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Original Article (Pages: 15945-15956)

Carotid Intima-Media Thickness in Children with Overweight/Obesity: A Single-center Study

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Abstract

Our study aimed to assess Carotid artery Intima-Media Thickness (CIMT) in a group of children with overweight/obesity as a good predictor for atherosclerosis.

We included 39 prepubertal children with Body Mass Indexes (BMI) above 85% for age and sex; 23% overweight, and 77% obese. Twenty matched non-obese healthy children were enrolled to compare CIMT results. About 44% of the cases had abnormal blood pressure, ~39% had dyslipidemia, and ~74% had an unhealthy metabolic state.

We observed higher CIMT in cases than controls, with no significant difference between overweight and obese status (at a confidence interval of 95% and $P < 0.05$). CIMT was positively associated with the BMI of the whole study group, and with HC and triglyceride in the children with obesity. CIMT was significantly higher among children with overweight/obesity than in average weight children, regardless of their metabolic status or blood pressure stage.

Key Words: Anthropometric Measures, Blood Pressure Stages, Carotid Artery Intima-Media Thickness, Metabolic Status, Obesity, Overweight, Pediatrics.

* Please cite this article as: Fouad HM, Shalaby SA, kamal M, Thabet MM, Shalaby SA, Khalifa I. Carotid Intima-Media Thickness in Children with Overweight/Obesity: A Single-center Study. Int J Pediatr 2022; 10 (5):15945-15956. DOI: **10.22038/ijp.2022.63367.4830**

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Received date: Jan.30,2022; Accepted date:Mar.07,2022

1- INTRODUCTION

Childhood obesity has reached an alarming level in both underprivileged and developed countries. Its rate increased markedly among children between 5-19 years of age, to reach about 18% in 2016, with similar distribution among genders (1).

In Egypt, a large study reported obesity in 15% of school-age children (2)**.** The underlying problem is mainly the excessive fat deposition that may negatively affect health, either during childhood or later adulthood. Its development's exact mechanism is not precise, but a disturbed balance between caloric consumption and expenditure has a significant contribution (3).

Obesity can impair child health via a variable decrease in physical fitness, social well-being, self-esteem, and overall poor life quality. Besides, obesity is considered a risk for many medical complications, including cardiovascular disease, type 2 diabetes, insulin resistance, metabolic syndrome, musculoskeletal disorders, fatty liver, and pulmonary disorders[3]**.** Obesity in adolescents is a significant risk factor for adulthood obesity (4)**.**

Coronary heart diseases as a complication of obesity were observed previously in adults only. In association with the obesity epidemic in the last decades, an increased fatty deposition with the development of atherosclerosis is observed in children (5)**.** Atherosclerosis in cases with obesity was linked to multiple factors, such as inflammation (6)**,** dyslipidemia, insulin resistance, and hypertension (7)**.**

The use of Carotid artery Intima-Media Thickness (CIMT) was found to be a good predictor for the development of atherosclerosis in long-term follow-up studies on at-risk groups of children (7, 8)**.**

2- MATERIALS AND METHODS

2-1. Objectives of the study

This study aimed to assess the CIMT in a group of children with overweight/obesity and to compare it with age- & sex-matched lean children; and to test the association between CIMT and characteristics of children with overweight/obesity.

2-2. Patients

We conducted a cross-sectional study (including a control group for Doppler measures) at the outpatient clinic of a university hospital. We included 39 children with overweight/obesity as cases and 20 controls to test for ultrasound measures. Recruitment started from December 2019 to December 2020, with considerations of the hospital's protocols of the medical services due to the COVID-19 SARS pandemic.

2-3. Measurements

All enrolled children with overweight /obesity underwent:

2-3-1. A thorough History taking: We emphasized the average birth weight, demographic data, the history of medical conditions, drug history, and family history of obesity.

2-3-2. Clinical examinations

Blood pressure was measured using a standardized mercury sphygmomanometer**.** Blood pressure percentiles were calculated online at the Canadian Pediatric endocrine group (11), using definition of hypertension provided by the American Academy of Pediatrics - Clinical Practice Guidelines for Management of Hypertension in Children and Adolescents**.** We examined the patients' skin for the detection of acanthosis nigricans and xanthomas.

