## **Original Research Article**

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# Carotid intima-media thickness and cardiovascular risk factors in childhood and adolescent obesity

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## **ABSTRACT**

**Background:** Childhood obesity is a significant health problem that has reached epidemic proportions around the world and it is a risk factor for atherosclerosis. The study aimed to investigate carotid intima-media thickness (CIMT) in obese children and evaluate the relationship of CIMT to various cardiovascular risk factors.

**Methods:** This was achieved through including 40 obese children aged 5-16 years who were referred to Alexandria University Children's Hospital (AUCH) and 20 non-obese age and sex-matched children as the control group. All obese children in this study were subjected to thorough history taking, thorough clinical examination stressing on anthropometric measurement, blood pressure measurement and laboratory investigations including lipid profile, liver function tests, fasting glucose and fasting insulin and ultrasonographic study for the liver and carotid intima-media thickness measurement.

**Results:** compared to the control, the obese children demonstrated a significantly thicker carotid intima-media (p<0.001). Univariate correlation analysis revealed that CIMT was significantly correlated with the body mass index (BMI), waist circumference measurement, diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDLC), fasting insulin, homeostasis model assessment- insulin resistance (HOMA-IR), quantitative insulinsensitivity check index (QUICKI) and fatty liver. In multiple linear regression analysis, CIMT correlated significantly with DBP in the obese group.

**Conclusions:** Atherosclerosis begins in obese children and adolescents and CIMT measurement is a noninvasive, feasible, reliable and inexpensive method to detect subclinical atherosclerosis.

Keywords: Obesity, Carotid intima media thickness, Atherosclerosis

## **INTRODUCTION**

Childhood obesity is a significant health problem that has reached epidemic proportions around the world. The long-term implications of this epidemic are extremely serious. Obese children are much more likely than children of healthy weight to become obese adults. Childhood obesity has been shown to have a tremendous impact on later health even independent of adult weight. Childhood obesity has become so severe that diseases that once affected only adults are now appearing in children. For instance, type 2 diabetes in children was rare 20 years ago; today, it constitutes nearly one half of

all new cases of diabetes among children in some settings. Also, obesity is strongly associated with several serious diseases, including hypertension, dyslipidemia, cardiovascular disease, osteoarthritis, obstructive sleep apnea and liver and gall bladder disease as well as social and psychological problem. Furthermore, there is also a strong association between obesity and cancers and can also lead to poorer treatment and increased cancer-related mortality.

Exposure to the cardiovascular risk factors in early life may induce changes in the arteries contributing to the development of atherosclerosis in adulthood. Childhood obesity is a risk factor for atherosclerosis and is associated with increased mortality due to cardiovascular disease in adulthood, independent of adult weight.<sup>7</sup>

The development of ultrasound measures of carotid intima-media thickness (CIMT) has greatly enhanced the ability to assess subclinical atherosclerosis and to track progression of abnormalities. It is a noninvasive, feasible, reliable and inexpensive method. Measures of CIMT have been strongly related to the atherosclerotic lesions in the aorta and coronary, cerebral, and peripheral arteries and have been associated with myocardial infarction, stroke, and cardiovascular death in elderly populations. <sup>8</sup> CIMT measures have also been used as a marker of preclinical atherosclerosis in pediatric populations with cardiovascular risk factors such as hypertension, diabetes, morbid obesity and familial hyperlipidemia. <sup>8,9</sup>

The aim of the present study was to investigate CIMT in obese children and to evaluate the relationship of CIMT to various cardiovascular risk factors and to find out other co morbidities associated with obesity.

### **METHODS**

This study was a case control which was conducted on the nutritional clinic at Alexandria University Children's Hospital (AUCH) during the period from February 2014 to January 2015 after the approval of the Ethical Committee of Alexandria University, Egypt.

The study included 40 obese children (16 girls and 24 boys, mean age 9.03±2.52 years). The control group consisted of 20 apparently healthy non obese children. They were 11 boys and 9 girls with mean age of 8.88±2.94 years.

Obesity was defined as body mass index (BMI)  $\geq 95^{th}$  percentile using the BMI for age and sex CDC growth charts. A non-obese subjects was defined as having a BMI less than the  $85^{th}$  percentile BMI. A detailed medical and family history was obtained from all children involved in the study. Obese children were excluded if they had any endocrinal disease (e.g. hypothyroidism, glucocorticoid excess) or a history of medication that alters blood pressure, glucose and lipid metabolism.

