COMMON CAROTID INTIMA MEDIA THICKNESS IN OBESE CHILDREN BORN SMALL FOR GESTATIONAL AGE VERSUS APPROPRIATE FOR GESTATIONAL AGE

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ABSTRACT

The intima media thickness of the common carotid artery (CIMT) is a well-known marker of subclinical atherosclerosis. The "catch-up growth" phenomenon in children born small for gestational age (SGA) has been linked to early onset obesity with the subsequent emergence of metabolic syndrome (MetS).

Aim: to determine the association between being born SGA and CIMT, a measure of atherogenesis and to establish cut off values for CIMT in obese children.

Material and methods. A prospective study was carried out over a 1 year period (Jul 2012-June 2013). We analyzed 122 obese patients, 96 patients appropriate for gestational age (AGA) and 26 patients SGA. Both groups were matched for age, sex and BMI. CIMT was measured in all the patients. Using ROC curve, cut off values have been obtained for both groups.

Results. CIMT in obese children born SGA was significantly increased as compared with obese children born AGA similar age, sex and BMI ($p = 0.0035$). A CIMT cut off value of 0.049 cm has been obtained with a high sensitivity and specificity.

Conclusion. Being born SGA increases the atherogenic risk. CIMT is a well-known marker of subclinical atherosclerosis and is a noninvasive and inexpensive method for detecting development of subclinical atherosclerosis. Further population studies regarding reference values for CIMT in obese children born SGA and AGA are necessary.

Keywords: small for gestational age, obesity, intima media thickness of the common carotid artery

INTRODUCTION

The intima-media thickness (CIMT) of extracranial carotid arteries provides an index of atherosclerosis in other vascular regions (1,2,3,4,5) and has been shown to be associated with most risk factors for atherosclerosis. (6,7,8) Recently, an increased thickness of carotid IMT determined by B-mode ultrasound has been shown to be directly associated with an increased risk of myocardial infarction and stroke in older adults without a previous history of cardiovascular disease. (9) Thus, carotid artery IMT has been proposed as a risk factor that may be included in the algorithms for cardiovascular risk assessment. (9)

CIMT is widely used as a surrogate marker of atherosclerosis, given its predictive association with cardiovascular disease (CVD). The interpretation of CIMT values has been hampered by the absence of reference values, however.

In adults, a CIMT>0.9mm it has been shown as a marker of cardiovascular risk caused by atherosclerosis.(10) In children, there are few data regarding reference values for CIMT.

The "catch-up growth" phenomenon in children born small for gestational age (SGA) has been linked to early onset obesity with the subsequent emergence of metabolic syndrome (MetS) or its components.

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About 3-5% of neonates are SGA. 85-90% of them recover weight, up to 2 years of age, majority of which become obese up to 4 years of age, later on developing components of MetS. The rapid "catch up" growth during the cell division period up to 2 years of age leads to hyperplasic obesity (11,12).

These children have a high risk of developing MetS with all its components: obesity, impaired glucose tolerance, insulin resistance with subsequent development of diabetes, arterial hypertension, dyslipidemia.

As indicated in previous studies (13,14,15), children and adolescents with risk factors such as obesity, dyslipidemia, elevated blood pressure and impaired glucose metabolism are at increased risk of developing atherosclerosis in adulthood. It has been found that obesity results in the early onset of adulthood chronic disease such as cardio-cerebrovascular disease.

There has been no statistical data about the association between CIMT and SGA. This study aimed to determine the association between being born SGA and CIMT, a measure of atherogenesis, in obese children and to to produce reference values.

MATERIAL AND METHODS

A prospective study was conducted over a period of 1 year, between July 2012 and June 2013, on cases of obesity in children diagnosed at the Emergency Hospital for Children "Louis Ţurcanu" Timişoara, in the departments of Diabetes and Nutritional Diseases, Endocrinology and Cardiology.

Children were considered obese on the basis of age specific BMI reference guidelines from Centers for Disease Control and Prevention Child Growth Standards 2000 (above 95th percentile) (8). When defining SGA, growth nomograms and charts proposed by Niklasson (9) are being used; newborns weighing less than 2 standard deviations (SD) from the average for gestational age, we considered as being SGA.

CIMT was measured by B-mode ultrasound using a 10-MHz linear transducer (General Electric). The subjects were examined supine with the neck extended and the probe in the antero-lateral position. All measurements of CIMT were made in the longitudinal plane at the point of maximum thickness on the far wall of the common carotid artery along a 1 cm section of the artery proximal to the carotid bulb. The CIMT was defined as the distance between the intimia-blood interface and the adventitia-media junction. After freezing the image, the measurements were made using electronic calipers. The maximal thicknesses of the intima-media width were measured to give three readings and the mean value was used for statistical purposes.