2-3-3. **Anthropometric measurements:** we used a stadiometer with a weight scale to measure weight and height while the

patient is standing in light clothes, without shoes (12)**.** We calculated BMI by dividing the weight in kilograms by the square of height in meters. Overweight was considered as the BMI >85th and <95th percentile, and obesity as the BMI >95th percentile, for age and sex (13)**.** We measured Waist Circumference (WC), Hip Circumference (HC), and Mid-Upper Arm Circumference (MUAC) using an elastic tape around the same anatomical site. We plotted the HC percentiles individually (14)**.** Waist/hip ratio was calculated as WC (cm)/HC (cm), and waist/height ratio as WC (cm)/ Ht (cm). The Z scores for weight, height, BMI, WC, waist/height percentiles were calculated online (11)**.**

2-3-4. Doppler examination: CIMT was assessed while the child was lying down, the head slightly tilted to the other side of the test, and shoulders elevated to stretch the neck. The left and the right common carotid arteries were examined 1 cm before the carotid bulb for 1 cm length (7)**,** and their mean was obtained**.** The same radiologist performed the color Doppler examination for all children using Toshiba aplio 400, with a linear PLT-704SBT probe.

2-3-5. Laboratory tests: We obtained a blood sample of 9 ml after 12 hours of fasting to test for Fasting blood sugar (normal range up to 100 mg/dL), Alanine aminotransferase (ALT) (normal range up to 38 mg/dL) and Aspartate aminotransferase (AST) (normal range up to 38 mg/dL). Also, Lipid profile, including Total cholesterol (normal values up to 200 mg/dL), high-density lipoprotein-cholesterol (normal values > 40 mg/dL), low-density lipoprotein (LDL) (normal values up to 130 mg/dL, and normal range less than 130 mg/dl), and Triglycerides (TG) (normal range up to 150 mg/dl). We defined dyslipidemia at the TG levels>150 mg/dL and/or HDL-c <40 mg/dL.

2-3-6. Associated comorbidities: We recorded comorbidities like hypertension, dyslipidemia, acanthosis nigricans, and unhealthy metabolic status. We used the following criteria for defining the healthy metabolic state: BMI >+2 SD on CDC growth references and HDL-c >40 mg/dl, TG level <150 mg/dl, both systolic & diastolic blood pressure <90th corresponding percentile, and FBS <100 mg/dl. Otherwise, they were considered metabolically unhealthy (15)**.**

The control group was subjected to weight & height measurements, BMI calculation, and CIMT measurement.

2-4. Inclusion and Exclusion Criteria

Recruitment criteria for cases were the ages of 3-14 years, and BMIs above 85% for age and sex, plotted on the CDC growth charts (9) of both genders. Only the prepubertal children were enrolled to exclude the confounding effect of pubertal hormones (10).

The exclusion criteria were causes of secondary obesity, e.g., syndromes, endocrine disorders, systemic diseases, medications- causing obesity, or conditions, or medications that may alter blood pressure, lipid, or glucose levels. The control group was healthy average-weight children with sex and age ranges matched to those of the cases, referred to the hospital accompanying their parents.

2-5. Data analysis

Data was collected and tabulated. Statistical Package for Social Science (SPSS, Chicago, IL 60606-6412) program version 17 was used for data analysis. We used mean $\pm$ standard deviation or median (interquartile range) to describe continuous measurements and frequency (percentage) to represent categorical or nominal data. Comparisons of measurements were made using the student's T-test, the Mann-Whitney test, and the Chi-Square test according to the data type. We used

Pearson correlations to test the linear association of CIMT with the anthropometric and laboratory results. Boxplots were used to present the difference in CIMT between the cases and controls. P-value was considered significant at <0.05.

3- RESULTS

Enrolled cases were 39 children; 9 (23.1%) overweight, 30 (76.9%) with obesity, and 20 children as controls. The control group was comparable to cases regarding age and gender. Weight indices and BMI indices were significantly higher in cases than in controls (**Table 1)**. None of the enrolled children received antihypertensive or long-term medications. They all had an average birth weight, and 15 (38.5%) cases stated that they had a brother or sister with obesity.