#### Clinical characteristics

Height was measured using weight and height scale with a fixed stadiometer with a movable head piece to the nearest 0.5 cm. The height values were expressed as height standard deviation score (Ht-SDS) to adjust sex and variation in age.

Body weight was measured to nearest 0.1 kg on standard weight and height scale with the patients dressed only light weight clothing and without shoes. The weight was expressed as BMI, (BMI= Body weight (kg)/Height (m).<sup>2</sup> Because the BMI varies according to age and sex, its

value was standardized for age and sex by calculating BMI-SDS which was obtained by the following equation: BMI-SDS=individual measurement-population mean /population SD.

Waist circumference (WC) (cm) was measured at a level midway between the lower rib margin and superior border of the iliac crest using a flexible tape all around the body in horizontal positions at the end of gentle expiration. Children with a waist circumference >90th percentile was detected according to waist circumference percentile values in the United States for children and adolescents according to sex.<sup>11</sup>

Waist-hip ratio (WHR): hip circumference (cm) was measured at the widest point around the greater trochanters. The (WHR) was calculated as the waist measurement divided by hip measurement.

The blood pressure was measured in all subjects in this study by same investigator. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice at the right arm after a 10-minute rest in the supine position using a standard mercury sphygmomanometer. Subjects were considered hypertensive if SBP or DBP or both were  $\geq$ the 95<sup>th</sup> percentile for age, sex and height. Prehypertention was defined as SBP or DBP were between 90<sup>th</sup> and 95<sup>th</sup> percentile. <sup>12</sup>

## **Biochemical measurements**

Patients were subjected to the following laboratory investigations

Fasting glucose, 2 hours plasma glucose after oral glucose load, fasting insulin, total cholesterol (TC), serum triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) alanine aminotransferease (ALT) and asparate, aminotransferease (AST). Glucose was determined quantitatively by colorimetric method after enzymatic oxidation in the presence of glucose oxidase.

Fasting TC, HDL-C, TG were determined enzymatically by quantitative colorimetric method).LDL-C was calculated using the Friedewald equation: LDL-C=TC – HDL-C- TG/5. ALT & AST were tested by kinetic method. We used the following indices for the determination of insulin resistance: Homeostasis model assessment- insulin resistance (HOMA-IR): =Fasting insulin ( $\mu$ U/ml) ×fasting glucose level (mg/dl)/405 and Quantitative insulin-sensitivity check index (QUICKI): =1/ (Log fasting insulin ( $\mu$ U/ml) + log fasting glucose (mg/dl)).

## **Imaging**

Longitudinal images of the both common carotid arteries were obtained by combined B-mode and color doppler ultrasound examinations with Toshiba Nemio Ultrasound Imager with a 7.5-MHz linear transducer. The value of the IMT was defined as the mean value of measurements between the right and left carotid arteries calculated from three consecutive measurements of the maximum far wall thickness on each side, 10 mm from the bifurcation of the common carotids. <sup>14,15</sup>

The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was conducted with a Toshiba Nemio ultrasound imager and a 5-MHz convex transducer. The participants were required to have hepatorenal contrast and liver brightness to be given a diagnosis of fatty liver.

## Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Quantitative data obtained in the study were expressed as mean±standard deviation. Comparison between different groups regarding categorical variables was tested using Chisquare test. For normally distributed data, comparisons between two independent populations were done using independent t-test. For abnormally distributed data, comparison between two independent populations were done using Mann Whitney test. Correlations between two quantitative variables were assessed using Pearson

coefficient. For ordinal variables Spearman coefficient correlations was assessed. Different multivariate linear regression was assessed to find the significant predicting variables affecting CIMT.

Receiver operating characteristic curve (ROC) was plotted for CIMT to analyze a recommended cutoff. The agreement of CIMT for cut off to diagnose control from cases, was expressed in sensitivity, specificity, positive predictive value, negative predictive value and accuracy. A p value of  $\leq 0.05$  was considered significant.

#### RESULTS

Clinical and laboratory characteristics for obese and control children are summarized in Table 1. The obese and control children showed no significant differences in term of age, sex and height. The obese children demonstrated significant differences in number of clinical factors including weight, BMI, BMI percentile, BMI-SDS, SBP, SBP percentile, DBP, DBP percentile, waist circumference (WC), hip circumference and (WHR) with WC in all obese children being >90<sup>th</sup> percentile. Also, prehypertension and hypertension were seen among obese children only (12.5% and 5% respectively). None of the control children had prehypertension or hypertension.

