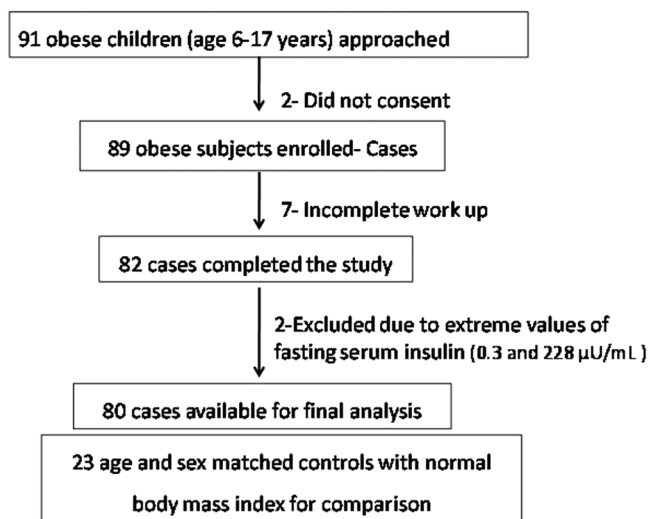
The mean CIMT was higher in cases than controls (0.54 ± 0.13 and 0.42 ± 0.08 mm, respectively); $P < 0.001$ across all ages (data not shown). There was no significant difference in

Table 1: Clinical and biochemical profile of study participants

Parameter	Mean±SD	Range
Clinical		
Systolic blood pressure±mmHg	119.7±12.1	96-150
Diastolic blood pressure±mmHg	79.3±7.9	60-100
Waist: hip ratio	0.91±0.06	0.77-1.09
Body fat percentage by DXA	40.6±6.4	25.1-55.5
Fat mass index (g/m^2)	11.9±3.0	5.9-18.9
Glucose homeostasis		
Fasting blood glucose (mg/dL)	95.3±11.8	74-139
Blood glucose 1 h (mg/dL)	135.6±32.8	80-292
Blood glucose 2 h (mg/dL)	119.4±22.6	59-189
Serum insulin at 0 h (µU/mL)	19.9±14.5	0.2-72.9
Serum insulin at 1 h (µU/mL)	126.2±150.1	10.5-1001.2
Serum insulin at 2 h (µU/mL)	117.2±158.6	4.8-959.3
HbA1c	5.35±0.4	4.2-6.7
HOMA-IR*	4.74±3.5	0.01-17.7
Matsuda index	4.02±3.7	0.6-23.6
Lipid homeostasis		
Serum total cholesterol (mg/dL)	158.3±30.8	89-235
Serum triglycerides (mg/dL)	122.9±47.9	45-256
Serum LDL-C (mg/dL)	93.8±25.1	37-148
Serum HDL-C (mg/dL)	39.2±5.4	28-60
Others		
Thyroid stimulating hormone (U/L)	3.8±2.1	0.55-12.8
AST (U/L)**	34.4±19.2	18-170
ALT (U/L)***	40.7±36.7	10-303

HOMA-IR: Homeostatic model assessment-insulin resistance, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standard deviation, HbA1c: Glycated hemoglobin, DXA: Dual-energy X-ray absorptiometry Significance - *$P<0.05$, **$P<0.01$, ***$P<0.001$

Figure 1: Flow of the study patients

91 obese children (age 6-17 years) approached

2- Did not consent

89 obese subjects enrolled- Cases

7- Incomplete work up

82 cases completed the study

2-Excluded due to extreme values of fasting serum insulin (0.3 and 228 µU/mL)

80 cases available for final analysis

23 age and sex matched controls with normal body mass index for comparison

Table 2: Correlation of homeostatic model assessment-insulin resistance and Matsuda index with clinical and laboratory parameters

Variable	Log HOMA-IR		Log Matsuda	
	r	P	r	P
BMI	0.37	<0.001**	−0.5	<0.0001**
WC	0.42	<0.001**	−0.5	<0.001**
Waist hip ratio	0.12	0.29	−0.13	0.76
Total body fat percentage - DXA	0.2	0.08	−0.22	0.02*
Systolic blood pressure	0.28	0.011*	−0.36	<0.0001**
Diastolic blood pressure	0.34	0.002**	−0.42	<0.0001**
Total cholesterol	0.24	0.04*	−0.2	0.07
LDL-C	0.22	0.06	−0.23	0.04*
HDL-C	0.19	0.09	−0.12	0.28
Triglyceride	0.08	0.5	−0.01	0.91

Significance - *$P<0.05$, **$P<0.01$. BMI: Body mass index, WC: Waist circumference, HOMA-IR: Homeostatic model assessment-insulin resistance, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, DXA: Dual-energy X-ray absorptiometry

CIMT between boys and girls in either group. There was no significant difference in CIMT across different pubertal age groups or between patients with or without acanthosis nigricans (data not shown). CIMT was significantly higher in the patients who were hypertensive than nonhypertensives (0.6 ± 0.11 vs. 0.53 ± 0.11 mm; $P = 0.04$).

The correlation between CIMT and other clinical and biochemical parameters is shown in Table 3. Among measures of body fat estimation, BMI and fat mass estimated by DXA showed better correlation with CIMT than WC or WHR. Matsuda index inversely correlated with CIMT ($r = -0.27$; $P = 0.004$) [Figure 2]. The correlation between CIMT and HOMA was weak; however, after arranging HOMA-IR into tertiles, a weak significant correlation was observed between CIMT and HOMA-IR values in the 1st and 2nd tertiles ($r = 0.0079$; $P = 0.04$).