Table-1: Demographic and anthropometric data of the cases and controls

	Variable	Controls (N=20)	Cases (N=39)	P-value
Sex; N (%)	Male	11 (55)	17 (43.6)	0.4
	Female	9 (45)	22 (56.4)	
Age in years	mean + SD	9.6 + 1.6	8.9 + 2.3	0.2
	Min-max	7-12	4.75-13.75	
Weight in Kg; mean + SD		30.8 + 5.6	46.5 + 16.4	0.000*
Weight percentile; mean + SD		45.7 + 7.4	94.7 + 6.2	0.000*
Weight Z score: median (IQR)		-0.1 (0.2)	1.8 (0.8)	0.000*
Height in cm; mean + SD		137.4 + 8.6	134.7 + 13.3	0.4
Height percentile; mean + SD		57.6 + 8.8	61.3 + 22.6	0.5
Height Z score: median (IQR)		0.2 (0.2)	0.3 (1)	0.8
BMI; mean + SD		16.1 + 1.1	25 + 5.3	0.000*
BMI percentile; mean + SD		40 + 11.5	96.4 + 3.6	0.000*
BMI Z score: median (IQR)		-0.2 (0.6)	2 (0.9)	0.000*

BMI: body mass index, IQR: interquartile range. P is considered significant at < 0.05*.

Among cases, elevated blood pressure was observed in ~28% and stage I hypertension in ~15%. Most children with obesity had unhealthy metabolic status ~ 74%. The characteristics and complications observed in cases are shown in **Table 2.** One child with obesity showed acanthosis, and another showed xanthoma. There was no clinically detected hepatomegaly.

Cases with overweight were comparable to those with obesity regarding age, gender, anthropometric measures, laboratory results, dyslipidemia, and CIMT. Children with obesity had significantly higher diastolic blood pressure percentiles (87.1 $\pm$ 5.9 vs. 76.9 $\pm$ 9.6; P: 0.000), and significantly more common abnormal blood pressure (elevated or stage I hypertension) than in children with overweight.

CIMT range was0.2-0.3 mm in controls, and 0.3-0.7 mm in cases, and was significantly higher in cases than in controls (0.4 $\pm$ 0.08 vs 0.2 $\pm$ 0.04, P=0.000) (**Fig. 1)**. CIMT showed a positive linear association with BMI (r: 0.6; P: 0.000), BMI percentile (r: 0.8; P=0.000), and BMI Z score (r=0.7; P=0.000) of the whole enrolled children (N=59).

In cases, CIMT showed positive correlations with hip circumference and triglycerides (**Fig. 2).** No correlation was observed between CIMT and the

demographic data, blood pressure indices, other anthropometric measures, or other laboratory results. CIMT was significantly higher in males than in females (0.5±0.09 vs. 04±0.06; P=0.005), in cases with low HDL than in those with normal HDL (0.5±0.09 vs. 0.4±0.07; P=0.04), in cases with high triglycerides (0.5±0.09, vs. 0.4±0.07; P=0.009), and dyslipidemia (0.5±0.08 vs. 0.4±0.07; P=0.03)**.**

Table-2: Characteristics of the cases and observed abnormal values (N=39)

Variable	Values (Mean + SD)	Abnormal values N (%)
Systolic blood pressure	110 + 4.8	Blood pressure Elevated: 11 (28.2) Stage 1: 6 (15.4)
Systolic blood pressure percentile	85.8 + 9.8	
Diastolic blood pressure	70.5 + 3.6	
Diastolic blood pressure percentile	84.7 + 8	
Waist circumference in cm	80.8 +14.2	> 90th percentile: 32 (82.1)
Waist circumference percentile	90.8+17.1	
Waist circumference Z score	1.7 + 0.8	
Hip circumference in cm	89.5 + 12.9	-
Waist/height ratio	0.6 + 0.08	-
Waist/height ratio percentile	89.4 + 19	
Waist/height ratio Z score	1.7 + 0.9	
Waist/hip ratio	0.9 + 0.1	-
Mid-upper arm circumference	28.2 + 3.7	-
Cholesterol	172.6 + 30.1	Elevated: 6 (10.4)
HDL mg/dL	44.3 + 6.5	Low: 13 (33.3)
LDL mg/dL	100.6 + 27	Elevated: 5 (12.8)
TG mg/dL	126.97 + 53.9	Elevated: 9 (23.1)
Dyslipidemia		15 (38.5)
FBG mg/dL	94.4+15.7	Elevated: 10 (25.6)
ALT mg/dL	23.5 + 6.4	Elevated: 0
AST mg/dL	24.9 + 7.1	Elevated: 3 (7.7)
Metabolic status among children with obesity (N=30)		Unhealthy: 29 (74.4)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, FBG: fasting blood glucose, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides.