Table 1: Comparison between obese and control children according to clinical and laboratory parameters.

	01 121 (37.40)	C 4 1(N 20)	D 1
	Obese children (N=40)	Control (N=20)	P value
Age (y)	9.03±2.52	8.88±2.94	$0.838^{b}$
Sex: male/female, n (%)	24 (60%)/16 (40%)	9 (45%)/11 (55%)	0.409 <sup>a</sup>
Height (cm)	137.04±13.42	134.55±18.41	0.533 <sup>b</sup>
Height SDS	0.68±1.29	$0.37\pm0.73$	$0.240^{b}$
Weight (kg)	59.24±20.29	32.28±12.70	<0.001*b
BMI	30.64±5.79	17.14±1.81	<0.001*b
BMI percentile	99.48±0.55	59.5±23.59	<0.001*b
BMI-SDS	2.59±0.27	0.31±0.63	<0.001*b
Waist circumference (cm)	92.30±13.71	60.35±6.18	<0.001*b
Waist circumference >90 <sup>th</sup> percentile	40 (100%)	0 (0%)	-
Hip circumference (cm)	98.03±14.49	72.55±9.68	<0.001*b
Waist/hip ratio	0.94±0.08	0.83±0.04	<0.001*b
SBP (mmHg)	109.20±7.87	103.75±7.76	0.014*b
SBP Percentile	71.02±17.72	57.55±15.40	$0.005^{\rm b}$
DBP (mmHg)	71.72±8.0	65.75±5.68	0.004*b
DBP percentile	79.25±15.29	68.70±11.24	$0.008^{*b}$
Fasting glucose (mg/dl)	89.15±15.27	87.75±9.08	$0.708^{\rm b}$
2 hr plasma glucose concentration after glucose load (mg/dl)	99.40±26.52	91.10±12.12	0.484 <sup>b</sup>
Cholesterol (mg/dl)	158.0±27.04	128.30±15.78	<0.001*b
Triglycerides (mg/dl)	82.07±35.48	74.85±21.56	0.333 <sup>b</sup>
HDL-C (mg/dl)	45.02±12.92	50.85±10.46	$0.086^{\rm b}$
LDL-C (mg/dl)	95.88±23.21	62.15±16.85	=0.001*b
VLDL-C (mg/dl)	14.50 (7.0–32.0)	15.50 (7.0–22.0)	0.588 <sup>c</sup>
Cholesterol/HDL	3.71±1.08	2.60±0.66	<0.001*b
LDL/HDL	2.25±0.92	1.33±0.63	<0.001*b
Fasting insulin (µU/ml)	15.70 (8.17–37.70)	7.40 (5.40–8.90)	<0.001*c

Continued.

	Obese children (N=40)	Control (N=20)	P value
HOMA IR	3.42 (1.56–11.30)	1.55 (1.20-2.10)	<0.001*c
QUICKI	0.32±0.02	0.36±0.01	<0.001*b
AST (mg/dl)	32.40±10.57	24.50±6.28	$0.003^{*b}$
ALT (mg/dl)	24.0 (11.0–61.0)	18.0 (7.0-26.0)	$0.005^{*b}$
Mean CIMT (mm)	$0.48\pm0.06$	0.38±0.047	<0.001*b

a: Chi square test; b: Student t-test; c: Mann Whitney test \*: Statistically significant at p≤0.05.

Table 2: Comparison between obese and control children according to mean CIMT.

	Obese children (N=40)	Control (N=20)	P value
Min-Max	0.35 - 0.58	0.30 - 0.50	
Mean-SD	$0.48\pm0.06$	0.38±0.047	<sup>t</sup> p <0.001*
Median	0.50	0.40	

p: p value for comparing between cases and control; t: Student t-test \*: Statistically significant at p≤0.05.

Table 3: Agreement (sensitivity, specificity and accuracy) for mean CIMT.

			Control	Obese children	Sensitivity	Specificity	PPV	NPV	Accuracy
Maa	n CIMT	≤0.4	19	10	75.0	95.0	96.7	65.5	81.67
wiea		>0.4	1	30	75.0				

Table 4: Correlation between the mean CIMT and some parameters of obese children.