Exclusion criteria were evidenced for syndromal, chromosomal, or infectious etiology of low birth weight, endocrine or syndromal disorders, systemic disease or acute illness.

We analyzed 122 patients diagnosed with obesity, including 96 patients AGA and 26 patients SGA. Both groups were matched for age, sex and BMI.

The data are expressed as means ± standard deviation or as frequencies. Statistical analysis was performed with SPSS 17.0. We used the unpaired t test (with a confidence interval of 95 percent) to evaluate the differences between the two groups SGA vs. AGA. Multiple stepwise linear regression analysis was used to examine relationships between mean CIMT and all other variables investigated. A $p<0.05$ was considered statistically significant ROC curve has been used for determining the optimal "cut-off" value for CIMT in obese children.

TABLE 1. *Anthropometric, metabolic and CIMT characteristics of the study groups*

Total number	Obese SGA-group I **26**			Obese AGA-group II **96**			
	Mean	SD	Range	Mean	SD	Range	P value
Age (years)	14.208333	3.33595911	5-17	14.79167	2.28457	4-20	0.68
Birth Weight (grams)	2550	403.51933	970-2860	3446.25	461.371	2400-5300	0.000285
Gestational age (weeks)	38	2.89827534	30-41	39.368	1.14902	34-41	0.025
Sex (%) Male Female	 42.3% 57.7%			 36.5% 63.5%			 0.78
Residence Urban/rural	 57%/43%			 60%/40%			 0.79
Antropometric data BMI (kg/m^2)	29.623	8.13	19-54.48	30.604	6.302	17-47	0.5
CIMT (mm)	0.057385	0.008537	0.4-0.9	0.043	0.008	0.3-0.7	0.0035

Consent was obtained from the parents and the Ethical Committee of the hospital.

RESULTS

The characteristics of the 2 groups:

The two groups were homogenous regarding BMI, age and sex. There was no statistical difference in the age, sex and BMI among the 2 groups (p = 0.68, 0.78, 0.79), as shown in Table 1.

There were significant differences between the two groups regarding birth weight and gestational age.

CIMT was increased in the SGA group (mean 0.057 vs 0.043); (Fig. 1 and 2) there was a significant differences between the two groups (p = 0.0035).

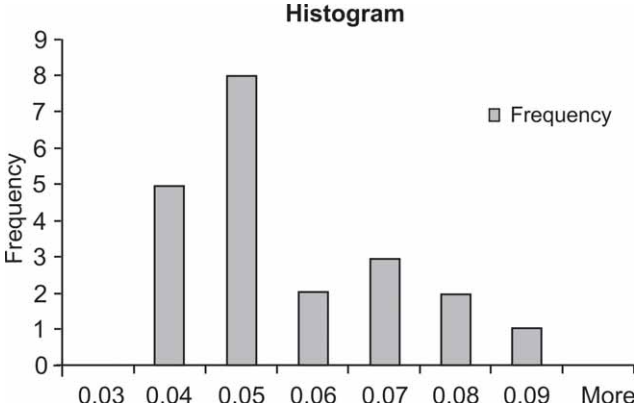

FIGURE 1. *CIMT histogram in group I*

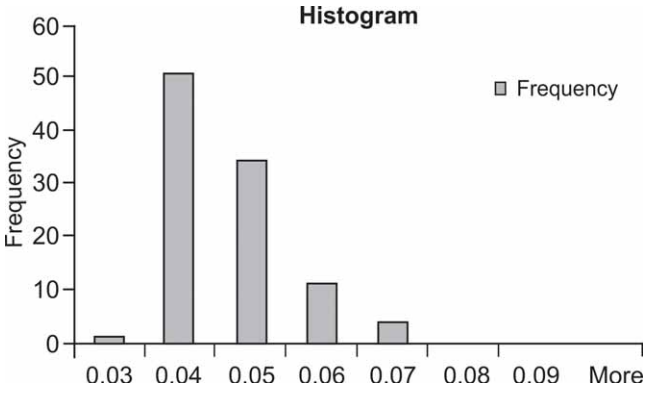

FIGURE 2. *CIMT histogram in group II*

Establishing cut off values using ROC curve in obese children born SGA versus AGA

We have determined using ROC curve "cut-off" values for the SGA group. (Fig. 3, Table 2). The limited number of the SGA group (26 patients) compel us to establish a cut-off value for both group together (Fig. 4, Table 3).