Children with obesity were classified and compared according to their metabolic status. Children with unhealthy metabolic status were comparable to those with healthy metabolic status regarding age (P=0.3), gender (P=0.3), and CIMT (0.4±0.09 vs. 0.4±0.06; P=0.9). Cases with unhealthy metabolic status had significantly higher ALT and AST than the metabolically healthy obese group (P=0.02).

Abnormal blood pressure cases (elevated or stage I hypertensive) had significantly higher BMI, WC, waist/height ratio, and indices than normotensive children. Also, cases with abnormal blood pressure showed lower HDL values with a near significant level. CIMT was comparable between the two groups **(Table 3).**

Table-3: Comparison between the normotensive children and those with abnormal blood pressure (elevated or stage I hypertensive) (N=39)

Variable		Normotensive (N=22)	Abnormal blood pressure (N=17)	P-value
Sex; N (%)	Male	8 (36.4)	9 (52.9)	0.3
	Female	14 (63.6)	8 (47.1)	
Age		9.4 + 2.2	8.3 + 2.4	0.2
Weight percentile		92.8 + 7.2	97.2 + 3.6	0.02*
Weight Z score		1.7 + 0.6	2.4 + 0.9	0.02*
BMI		23.4 + 3.9	27.1 + 6.3	0.03*
BMI percentile		95.1 + 3.8	98.2 + 2.7	0.006*
BMI Z score		1.8 + 0.5	2.5 + 1.2	0.03*
Waist circumference in cm		76.6 + 12.7	86.4 + 14.6	0.04*
Waist circumference percentile		85.7 + 21.4	97.3 + 3.3	0.03*
Waist circumference Z score		1.3 + 0.8	2.2 + 0.5	0.000*
Waist/height ratio		0.6 + 0.06	0.7 + 0.1	0.000*
Waist/height ratio percentile		83.3 + 23.6	97.3 + 3.8	0.02*
Waist/height ratio Z score		1.2 + 0.9	2.2 + 0.6	0.000*
High-density lipoprotein mg/dL		46.1 + 6.7	42.1 + 5.7	0.05
Carotid intima-media thickness in mm		0.4 + 0.06	0.4 + 0.1	0.9

Data are shown as mean±SD unless those described otherwise. P is considered significant at < 0.05*.

4- DISCUSSION

Enrolled cases were 39 children; 9 (23.1%) overweight, 30 (76.9%) with obesity, and 20 comparable age and gender children as controls; they were all prepubertal. Our study group with obesity had abnormal blood pressure in ~44%, dyslipidemia in ~39%, and an unhealthy metabolic state in ~74%.

We observed a significantly higher CIMT in cases than in controls (**Fig. 1**), with no significant difference between children with overweight and those with obesity. Similarly, Önal et al. (16) reported statistically higher median CIMT in children with obesity than in the average-weight children aged 6-15 years among a sample of 200 children. The children with obesity also showed high lipid profiles unlike the controls. They concluded that the high CIMT, which is obesity-induced, is the cornerstone of the pre-atherosclerotic changes later in life. Besides, Al-Shorman et al. (17) reported similar findings in their study of 125 school children (60 lean & 65 obese) aged 10-15 years. Their obese participants exhibited greater CIMT than normal-weight students. They concluded that obesity in school children is associated with greater CIMT and other cardiovascular risk factors. Other pediatric reports observed higher CIMT in children with obesity in comparison to lean children (8, 18, 19), while others did not observe the significant difference (20).

From our results, CIMT correlated positively with BMI and its indices in the whole studied group (N=59), but not in cases when tested separately. In cases, CIMT positively correlated with HC values but not with other anthropometric measures. Associations between CIMT and BMI (16, 17), HC, and WC (17) were previously reported. Using univariate analysis, WC was declared to be the most sensitive anthropometric measure in predicting greater CIMT (17,18). Also,

high WC was positively correlated with risk factors of atherosclerosis, i.e., dyslipidemia and hypertension. WC was considered a valuable predictor of asymptomatic atherosclerosis in school children (21).