	Mean CIMT		
	R	P value	
BMI	0.404*	$0.010^{*}$	
BMI Z score	-0.012	0.943	
BMI percentile	-0.084	0.608	
Waist circumference (WC)	0.425*	$0.006^{*}$	
Hip circumference (HC)	$0.400^{*}$	$0.011^{*}$	
Waist/hip ratio (WHR)	-0.125	0.443	
SBP	0.152	0.349	
SBP percentile	0.002	0.988	
DBP	0.495*	$0.001^{*}$	
DBP percentile	0.437*	0.005*	
Cholesterol	-0.175	0.279	
Triglycerides	0.108	0.506	
HDL	-0.335 <sup>*</sup>	0.035*	
LDL	-0.091	0.576	
VLDL(r <sub>s</sub> )	0.138	0.395	
FPG	0.263	0.102	
Fasting insulin (r <sub>s</sub> )	0.352*	$0.026^{*}$	
HOMA IR (r <sub>s</sub> )	0.410*	$0.010^{*}$	
QUICKI	-0.348*	$0.028^{*}$	
AST	0.138	0.395	
$ALT(r_s)$	0.010	0.953	
Fatty liver (r <sub>s</sub> )	0.354*	0.025*	

r: Pearson coefficient; rs: Spearman coefficient; \*: Statistically significant at p  $\leq$  0.05.

Table 5: Multiple linear regression to evaluate the correlation between mean CIMT and other main parameters.

Dependent variable	Independent variable	В	SE	Beta	t	P value	95% confidence Interval for B Lower bound	Upper bound
Mean CIMT	DBP	0.003	0.001	0.335	$2.059^{*}$	0.048	0.0	0.005
Mean CIVII	F=2.978* p=0.014, R=0.659							

Associated co morbidities	No.	%
NAFLD	27	67.5
Prehypertension	9	22.5
Hypertension	8	20
Impaired fasting glucose	6	15
Diabetes	2	5
Bronchial asthma	2	5
Obstructive sleep apnea	2	5

Table 6: Distribution of obese children regarding the presence of co morbidities.

The obese children recorded higher levels of cholesterol, triglycerides, LDL-C and VLDL levels and lower levels of HDL-C. Only there was significant difference between obese children and the control in the level of cholesterol and LDL-C.

There was a significant difference between obese children and control group as regard the insulin level, HOMA-IR, QUICKI, ALT and AST.

Prevalence of metabolic syndrome (MS) among obese children was 25% and fatty liver was detected in 67.5% among obese children.

There was a significant difference between obese children and control children as regard the mean of CIMT. In obese children, CIMT ranged from 0.35 - 0.58 mm with a mean of 0.48±0.06, while in control children it ranged from 0.30-0.50 mm with a mean of 0.38±0.047 (Table 2). ROC curve of mean CIMT was used to compute the cut off value that help to differentiate between obese and control children. Sensitivity and specificity were calculated using area under the ROC curve, it yielded a cut-off point which was 0.4mm with 95% specificity and 75% sensitivity The results are illustrated in Figure 1 and summarized in Table 3.

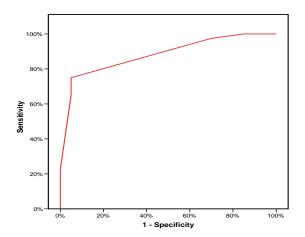


Figure 1: ROC curve for mean CIMT.

Univariate correlation analysis revealed that CIMT was significantly correlated with BMI, waist circumference measurement, DBP, HDL-C, fasting insulin, HOMA-IR,

QUICKI and fatty liver (Table 4). Moreover, multiple linear regression analysis revealed a significant correlation between carotid IMT and diastolic BP (Table 5).

Table 6 explore the co morbidities among obese children, NAFLD was the most common morbidities observed among obese children (67.5%) followed by prehypertension and hypertension (22.5%, 20% respectively).

