Original Research

Blood Pressure and Carotid Artery Intima-Media Thickness in Children and Adolescents: The Role of Obesity

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Introduction: The measurement of carotid artery intima-media thickness in children and adolescents has attracted a great deal of research and clinical interest in recent years, because it can provide evidence that early arterial lesions are already present in asymptomatic subjects who have risk factors for cardiovascular disease. The aim of the present study was to investigate possible correlations between parameters of 24-hour ambulatory blood pressure monitoring (ABPM) and carotid artery intima-media thickness in obese and non-obese children and adolescents.

Methods: We studied 128 children and adolescents who were referred for investigation for possible hypertension. All participants in the study underwent ABPM and ultrasound measurement of the intima-media thickness of the common and internal carotid arteries. Obesity was defined as a body mass index (BMI) ≥ the 95th percentile for age and sex.

Results: Carotid artery intima-media thickness was significantly greater in obese than in non-obese children and adolescents. Linear correlations were observed between common and internal carotid artery intima-media thickness and the BMI percentile, the BMI z score, and parameters from ABPM. Multifactorial analysis of covariance showed that obesity and age were correlated with mean carotid artery intima-media thickness, independently of sex and values of clinic blood pressure and ABPM.

Conclusions: Obese children and adolescents have greater carotid artery intima-media thickness than non-obese subjects, independently of blood pressure. These findings suggest a possible role for childhood obesity in the early onset of carotid artery atherosclerosis.

B-mode echo is a widely accepted, non-invasive, safe and economic method for measuring the intima-media thickness (IMT) of the carotid arteries.[1] An increase in carotid artery IMT in adults is considered to reflect early atherosclerosis and is a predictor of cardiovascular morbidity and mortality.[2] IMT increases in response to haemodynamic load from the embryonic stage onward,[3] while during childhood and adolescent life IMT increases progressively and is correlated with an increase in blood pressure (BP) and age.[2,4] It is noteworthy that IMT is correlated with BP even for normal values. The range of the physiological adaptation (normal increase in IMT in response to an enlarged arterial lumen resulting from an increase in BP) and of the pathological response to haemodynamic load is determined by metabolic and genetic factors.[3]

The measurement of carotid IMT in children and adolescents has attracted a great deal of research and clinical interest, because it can provide evidence that early arterial lesions are already present in asymptomatic subjects who have risk factors for cardiovascular disease.[5] The Bogalusa Heart Study reported that, in young people aged 20-38 years, carotid IMT increased with the number of risk factors.[6] Sass et al measured carotid IMT in healthy children, adolescents and adults, and determined that IMT values were independent of sex up to the age of 18 years.[7] In addition, Jourdan et al measured common carotid IMT in healthy adolescents.[4] The results of these studies provided normal reference values for IMT in children and adolescents.

In the present study we examined possible correlations between carotid artery IMT and clinic and 24-hour BP measurements in obese and non-obese children and adolescents. We also studied the parameters that might influence carotid IMT and variables that could have an independent effect.

Methods

Patients

The study population consisted of children and adolescents who were referred to their paediatrician for investigation of possible hypertension, having exhibited clinic BP above the 95th percentile for their age, sex and height on more than 3 different visits. Children with evidence of clinical or laboratory secondary hypertension, and those who were receiving lipid-lowering or antihypertensive medication, or drugs that increase BP, were not included in the study.[8]

Body mass index (BMI) was calculated using the standard formula.[9] Obesity was defined as a BMI ≥ the 95th percentile for age and sex. The BMI z score was calculated using Cole's LMS method.[10]

The children and their parents were informed about the research protocol and gave their consent to participation in the study. The scientific and ethics committees of the "P & A Kyriakou" hospital, Athens, approved the research protocol.

BP measurements

Clinic BP was measured 3 times, at 1-minute intervals, using a mercury sphygmomanometer. Before the BP measurements, the study participants remained seated at rest for 5 minutes. During the measurements they were seated, with their back supported, feet on the floor, and their arm in a relaxed position at the level of the heart. A proper sized cuff, according to age and arm size, was used for the precise measurement of BP. Clinic BP was calculated as the mean of the 3 measurements. Hypertension was defined as a clinic BP ≥ the 95th percentile for age, sex and height.[11]