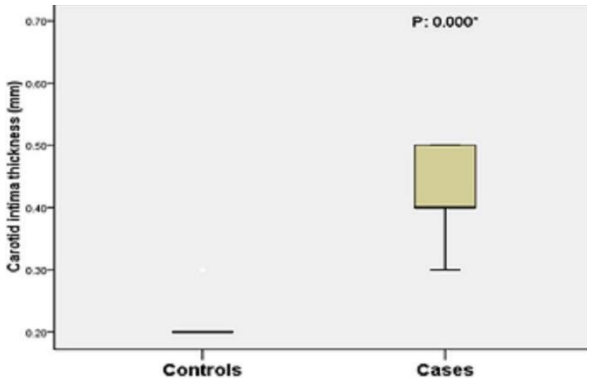
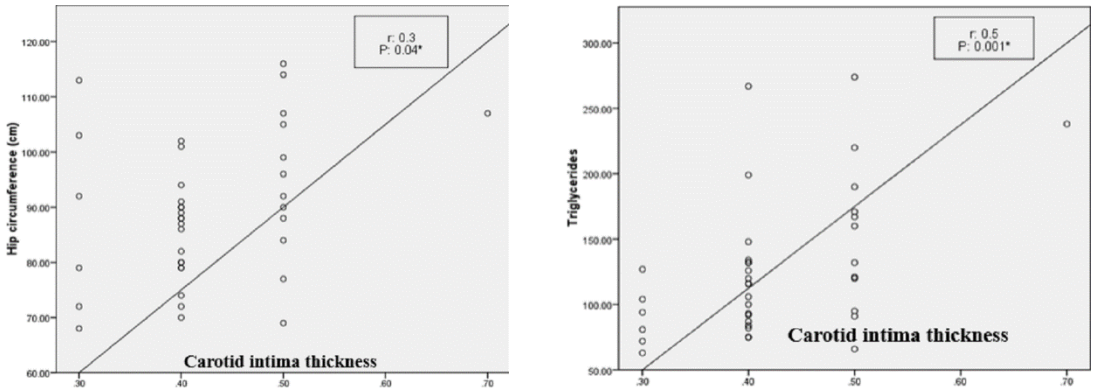


Fig. 1: Carotid intima-media thickness in the cases and controls.



(A) **(B)**

Fig. 2: Correlations between hip circumference, triglycerides, and carotid intima thickness in children with overweight/obesity

The CIMT of our cases showed positive correlations with triglycerides, and it was significantly higher in cases with low HDL, high triglycerides, and dyslipidemia. Similarly, Önal et al. (16) reported a positive association between the CIMT and lipid levels in both children with obesity and the control group. Contrary to their results, Sönmez et al. (18) did not observe any relation between CIMT and laboratory findings, including lipid profile.

No correlation was observed between CIMT and neither systolic/diastolic blood pressure nor their percentiles in our cases. CIMT measures showed no significant difference between normotensive cases and those with abnormal blood pressure. Unlike our findings, Day et al. (22), in their systematic review, reported a positive correlation between CMIT and blood pressure in children aged 0-19 years after adjustment for other cardiovascular risk factors. Previous studies describe an excellent association between obesity and hypertension in children (23). Sönmez et al. (18) observed an independent association between CIMT SD and high 24-hour systolic pressure SD in their multivariate regression analysis.

Interestingly, office reading did not achieve a significant association (most of their patients were on antihypertensive medications).

Though our children with obesity had significantly higher CIMT than controls, no difference was observed between children with unhealthy metabolic status and those with healthy metabolic status. It seems that being metabolically healthy or not does not exclude cardiovascular risk. Consistent with our findings, some pediatric studies have reported significantly greater CIMT in all children with obesity, regardless of the metabolic aberrations, than in average-weight children (8, 19). They have concluded that greater CIMT as a marker of cardiovascular disease is like obesity at any metabolic state. Even children with a healthy metabolic state are still at risk of early-age cardiovascular affection. In contrast, others have reported significantly higher CIMT values in children with an unhealthy status more than in those with healthy status (24, 25), some without statistical significance (18).

