Is Small for Gestational Age Status Associated with an Increased Risk of Atherogenesis?

Ramona STROESCU\textsuperscript{a,b}; Ioana MICLE\textsuperscript{b}; Otilia MARGINEAN\textsuperscript{a,b}; Teofana BIZEREA\textsuperscript{a}; Monica MARAZAN\textsuperscript{c}; Maria PUIU\textsuperscript{a,b}; Ciprian SIPOS\textsuperscript{b}; Gabriela DOROS\textsuperscript{a,b}

\textsuperscript{a}"Louis Turcanu" Emergency Hospital for Children Timisoara, Romania
\textsuperscript{b}"Victor Babes" University of Medicine and Pharmacy Timisoara, Romania
\textsuperscript{c}West University of Timisoara, Romania

\textbf{ABSTRACT}

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.

\textbf{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.

\textbf{Material and methods:} A prospective study was carried out over a 1 year period (July 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. 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.

\textbf{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.

\textbf{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.

\textbf{Keywords:} small for gestational age, obesity, intima media thickness of the common carotid artery
INTRODUCTION

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.

About 3-5% of neonates are born small for gestational age (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 (3-5), 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).

There has been no statistical data about the association between CIMT and SGA or between CIMT and the components of MetS in SGA children. This study aimed to determine the association between being born SGA and CIMT, a measure of atherogenesis, in obese children and to investigate metabolic risk factors which impact on CIMT in obese children.

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 “Louis Turcanu” Emergency Hospital for Children Timisoara, 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.

Blood pressure was measured; systolic (SBP) and diastolic (DBP) blood pressure were measured at the right arm twice after a 10 minutes rest in the supine position, by using a calibrated sphygmomanometer and averaged. 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 using commercially available test kits (lipids and plasma glucose levels COBAS INTEGRA-400 Roche Diagnostics), plasma insulin levels DPC-Immulite-One (Siemens Medical solutions). oGTT was performed in all children.

Impaired glucose tolerance was defined by 2 h serum glucose >140 mg/dl in the oGTT according to definition of MetS by Weiss (11). Dyslipidemia was defined by triglycerides >95th percentiles, LDL-cholesterol >95th percentiles or HDL-cholesterol <5th percentile (12).

Basal glucose and insulin levels of the patients were measured and IR index was assessed by homeostasis model assessment (HOMA-fasting glucose in mmol/l multiplied by baseline insulin in microunits per milliliter, divided by 22.5). 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 intima-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 IMT and all other variables investigated. A p<0.05 was considered statistically significant.

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.

HOMA-IR was significant different between the two groups. Lipids profile shown differences in triglycerides value more then in HDL-cholesterol values.

We did not find significant differences between the two groups AGA vs SGA regarding systolic blood pressure, baseline glucose and 2 hours serum glucose.

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

The relationship between CIMT and all other variables investigated.

Multiple R is closed to r, meaning a strong correlation between CIMT and all other factors. R square shows that 97.12% from CIMT variation in group I and 99.3% in group II is due to the cumulative influence factors (Table 2, Table 3).

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 (4,5). CIMT is a well-known marker of subclinical atherosclerosis and it also can indicate future cardio-cerebrovascular disease (6,7,13). 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 (14,15), one that could not demonstrate an association between birth weight and CIMT (16).

In our study, CIMT was significantly related to IR, triglycerides and HDL-cholesterol in both groups, suggesting a link between IMT, insulin resistance 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 (17) demonstrated an association between IR and premature carotid atherosclerosis in children obesity. Insulin not only directly stimulates the expression of vascular cell adhesion molecule (18), but disrupts the balance between the production of NO and ET-1 leading to endothelial dysfunction (19).

Dyslipidemia is related to cardio-cerebro-vascular disease (20,21). According to Pearson correlation analysis triglycerides and HDL-cholesterol were related to IMT. Hypertension was the less frequent component of MetS in our study. It was equal distributed. 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 did (22,23). Perry and colleagues (24) found that in subjects aged under 40 years, DBP is a stronger predictor of cardiovascular risk than SBP.

**LIMITATIONS**

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**

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.

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. IR is a significant determinant of mean CIMT level, which indicates that it is closely related to cardio-cerebrovascular disease.

Conflict of interests: none declared.

Financial support: none declared.

**REFERENCES**


**TABLE 4.** Correlation between CIMT and other variables group I

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<tr>
<th>Variable</th>
<th>t Stat</th>
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<th>Upper 95%</th>
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**TABLE 5.** Correlation between CIMT and other variables group II

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<td>0.33</td>
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15. Trevisanuto D, Avezzù F, Cavallin F, et al. – Arterial wall thickness and blood pressure in children who were born small for gestational age: correlation with umbilical cord high-sensitivity C-reactive protein. *Arch Dis Child* 2010; 95:31-4