## **DISCUSSION**

The worldwide problem of obesity in children has become a crisis in public health. Obesity used to manifest in adult life and is beginning to manifest in childhood. Atherosclerosis is slow and progressive disease that can start in childhood. CIMT is well known marker of atherosclerosis and can indicate further cardiovascular disease.<sup>8</sup>

For assessing early signs of subclinical atherosclerosis in obese children, we investigated CIMT as a surrogate marker of atherosclerosis in obese children and accordingly a significant difference between CIMT in obese children was found being higher in comparison to nonobese children of similar age and sex which was in accordance with other studies, whereas Tounian et al did not observe any difference. <sup>17-21,22</sup>

The mean CIMT values in our control children and obese children were 0.38 mm and 0.47 mm respectively. Simsek et al reported values for mean CIMT in control and obese children 0.35 mm and 0.52 mm respectively. The et al reported that the values for mean CIMT was significantly increased (0.62 mm vs. 0.46 mm) in obese and non obese children. Hacihamdioglu et al reported that the obese children had significantly higher mean CIMT than did the controls (0.49 mm versus 0.40 mm). Also, the current study found a significant difference between obese children with and without metabolic syndrome as regard CIMT. This is in accordance to the results of Huang et al. However, Fang et al reported no significant difference.

Moreover, in agreement with our results Pacifico et al found that obese children with fatty liver had significantly increased CIMT than obese children without liver involvement and stated that non alcoholic fatty liver disease (NAFLD) is strongly associated with carotid atherosclerosis even in childhood.<sup>24</sup> On the contrary, Manco et al found no association between CIMT and NAFLD in children and adolescents.<sup>25</sup>

Ezzat et al detected fatty liver in 65.3% among overweight/obese children and stated that NAFLD is a health problem affecting Egyptian community. The size of this problem is not well determined. The disease is so dangerous because it is what the National Institutes of Health refers to as a "silent disease". This is in accordance to the results of our study in which fatty liver was detected in 67.5% among obese children. Also, Shi et al, found that among all the obese children, the prevalence of fatty liver was 65.9%. 27

In a systematic review of the literature held by Friend et al found that the median prevalence of metabolic syndrome (MS) in obese populations was 29.2% (range 10%-66%).<sup>28</sup> This finding is consistent with the present study, which reported that prevalence of metabolic syndrome among obese children was 25%. Moreover, many studies concluded nearly similar results: Shi et al (24.7%), Gupta et al (28%) and Guijarro de Armas et al (19.6%).<sup>27,29,30</sup>

Many studies have reported that CIMT is associated with obesity related risk factors including the BMI, hypertension dyslipidemia and insulin resistance. 19,31,33 Nearly similar findings were detected in the present study, which showed significant correlations between CIMT and BMI, waist circumference measurement, DBP, HDL-C, fasting insulin, HOMA-IR, QUICKI and fatty liver.

Moreover, multiple linear regression analysis revealed a significant correlation between IMT and diastolic BP. This finding was in agreement with the finding of Elkiran et al who stated that diastolic BP had more of a contribution to early atherosclerosis. <sup>19</sup>

Insulin resistance is a common phenomenon and plays an important role in the cardio-cerebrovascular disease in obese population.<sup>34</sup> In our study, obesity and insulin resistance were found to have a close association with CIMT, by the observation of a significant association between CIMT and BMI, (r=0.404, p=0.10), fasting insulin (r=0.388, p=0.013), HOMA-IR (r=0.384, p=0.014) and QUICKI (r=-0.348, p=0.02). However, fasting blood glucose was not related. This information demonstrates that an increased insulin levels seem to be an earlier predictor for atherogenic changes than hyperglycemia and is consistent with data published by Atabek et al and Fang et al. <sup>17,35</sup>

In their observational longitudinal study, Ferreira et al, (36) found a relation between central fat accumulation and future carotid atherosclerosis in adolescents and concluded that atherosclerotic events could be avoided by

preventing abdominal obesity. Similarly we found a statistically significant correlation between CIMT and waist circumference measurement in univariate analysis in obese group. In accordance to our results, Elkiran et al, showed that waist circumference measurement is more important than BMI for prediction of early atherosclerosis. <sup>19</sup>

#### **CONCLUSION**

The present study supports the nation that there is clustering of various cardiovascular risk factors in obese children, namely hypertension, dyslipidemia, insulin resistance and evidence of subclinical atherosclerosis by increased CIMT. Moreover, CIMT is increased in the presence of MS or NAFLD

Thus interventions to reduce body weight, dyslipidemia, insulin resistance and hypertension may be effective in obese children, as primary cardiovascular events prevention, to avoid translation of these risk factors into subsequent cardiovascular events.

This study showed that diastolic BP had more of a contribution to early atherosclerosis

Our study suggests that waist circumference is a useful clinical predictor of central obesity and its associated cardiovascular complications. Measurement of waist circumference is suggested for all pediatric studies evaluating cardiovascular and metabolic risk factors in obese children.

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