The complications among our group were frequently observed. About ~44% had abnormal blood pressure, ~28% had elevated blood pressure, and ~15% stage 1 hypertension. Abnormal blood pressure was more common in children with obesity than in those with overweight. None of the studied children was on regular use of antihypertensive. Cases with abnormal blood pressure were comparable to normotensive children regarding age and gender. We observed significantly higher BMI, WC, waist/height ratio, and indices in cases with abnormal blood pressure than in normotensive children. Also, lower HDL values were observed with a near significant level in cases with abnormal blood pressure. Sönmez et al. (18) studied 53 children with obesity aged 10-18 years, and 20 healthy control groups were reported to have similar hypertension frequencies. They reported hypertension in 57% of their studied obese group, with significantly higher WC SD in the hypertension cases than normotensive. Unlike our results, they found comparable results regarding age, gender, weight SD, height SD, BMI SD, and lipid profile between the two groups.

We used the definition of Damanhoury et al. (15) for metabolically healthy children, which is the first internationally consensus-based guidance. We observed a healthy metabolic status in ~26% of our studied children with obesity. The healthy metabolic state in children with obesity is defined as the state of having excess fat deposition but still regarded as enjoying a favorable metabolic profile, i.e., preserved insulin sensitivity, normal blood pressure, glucose regulation, lipids, liver enzymes, and absence of hepatic steatosis. They are less prone to developing metabolic disturbances (15, 26). A similar prevalence of healthy metabolic status was reported in previous pediatric studies (27, 30). Our rate is less than that observed by Reinehr et al. (31), who reported healthy status in 49% of their German children participants. The rates of the healthy metabolic status in children with obesity/overweight varied from 3 to 87%, and from 7 to 21% in children of all weights. The wide variability is related to the differences in age including the pubertal stage, race, social class, environmental factors, and the definition used (30, 32).

About 74% of our studied children with obesity were metabolically unhealthy. The metabolic derangement early in life critically determines the prognosis of children with obesity. Higher rates of metabolic abnormalities in children with obesity have a prospect of a shorter lifespan than their peers (33).

This high rate of metabolic abnormalities in our studied prepubertal children is contrary to the suggested role of puberty in metabolic abnormalities. Previous studies

have hypothesed that puberty with the influx of sex hormones is the leading risk for the development of unhealthy metabolic status (31). Besides, puberty was associated with a decline in insulin sensitivity and transforming from a healthy state to an unhealthy state (28, 31).

Our studied prepubertal children with healthy & unhealthy metabolic status were statistically comparable regarding age and gender, though female-gender was more common in the healthy group. Similarly, some previous studies have reported similar ages between the two groups[18], though some researchers have reported the healthy metabolic status preponderance in girls[34]. And in some other studies, unlike ours, healthy metabolic status was observed more commonly in boys (30, 35) and younger ages (34, 36).

Our studied children with healthy & unhealthy metabolic status were statistically comparable regarding all anthropometric measures, blood pressure stages. Similarly, Sönmez et al. (18) reported no differences regarding most anthropometries between cases with metabolic syndrome and those without metabolic syndrome. They observed slightly lower WC in metabolically healthy cases. Regarding blood pressure, they observed significantly higher 24-hour SBP-SDS among cases with an unhealthy metabolic state. Previous reports highlighted that lower WC measurements and lower BMI-SD were predictors of healthy metabolic conditions in children with obesity/overweight (34, 36).

5- CONCLUSION

The CIMT was significantly higher among children with overweight/obesity in our studied prepubertal children than among those with average weights, with no difference between overweight and obese cases. This significant difference was observed regardless of the metabolic status of the participants, i.e., high CMIT was constantly observed in metabolically healthy and unhealthy children with obesity. Our findings denote the presence of a cardiovascular risk regardless of the metabolic status of children with obesity. CIMT was positively associated with the BMI of the whole study group, including children with normal and high BMIs. Furthermore, CIMT was positively associated with HC and triglyceride in children with obesity.

In general, to the best of our knowledge, this study is the first of its kind among Egyptian children; The findings reflecting the increased likelihood of cardiovascular diseases in children with obesity regardless of having metabolic disturbances would change the follow-up and management, solely, based on the metabolic status.

6- LIMITATIONS OF THE STUDY

Our limitations included the absence of data regarding the duration of obesity. No anthropometry was kept by the families denoting the start of having high BMI. We only know they have an average birth weight.

7- ETHICAL CONSIDERATIONS

The protocol of the present non-funded research was approved by the research ethics committee of the faculty of Medicine, Helwan University, Cairo, Egypt. All participants were enrolled after obtaining written informed consent from one of their parents.

8- CONFLICT OF INTEREST

None.

9- REFERENCE

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