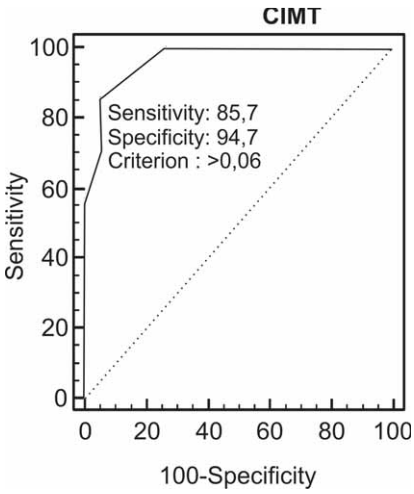

FIGURE 3. *ROC curve for the SGA group*

TABLE 2. *Statistical analysis using ROC curve for the SGA group*

Sample size		26
Positive group:	SM = 1	7
Negative group:	SM = 0	19

Disease prevalence (%)	Unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.966
Standard Error[a]	0.0292
95% Confidence interval	0.811 to 0.999
z statistic	15.949
Significance level P (Area = 0.5)	< 0.0001

Youden index

Youden index J	0.8045
95% Confidence interval	0.5263 to 0.9474
Associated criterion	> 0.06
95% Confidence interval	0.056 to 0.06

Estimated specificity at fixed sensitivity			
Sensitivity	Specificity	95% CI	Criterion
80.00	94.74	71.56 to 100.00	> 0.0608
90.00	88.42	65.41 to 100.00	> 0.0594
95.00	81.05	55.68 to 100.00	> 0.0587
97.50	77.37	51.05 to 95.66	> 0.0583
Estimated sensitivity at fixed specificity			
Specificity	Sensitivity	95% CI	Criterion
80.00	95.71	42.86 to 100.00	> 0.0586
90.00	88.93	42.14 to 100.00	> 0.0595
95.00	70.71	9.92 to 98.57	> 0.0621
97.50	63.93	7.68 to 92.50	> 0.063

Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥ 0.04	100.00	59.0-100	0.00	0.0-17.6	1.00	
> 0.058	100.00	59.0-100	73.68	48.8-90.9	3.80	0.00
> 0.06	85.71	42.1-99.6	94.74	74.0-99.9	16.29	0.15
> 0.062	71.43	29.0-96.3	94.74	74.0-99.9	13.57	0.30
> 0.064	57.14	18.4-90.1	100.00	82.4-100.0		0.43
> 0.08	0.00	0.0 41.0	100.00	82.4-100.0		1.00

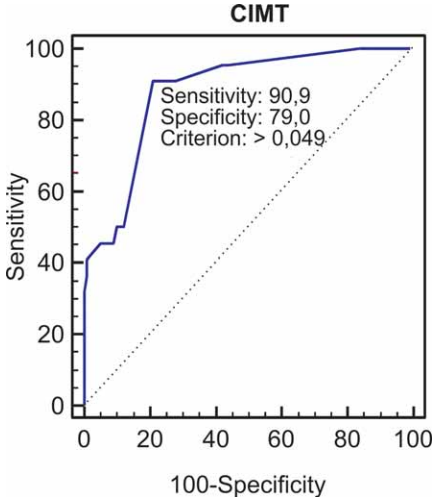

FIGURE 4. *ROC curve for SGA+AGA group*

We obtained for both groups a cut-off value of CIMT 0.049 cm with a sensitivity of 90.9% and a specificity of 79%.

DISCUSSIONS

Regarding the distribution of obese patients according to birth weight, as expected, it appears that SGA group is lower than AGA group, accounting for about a quarter of it.

Recent reports indicate that the presence of obesity in childhood is associated with increased adult CIMT (14,15). CIMT is a well-known marker of subclinical atherosclerosis and it also can indicate future cardio-cerebrovascular disease (16,17,23). In our study we measured the CIMT in obese SGA and non SGA subjects. We found that CIMT in obese children born SGA was significantly increased as compared with obese children born AGA similar age, sex and BMI. Several reports suggest increased CIMT in obese children, to date very few studies regarding CIMT in SGA children have been carried out. We found two other studies that are in accordance with our study (24,25), one that could not demonstrate an association between birth weight and CIMT (26).