All participants in the study underwent 24-hour ambulatory BP monitoring (ABPM) during a normal day, using a Spacelabs 90217 ambulatory BP monitor (Spacelabs Inc., Redmond WA, USA). A proper sized cuff, according to the subject's age and arm size, was placed on the non-dominant arm. BP measurements were recorded automatically, every 15-20 minutes during the day and every 20-30 minutes during the night. The study participants and their parents were informed about the function of the device and were instructed to sleep from 00:00 to 06:00 hours (nighttime) and to perform daily activities between 08:00 and 22:00 (daytime). Hypertension based on ABPM was defined as a mean systolic and/or diastolic BP, during the 24 hours, daytime, or nighttime, ≥ the 95th percentile for sex and height.[12] The daytime BP index was calculated as mean daytime BP divided by the 95th percentile value for sex and height.[13]

Carotid artery ultrasonography

The examination was performed using a high-resolution echo-Doppler device with a 7 MHz linear transducer. All participants in the study were examined in the supine position, with the head overextended and turned 45° away from the examined side. Both carotid arteries were visualised longitudinally, so that the IMT of their distal wall was apparent.[1,14] The best images of the distal wall were used to calculate the IMT of the common and internal carotid arteries. The value of the IMT was defined as the mean value of measurements between the right and left carotid arteries, calculated from 10 measurements on each side, 10 mm from the bifurcation of the common carotids.

Statistical analysis

The SPSS software package (SPSS Inc., Chicago IL, USA) was used for the statistical analysis. The t-test was used to examine differences between obese and non-obese children and adolescents. The Levene test for equality of variances of the mean values of the study parameters was used to examine the normal distribution of parameters in the groups. Correlations between parameters were evaluated with Pearson's test. Multifactorial analysis of covariance (ANCONA) was used for the study of independent correlations between carotid IMT and parameters such as obesity, sex, age, and BP values. A p-value <0.5 was considered statistically significant.

Results

A total of 128 children and adolescents aged 10-19 years were enrolled in the study. Of these, 50 were obese and 78 non-obese; the 2 groups were similar as regards age, sex and height. The baseline demographic data are given in Table 1. Table 2 shows the clinic BP values and the ABPM parameters (mean ± standard deviation).

The obese group had a significantly greater mean common carotid IMT than the non-obese group ($p<0.001$). The same finding applied to the internal carotid artery (Figure 1).

Table 1. Demographic characteristics of the study population.

	Non-obese (N=78)	Obese (N=50)	p
Age (years)	13.7 ± 4.1	12.7 ± 4.0	0.24
Sex (male/female, %)	34.4/26.6	25.8/13.3	0.18
Body weight (kg)	63.6 ± 17.3	80.4 ± 29.2	0.000
Height percentile	66.3 ± 28.3	67.6 ± 28.0	0.72
Body mass index (kg/m^2)	22.1 ± 3.3	30.1 ± 6.0	0.000
Body mass index percentile	55.3 ± 28.3	96.4 ± 0.9	0.000

Systolic and diastolic clinic BP were positively correlated with the mean IMT of both the common and internal carotid arteries. Of the ABPM parameters, mean systolic BP and pulse pressure, for 24 hours, daytime and nighttime, were all positively correlated with the mean IMT of both the common and internal carotid arteries (Table 3). The mean IMT of the common carotid arteries was positively correlated with the BMI percentile ($r=0.29$, $p<0.01$) and the BMI z score ($r=0.31$, $p<0.01$). Similar results were found for the internal carotid arteries ($r=0.28$ and $r=0.33$, respectively, $p<0.01$). A linear increase in the common and internal carotid IMT was observed with the BMI percentile, the BMI z score, and the ABPM parameters (Figure 2).

Multifactorial analysis of covariance showed that obesity was correlated with the mean IMT of the common and internal carotid arteries, independently of parameters such as sex, and clinic and Holter BP values ($R^2=0.36$, $R^2=0.30$, respectively; Table 4). The mean values of IMT in the obese and non-obese groups were then calculated after correction for age, sex, clinic BP, and mean systolic and diastolic Holter BP. After these corrections the mean IMT of the common carotid arteries in the non-obese group was 0.43 mm (95% confidence interval, CI: 0.40–0.45), compared with 0.51 mm for the obese group (95% CI: 0.48–0.54). The difference between these corrected mean values (EMMEANS) for the 2 groups was statistically significant ($p<0.001$, after the Bonferroni correction for multiple comparisons.

Table 2. Clinic blood pressure and parameters from 24-hour ambulatory blood pressure monitoring in children and adolescents.

