Is small for gestational age status associated with an increase risk of atherogenesis?

Ramona Stroescu1,2, Teofana Bizerea1,2, Ioana Micle1, Monica Mărăzan, Maria Puiu1,2, Otilia Mărginean1,2
1 Emergency Hospital for Children "Louis Ţurcanu" Timisoara, Romania
2 University of Medicine and Pharmacy "Victor Babes" Timisoara, Romania

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). The intima media thickness of the common carotid artery (CIMT) is a well-known marker of subclinical atherosclerosis. Aim: to determine the association between being born SGA and CIMT, a measure of atherogenesis and to investigate metabolic risk factors which impact on CIMT in obese children. Material and methods: A prospective study was carried out over a 1 year period (March 2013-March 2014). 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. Blood pressure, lipids and glucose were determined. Oral glucose tolerance tests (oGTT) were performed. Insulin resistance (IR) was assessed by homeostasis model assessment (HOMA). CIMT was measured in all the patients. 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). We demonstrated a strong correlation between CIMT and all other metabolic factors (r=0.98). In both groups, mean CIMT of was significantly related to diastolic blood pressure, triglycerides and HOMA. CIMT was not significantly related to systolic blood pressure and baseline glucose. Conclusion: High triglycerides levels and low HDL-cholesterol levels, IR and diastolic blood pressure, which are all components of MetS are strong predictors of increased CIMT in obese children. Being born SGA increases the atherogenic risk.

Key word: small for gestational age, common carotid intima media thickness, obesity

Introduction

The "catch-up growth" phenomenon in children born SGA has been linked to early onset obesity with the subsequent emergence of metabolic syndrome (MetS) or its components.
About 3-5% of neonates are born 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 (1,2).
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 (3,4,5), 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.
The intima media thickness of the common carotid artery (CIMT) is a well-known marker of subclinical atherosclerosis and is a noninvasive and inexpensive method for detecting development of subclinical atherosclerosis. Studies in adults have revealed that CIMT was related to cardiovascular risk factors and could predict the possibility of future cardio-cerebrovascular disease (6,7).

Material and Methods

A prospective cross sectional study was conducted over a period of 1 year :March 2013 and March 2014
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.
Blood pressure was measured;. Hypertension was defined by blood pressure above the 95th percentile for height, age, and gender (10). Blood sampling was performed in the fasting status. Serum triglyceride, HDL-cholesterol, LDL-cholesterol, insulin, and glucose concentrations were measured in all children. oGTT was performed in all children.
Impaired glucose tolerance was defined by 2 h serum glucose >140 mg/dl in the oGTT (11).
Dyslipidemia was defined by triglycerides >95th percentiles, LDL-cholesterol > 95th percentiles or HDL-cholesterol <5 th percentile (12).
A cut-off HOMA level above 2.5 in the prepubertal period and of > 3.5 for adolescents was used to define an IR status.
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.
=>122 patients : 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.
Consent was obtained from the parents and the Ethical Committee of the hospital.

Results and Discussions

Tabel 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	14.208333	3.33595911	5-17	14.79167	2.28457	4-20	0.68
Birth Weight	2550	403.51933	970-2860	3446.25	461.371	2400-5300	0.000285
Gestational age	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/m2)	29.623	8.13	19-54.48	30.604	6.302	17-47	0.5
Haemodinamic data SBP(mmHg) DBP(mmHg)	114 70	22.6 12.7	70-160 50-100	117.270 74.010	19.10 12.344	70-180 40-120	0.474 0.0151
Biological data Baseline glucose (mmol/l) 2 hours glucose (mmol/l) HOMA IR Triglycerides (mmol/l) HDL-cholesterol (mmol/l)	4.38307 5.6177 3 2 1	0.406012 1.183376 1.968 0.714 0.313	3.8-5.2 3.55-8.18 0.4-9.2 0.47-3 0.65-2.28	4.500 5.930 3.418 1.141 1.105	0.9342 1.4362 2.5695 0.5343 0.3756	3.8-11.3 4-11.8 0.35-28.2 0.33-2.94 0.26-2.91	0.346 0.228 0.035 0.000986 0.523
CIMT(mm)	0.057385	0.008537	0.4-0.9	0.043	0.008	0.3-0.7	0.0035