In an adult reference values for CIMT are 0.04-0.07 cm. (27). There is an increase in CIMT with each decade of age (0.066 cm / decade), reaching in the group 70-79 years values of 0.0733cm (28). An increase of 0.1 mm of CIMT increases the risk of myocardial infarction by 11%. (29) In children, there are few studies on CIMT values; normal CIMT value is considered 0.04 cm. (30)

In a study of children aged 6-14 were found following values regarding CIMT: a median value of 0.48 mm in non-obese children and a value of n in obese children. (31) Another study which enrolled 128 patients between 6 -18 years shown a CIMT of 0.43 mm in non-obese children versus 0.51 mm in obese children. (32)

In the literature we found few data regarding reference values for CIMT in obese children; with this study we achieved threshold values of CIMT maintaining sensitivity and high specificity. For both groups we obtained a cut off value of 0.049

TABLE 3. *Statistical analysis using ROC curve for the SGA and AGAgroup together*

Variable	IMc	
Classification variable	SM	
Sample size		122
Positive group:	SM = 1	22
Negative group:	SM = 0	100
Disease prevalence (%)		10

Area under the ROC curve

Area under the ROC curve (AUC)	0.881
Standard Error	0.0368
95% Confidence interval	0.810 to 0.933
Z statistic	10.353
Significance level P (Area = 0.5)	< 0.0001

Youden index

Youden index J	0.6991
95% Confidence interval	0.5432 to 0.8200
Associated criterion	> 0.049
95% Confidence interval	0.04 to 0.049

Estimated specificity at fixed sensitivity

Sensitivity	Specificity	95% CI	Criterion
80.00	81.40	68.68 to 88.69	> 0.0493
90.00	79.20	54.30 to 88.29	> 0.049
95.00	59.40	26.36 to 83.11	> 0.0432
97.50	38.00	20.70 to 81.19	> 0.0391
80.00	86.36	62.02 to 100.00	> 0.0491
90.00	50.00	22.73 to 70.32	> 0.054
95.00	45.45	22.73 to 63.64	> 0.058
97.50	42.61	22.73 to 63.64	> 0.0592

Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	LR	LR	+PV	-PV
≥ 0.03	100.00	84.6-100.0	0.00	0.0-3.6	.00		0.0	
> 0.038	100.00	84.6-100.0	16.00	9.4-24.7	.19	.00	1.7	00.0
> 0.04	95.45	77.2-99.9	56.00	45.7-65.9	.17	.081	9.4	9.1
> 0.043	95.45	77.2-99.9	58.00	47.7-67.8	.27	.078	0.2	9.1
> 0.045	90.91	70.8-98.9	72.00	62.1-80.5	.25	.13	6.5	8.6
> 0.049	90.91	70.8-98.9	79.00	69.7-86.5	.33	.12	2.5	8.7
> 0.05	50.00	28.2-71.8	88.00	80.0-93.6	.17	.57	1.6	4.1
> 0.054	50.00	28.2-71.8	90.00	82.4-95.1	.00	.56	5.7	4.2
> 0.055	45.45	24.4-67.8	91.00	83.6-95.8	.05	60	5.9	3.8
> 0.058	45.45	24.4-67.8	95.00	88.7-98.4	.09	.57	0.3	4.0
> 0.06	40.91	20.7-63.6	99.00	94.6-100	0.9	.60	2.0	3.8
> 0.062	36.36	17.2-59.3	99.00	94.6-100	6.3	.64	0.2	3.3
> 0.064	31.82	13.9-54.9	100.00	96.4-100		.68	00.0	3.0
>0.09	0.00	0.0-15.4	100.00	96.4-100		.00		0.0

cm, value with a sensitivity of 90.9% and a specificity of 79%.

When we analyzed the SGA group, we obtained a higher cut off value (0.06 cm), with high sensitivity and specificity. Given the small numbers of patients born SGA, further studies are regarding the cut off value of 0.06 cm, with the risk of losing subjects with cardiovascular risk with a CIMT value slightly less than 0.06cm.

I believe these cut off values are "pilot values", requiring extensive population studies in children to refine the values obtained to determine cardiovascular risk in obese children.

LIMITATION

Data from our small clinical samples and the limited number of SGA group may not be representative for general populations. The CIMT may also probably be influenced by other risk factors which have not been tested in our study..

CONCLUSION

Metabolic impairment in SGA children is amplified by weight gain and influenced by fetal programming; CIMT is a well-known marker of subclinical atherosclerosis and is a noninvasive and inexpensive method for detecting development of subclinical atherosclerosis. CIMT in obese children born SGA was significantly increased as compared with obese children born AGA similar age, sex and BMI; being born SGA is associated with an increase risk of atherogenesis. Further population studies regarding reference values for CIMT in obese children born SGA and AGA are necessary.

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