	Non-obese (N=78)	Obese (N=50)	p
Clinic SBP (mmHg)	120.2 ± 14.4	132.4 ± 18.6	0.000
Clinic DBP (mmHg)	74.9 ± 9.9	80.0 ± 11.6	0.001
Mean 24-hour SBP (mmHg)	116.6 ± 12.0	122.3 ± 13.2	0.002
Mean 24-hour DBP (mmHg)	68.7 ± 7.5	69.0 ± 8.7	0.80
Mean 24-hour heart rate (beats/min)	78.7 ± 10.6	83.5 ± 10.3	0.003
Mean 24-hour pulse pressure (mmHg)	47.9 ± 9.1	53.1 ± 9.0	0.000
Mean daytime SBP (mmHg)	118.8 ± 12.4	124.3 ± 12.7	0.005
Mean daytime DBP (mmHg)	70.9 ± 7.7	71.4 ± 7.9	0.69
Mean daytime heart rate (beats/min)	81.6 ± 11.2	87.1 ± 11.5	0.001
Mean daytime pulse pressure (mmHg)	47.8 ± 9.4	52.9 ± 8.9	0.000
Daytime SBP index	0.90 ± 0.08	0.95 ± 0.9	0.000
Daytime DBP index	0.85 ± 0.09	0.86 ± 0.09	0.54
Mean nighttime SBP (mmHg)	111.8 ± 12.7	117.1 ± 14.7	0.008
Mean nighttime DBP (mmHg)	63.7 ± 8.5	63.6 ± 11.5	0.91
Mean nighttime heart rate (beats/min)	71.9 ± 11.5	75.8 ± 10.0	0.02
Mean nighttime pulse pressure (mmHg)	48.0 ± 9.1	53.5 ± 9.9	0.000

DBP – diastolic blood pressure; SBP – systolic blood pressure.

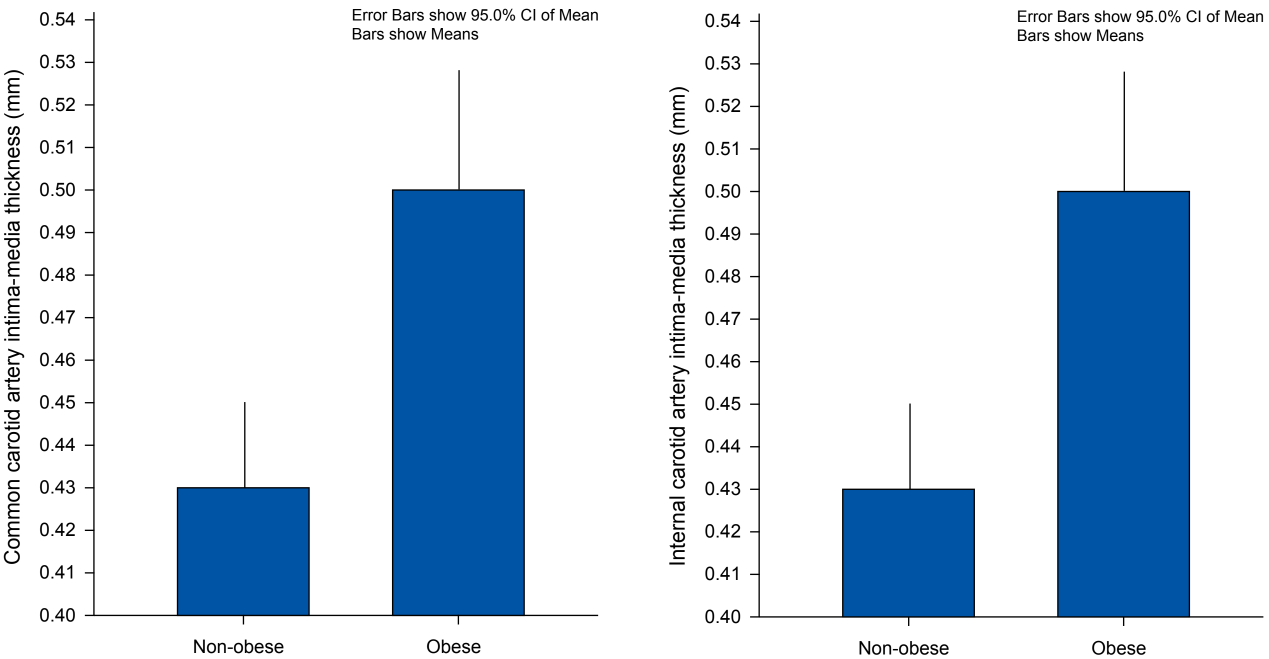

Figure 1. Carotid artery intima-media thickness in obese and non-obese children and adolescents.