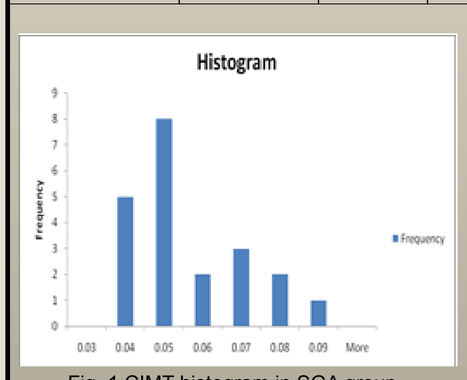

Fig. 1 CIMT histogram in SGA group

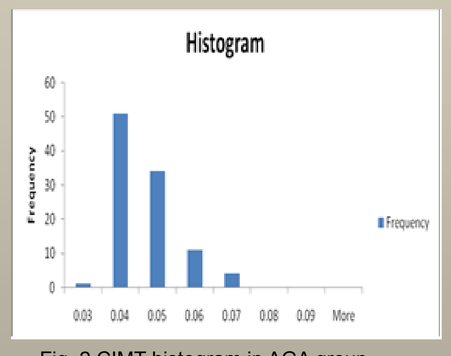

Fig. 2 CIMT histogram in AGA group

Table 2. Correlation between CIMT and other variables SGA group

	t Stat	P-value	Lower 95%	Upper 95%	r
Gestational age (weeks)	4.55302		0.00049	0.00127	0.579896
HDL cholesterol	8	1.75E-05	8	1	9
HOMA-IR	1.59872 7	0.011359	- 0.00158	0.00506 8	0.464708
Triglycerides	1.51744 2	0.013287	- 0.00026	0.00192 9	0.414227
DBP	1.83301	0.050302	- 0.00033	0.00805 1	0.498442
Cholesterol	0.48779 2	0.053695 3	- 0.00016	0.00026 8	0.392482 5
SBP	1.04437 9	0.299271	- 0.00158	0.00506 8	0.269925 7
baseline glucose	0.74256	0.459797	- 0.00019	8.59E- 05	0.334785 1
2 hour glucose	0.28675	0.775001	- 0.00261	0.00195 1	0.170452
	0.14665	0.883752	-0.0018	0.00155 7	0.189122

Table 3. Correlation between CIMT and other variables AGA group

	t Stat	P-value	Lower 95.0%	Upper 95.0%	r
Cholesterol	2.865656	0.012459	0.002695	0.018731	0.2699257
2hours glucose	0.949927	0.035826	-0.00182	0.00471	0.589122
DBP	0.929466	0.0368398	-0.00024	0.000595	0.67
Gestational age (weeks)	1.364831	0.043841	-0.0004	0.00178	0.3798969
HOMA-IR	0.53508	0.05	-0.00551	0.003307	0.45
SBP	0.50792	0.619418	-0.00024	0.000382	0.23
baseline glucose	0.49281	0.629785	-0.01147	0.007187	0.15
HDL cholesterol	0.300814	0.767978	-0.01232	0.016335	0.33

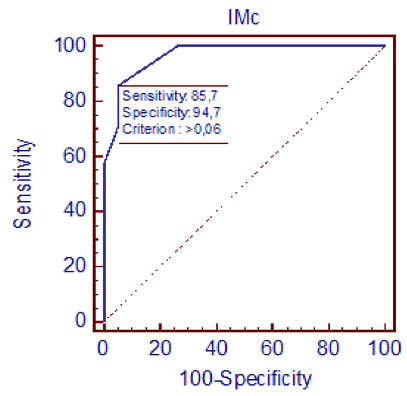

Fig. 3 ROC curve for SGA group

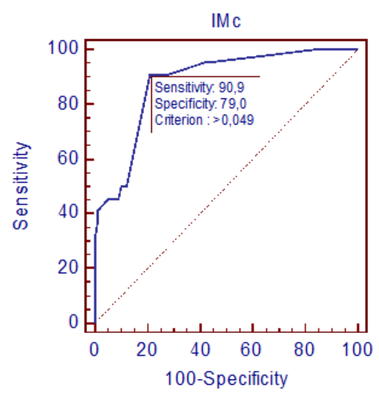

Fig. 4 ROC curve for SGA + AGA group

Discussions

- Presence of obesity in childhood is associated with increased adult CIMT (4,5).
- CIMT in obese children born SGA was significantly increased as compared with obese children born AGA similar age, sex and BMI.
- CIMT was significantly related to IR , triglycerides and HDL-cholesterol a in both groups, suggesting a link between CIMT, IR and dyslipidemia.
- Baseline glucose levels were almost similar in both groups. A difference in HOMA has been noticed.
- Fasting insulin and HOMA-IR levels were significantly related to CIMT. We could not say the same for fasting blood glucose. We speculated that an early phase of increased insulin level during childhood might precede the onset of insulin resistance in young adult SGA subjects. Atabek et al (13) demonstrated an association between IR and premature carotid atherosclerosis in children obesity. Insulin not only directly stimulates the expression of vascular cell adhesion molecule, but disrupts the balance between the production of NO and ET-1 leading to endothelial dysfunction.
- There is also a significant correlation between DBP and CIMT but not between SBP and CIMT and this finding is in accordance to other studies.(14,15) Perry and colleagues (16) found that in subjects aged under 40 years, DBP is a stronger predictor of cardiovascular risk than SBP.
- 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 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, existing the risk of losing subjects with cardiovascular risk with a CIMT value slightly less than 0.06cm.

Conclusions

1. High tryglyceride level and low HDL-cholesterol level, IR and blood pressure, which are all components of MetS are strong predictors of increased CIMT in obese children. Being born SGA increases the atherogenic risk.
2. Metabolic impairment in SGA children is amplified by weight gain and influenced by fetal programming; developing intrauterine IR as a prenatal surviving mechanism is a risk factor for postnatal MetS.
3. IR is a significant determinant of mean CIMT level, which indicates that it is closely related to cardio-cerebrovascular disease.
4. CIMT in obese children born SGA was significantly increased as compared with obese children born AGA similar age, sex and BMI
5. Being born SGA is associated with an increase risk of atherogenesis.
6. Further population studies regarding reference values for CIMT in obese children born SGA and AGA are necessary.

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