DISCUSSION

In the present study, we evaluated CIMT in obese Indian children in the age group of 6–17 years and found it to be significantly raised than in healthy controls. CIMT correlated to insulin sensitivity, BP, and FMI in obese children.

CIMT is a well-established screening tool for CV risk in adults.[6] In addition, it correlates to IR even in apparently healthy individuals as reported among Caucasian populations.[19,20] Among studies in obese children, Atabek *et al.* demonstrated significant correlations between CIMT and ISIs, quantitative insulin-sensitivity check index, and HOMA-IR.[8] Similarly, Beauloye *et al.* showed significant correlation of CIMT with fasting insulin levels and HOMA-IR in obese children, unlike with classical CVD risk factors such as familial history of diabetes or premature CVD, visceral obesity, and dyslipidemia.[7] We found a higher correlation between CIMT and whole body insulin sensitivity than with HOMA-IR probably as the former parameter measures both hepatic and peripheral tissue insulin sensitivity unlike HOMA-IR which is a reflection of hepatic IR.

As per a systematic review, CIMT significantly correlated with adiposity in adolescents from Western Europe and US ($r = 0.13$–0.59).[21] Increased adiposity can lead to increased resistin and reduced adiponectin, both of which are associated with endothelial dysfunction.[22] The presence of hypertension further compounds the CV risk in obese children.[23] Among measures of adiposity in South Asians, WHR[24] and WC[25] correlated better to CIMT than BMI. In our study, FMI showed better correlation to CIMT than BMI or WHR suggesting it to be a more sensitive parameter of adiposity for risk of atherosclerosis.

The risk of CVD in adiposity increases in the presence of deranged glucose homeostasis.[20] IR frequently occurs in obese patients and gets exaggerated during the period of growth and puberty.[26] Abnormal insulin signaling induces lipolysis and elevated free fatty acids which may stimulate vascular smooth muscle cell proliferation, oxidative stress, cell apoptosis, and

Table 3: Correlation between CIMT and clinical and biochemical parameters

Parameter	Correlation coefficient (*r*)	*P*
Body mass index	0.23	0.02*
Waist circumference	0.19	0.05*
Waist hip ratio	0.12	0.3
Total body percentage fat	0.28	0.011*
Fat mass index	0.3	0.003**
Systolic blood pressure	0.15	0.17
Diastolic blood pressure	0.05	0.59
Fasting blood glucose	0.10	0.33
Blood glucose at 60 minutes	0.22	0.04*
Fasting serum insulin	0.08	0.47
Serum insulin at 60 minutes	0.28	0.009**
Serum cholesterol	0.09	0.40
Serum LDL-C	0.11	0.29
Serum HDL-C	−0.003	0.97
Serum triglyceride	0.01	0.92
Matsuda index	−0.27	0.004**
HOMA-IR	0.10	0.35
Glycated haemoglobin	0.05	0.33

*$P \leq 0.05$, **$P \leq 0.01$: Statistically significant. BMI: Body mass index, WC: Waist circumference, HOMA-IR: Homeostatic model assessment insulin resistance, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol
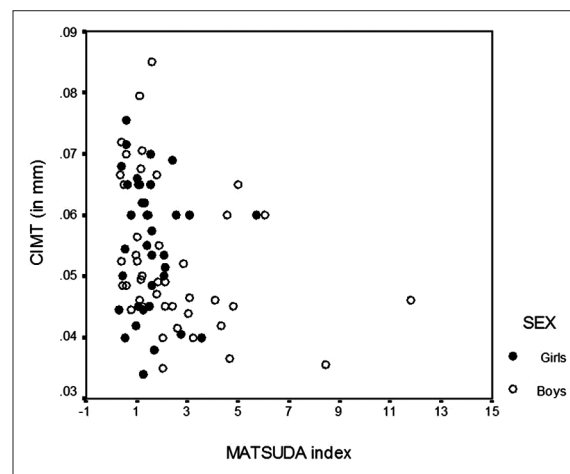

Figure 2: Correlation of carotid intima-media thickness with Matsuda index in obese patients

inflammation predisposing to atherosclerosis.[27] Indians also have propensity for hyperinsulinism which further increases their risk for CVD.[9] The obese patients in the present study also had high insulin values.

Dyslipidemia characterized by hypertriglyceridemia and low HDL may also coexist with IR.[26] This pattern is proatherogenic and correlated with CIMT among Indian obese children[28] and apparently healthy young Indian adults.[25] A similar pattern of proatherogenic dyslipidemia was seen in our obese cohort. The lack of correlation to CIMT was postulated to lesser duration of disease as also seen by Beauloye *et al.*[7]

The main strength of the study was that it correlated CIMT with adiposity which was measured by FMI instead of only anthropometric indices. In addition, it also estimated both glucose and lipid homeostasis in obese Indian children. The present study had few limitations. Arterial distensibility, which measures physiological arterial dysfunction was not measured due to logistic reasons. The second limitation of our study was lack of comparative metabolic workup of the apparently healthy controls which was not undertaken due to ethical reasons.

Conclusion

Indian obese children and adolescents had a higher CIMT than children with normal BMI. These children should be screened for early derangements in lipid and glucose metabolism and lifestyle measures should be reinforced to prevent long-term CV morbidity.

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Conflicts of interest

There are no conflicts of interest.

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