Discussion

This study provides significant evidence for the presence of early vascular lesions in obese children and adolescents. Carotid artery IMT was positively correlated with age, BP values, and BMI percentile and z score, but only age and obesity were independent prognostic factors for carotid IMT. Studies in adults have shown that carotid artery IMT increases from the lowest to the highest BMI quartile.[15] Carotid IMT has been found to be significantly greater in obese individuals compared to those with normal weight, in groups of patients with similar age, sex and ABPM values, proving that obesity *per se* is a major risk factor for carotid artery atherosclerosis.

The role of systolic hypertension in cardiovascular morbidity and mortality has been described in many studies of adults.[16,17] Sorof et al showed that only elevated ABPM values were associated with left ventricular hypertrophy in hypertensive children.[13] In the present study, systolic ABPM values were correlated with carotid IMT, though diastolic values were not. In addition, the linear correlation between IMT and ABPM index shows that the severity of systolic

Table 3. Multifactorial Pearson correlation between blood pressure and carotid artery intima-media thickness.

	Common carotid IMT		Internal carotid IMT	
	r	p	r	p
Clinic SBP (mmHg)	0.41	0.000	0.33	0.000
Clinic DBP (mmHg)	0.32	0.000	0.30	0.001
Mean 24-hour SBP (mmHg)	0.29	0.001	0.23	0.007
Mean 24-hour DBP (mmHg)	0.07	0.43	0.07	0.43
Mean 24-hour pulse pressure (mmHg)	0.32	0.000	0.25	0.004
Mean daytime SBP (mmHg)	0.29	0.001	0.23	0.006
Mean daytime DBP (mmHg)	0.08	0.32	0.08	0.32
Mean daytime pulse pressure (mmHg)	0.31	0.000	0.24	0.005
Mean nighttime SBP (mmHg)	0.26	0.002	0.21	0.01
Mean nighttime DBP (mmHg)	0.05	0.58	0.05	0.51
Mean nighttime pulse pressure (mmHg)	0.32	0.000	0.25	0.004

IMT – intima-media thickness. Other abbreviations as in Table 2.

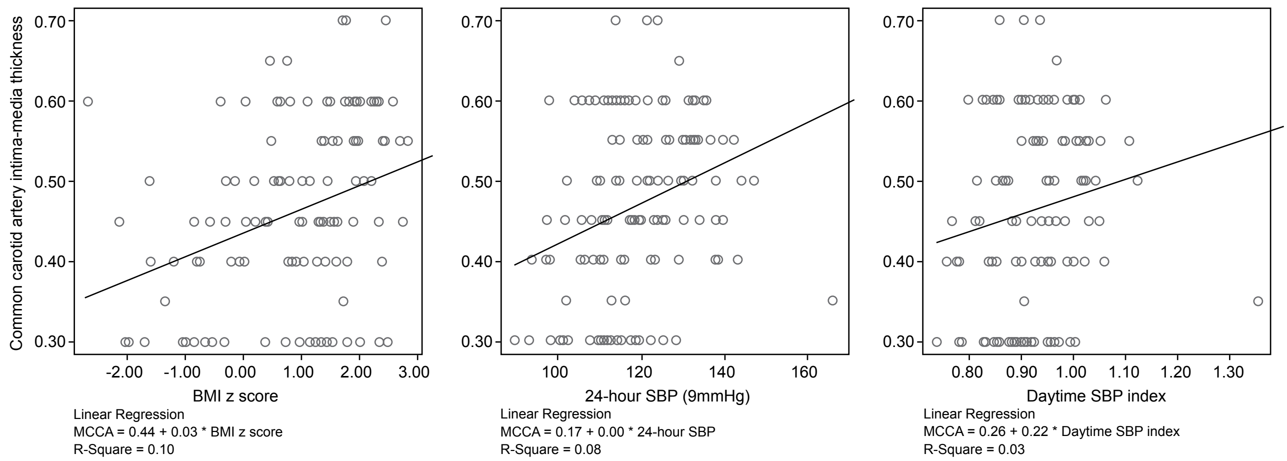

Figure 2. Linear correlations between common carotid artery intima-media thickness and body mass index z score, 24-hour systolic blood pressure, and 24-hour systolic blood pressure index.

hypertension may play a significant role in causing early vascular lesions. We found strong positive correlations between the ABPM pulse pressure and carotid IMT. Pulse pressure has been recognised as a significant prognostic factor for morbidity and mortality from coronary artery disease and stroke in adult populations.[18-20]

Most studies of children and adolescents have not succeeded in demonstrating an independent effect of obesity and hypertension to explain the increased carotid IMT. Given that children with primary hypertension are usually overweight or obese, a high BP and the metabolic consequences of obesity act synergistically and it is difficult to separate the effect of BP from the metabolic disturbances. Sorof et al measured carotid IMT in hypertensive children and adolescents and found that it was positively correlated with BMI and left ventricular mass index, but not with clinic BP values.[21] Litwin et al reported greater carotid IMT in hypertensive than in normotensive children. However, when they examined the carotid IMT in subgroups of their population they found no differences between obese normotensive and hypertensive children, suggesting that the coexistence of hypertension and obesity led to increased carotid IMT.[22] Lande et al compared hypertensive with normotensive children of the same age and BMI in order to correct for the effect of obesity in their population and found that hypertensive children had greater carotid IMT values.[23]

Functional disturbances of the vascular wall and endothelial dysfunction have been reported in children and adolescents.[24] Litwin et al reported increased carotid artery stiffness in hypertensive chil-

Table 4. Multifactorial analysis of covariance for the effect of age, sex, blood pressure and obesity on carotid artery intima-media thickness.

	Dependent variable[1,2]			
	Common carotid IMT (mm)		Internal carotid IMT (mm)	
Model	B (95% CI)	p	B (95% CI)	p
Intercept	0.252 (0.045–0.458)	0.01	0.302 (0.115–0.489)	0.002
Obesity (no-yes)	-0.082 (-0.126–0.039)	0.000	-0.083 (-0.122–0.044)	0.000
Age	0.007 (0.003–0.012)	0.001	0.007 (0.003–0.011)	0.002
Clinic SBP	0.001 (-0.001–0.002)	0.37	0.000 (-0.001–0.001)	0.95
Clinic DBP	0.001 (-0.001–0.003)	0.53	0.000 (-0.001–0.002)	0.65
Mean 24-hour SBP	0.002 (-0.001–0.004)	0.14	0.001 (-0.001–0.003)	0.89
Mean 24-hour DBP	-0.002 (-0.006–0.001)	0.20	0.000 (-0.003–0.003)	0.93

[1]Computed using alpha = 0.05. [2]Weighted least squares regression for sex. Abbreviations as in Tables 2 & 3.

dren, while Tounian et al demonstrated increased coronary artery stiffness in normotensive obese children.[22,25] Neither of these studies found differences between obese and non-obese children as regards carotid IMT. Aggoun et al[26] showed that obese prepubescent children had significantly reduced brachial artery flow-mediated vasodilation, impaired brachial artery nitroglycerine-mediated dilation, and systolic and diastolic hypertension on ABPM. However, obese children did not have greater carotid IMT compared to controls. These results show that in obese prepubescent children there are disturbances of vascular endothelial function that may represent the earliest stage in the atherosclerotic process. The long-term effect of obesity may lead to an increase in carotid IMT during adolescence.

In contrast to the above studies, Meyer et al and Pilz et al found increased carotid IMT in obese children aged 9-16 years.[27,28] As in the present study, the IMT of the common and internal carotid arteries was significantly greater in obese than in non-obese children and adolescents. The inconsistencies among the results of the above studies may be due to the populations examined. Age, the duration and degree of obesity, the coexistence of hypertension, the duration and severity of hypertension, the number of concomitant cardiovascular risk factors, physical exercise or a sedentary lifestyle, and a genetic predisposition to target organ lesions, could all have affected the results.[29] Future research should distinguish the role of the duration and degree of the above factors in the development of early atherosclerosis in children and adolescents.

Conclusions

The present study provides evidence that childhood obesity is a significant risk factor for the early appearance of hypertension and atherosclerotic changes in the carotid arteries. The prediction of atherosclerotic risk in obese children has acquired great clinical importance in recent years. Prospective studies aimed at the further investigation of the mechanisms causing vascular lesions in obese children and adolescents with hypertension and other cardiovascular risk factors will help improve their cardiovascular prognosis. In addition, the long-term follow up of children and adolescents with increased carotid IMT, so as to determine the boundary values of carotid IMT in childhood and adolescence that are associated with increased morbidity and mortality in adult life, will help improve cardiovascular risk stratification. Until then, carotid IMT and ABPM can be useful tools in clinical practice for the identification and monitoring of obese children and adolescents who are at high risk for future cardiovascular complications.

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