Relationship between carotid intima-media thickness, atherosclerosis risk factors and birthweight in young males

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Abstract

Background: Autopsy and ultrasonographic studies reveal atheromatous lesions in many young subjects. The progression of these changes depends on the presence of cardiovascular risk factors. Some studies have suggested that coronary risk may depend also on birthweight.

Aim: To estimate the relationship between carotid intima-media thickness (CIMT), atherosclerosis risk factors and birthweight in young males.

Methods: The study group consisted of 110 males aged 27–32 years, born after 36 weeks of gestational age. We took their anthropometric measurements, performed blood tests, and measured blood pressure and right CIMT.

Results: Subjects with CIMT > 0.6 mm (n = 30), in comparison with the group with CIMT ≤ 0.6 mm (n = 80), had significantly lower mean birthweight (3,224 g vs 3,556 g, p = 0.001), lower mean serum HDL-cholesterol level (1.19 vs 1.36 mmol/L, p = 0.012), higher TC/HDL ratio (4.36 vs 3.71, p = 0.009), higher fasting serum glucose level (5.48 vs 5.28 mmol/L, p = 0.045), higher HbA1c (5.63 vs 5.40%, p = 0.044), and slightly higher (at the border of statistical significance) insulin resistance index HOMA-IR (2.56 vs 2.25, p = 0.074). In the group with CIMT > 0.6 mm, metabolic syndrome was more prevalent (43.3% vs 22.5%, p = 0.031). Adjustment either for body mass index or waist circumference, and for HDL-cholesterol level or TC/HDL ratio or fasting glucose level or HbA1c or HOMA-IR did not remove the negative effects of lower birthweight on the risk of CIMT > 0.6 mm as well as the adjustment for the presence of metabolic syndrome.

Conclusions: The CIMT value in young males is independently related both with birthweight and disturbances of carbohydrate and lipid metabolism.

Key words: atherosclerosis, cardiovascular risk factors, birthweight

INTRODUCTION

Autopsy studies reveal early atheromatous lesions in many young subjects, even children. The progression of these changes depends on the presence of cardiovascular (CV) risk factors, particularly smoking, dyslipoproteinaemia, arterial hypertension, and overweight [1]. Recent studies performed by means of ultrasound scan have shown that the progression of atheromatous lesions in young subjects was influenced by arterial hypertension, smoking, serum total cholesterol to HDL-cholesterol ratio, and clustering of atheromatous risk factors [2]. Epidemiological studies demonstrate that the risk of CV diseases may also depend on birthweight. It has been sugge-
tested that foetal malnutrition, resulting in foetal growth retardation, may increase the risk of atheromatous lesions development. It has been proposed that the mechanism of this phenomenon is the relationship between low birthweight and higher intensity of classical risk factors, such as lipid abnormalities, insulin resistance and resulting carbohydrate metabolism disturbances, and elevated blood pressure (BP) in later life [3].

The aim of our study was to estimate the relationship between the carotid intima-media thickness (CIMT) and atherosclerosis risk factors and birthweight in young males.

**METHODS**

**Study group**

The study was performed between 2005 and 2007 in a subgroup of 110 males aged 27–32 years born after 36 weeks of gestational age who had previously, in 2000–2004, taken part in a study aimed at estimating the relationship between birthweight and coronary risk factors in adulthood [4]. We invited all 194 male participants of the original study to take part in our current study: 119 agreed to have an ultrasound scan. For the analysis presented below, nine subjects who had been born prematurely were excluded.

Data concerning anthropometric features, BP and coronary risk factors were collected in the current study. Data on birthweight and duration of pregnancy was taken from the archives of a population-based study of women observed from the first visit during pregnancy in one district of Warsaw in 1974–1977.

Metabolic syndrome was diagnosed using the definition of the International Diabetes Federation [5]. The subjects were stratified into two subgroups: the first with CIMT ≤ 0.6 mm and the second with CIMT > 0.6 mm. The cut-off point was accepted arbitrarily.

Approval was granted by the Bioethics Committee of the National Research Institute of Mother and Child in Warsaw. The participants signed informed consents.

**Carotid intima-media thickness evaluation**

Right CIMT was measured by an ALOKA SSD 3500 device, with a linear probe of 7.5 MHz. In each subject, the thickness of the internal and central membrane complex in the carotid arteries was measured at three points: the first in the common carotid artery, the second in the sinus of the common carotid artery, and the third in the opening part of the internal carotid artery. The results of the three measurements were averaged.

**Physical examination**

Physical examination included: body height and mass, waist and hip circumference and arterial BP. Height was measured to the nearest 0.5 cm without shoes. Body mass was measured to the nearest 0.1 kg using a medical balance after the subjects took off their shoes and all clothes except undergarments. Waist and hip circumferences were measured by means of an anthropometric tape after the subjects had rolled down undergarments. Waist was measured midway between the iliac crest and the lower rib margin, and hip at the widest circumference over the buttocks, both to the nearest 0.5 cm.

Arterial BP was measured using a mercury sphygmomanometer, at the right arm, in the sedentary position, after at least 5 min of rest, to the nearest 2 mm Hg.

**Laboratory tests**

Laboratory tests included fasting venous blood concentrations of total cholesterol (TC), triglycerides, glucose, insulin, fibrinogen, and glycated haemoglobin (HbA1c). Cholesterol, triglycerides and glucose levels were determined according to the colorimetric method using Ektachem Clinical Chemistry Slides, and HDL-cholesterol by the magnetic method, using a Vitros-250 device produced by Johnson and Johnson Poland Ltd. LDL-cholesterol level was calculated using the Friedewald formula. Insulin concentration was determined according to the immunochemistry method using an IMX device (Abbott). Fibrinogen was measured using the Clauss method by means of a Biomerieux kit and an Option 2 Plus device. Blood glycated haemoglobin was calculated according to the ion capture assay using an IMX device (Abbott).

Laboratory tests were performed in the Biochemical Diagnostics Laboratory of the Outpatient Clinic of Metabolic Diseases of the National Food and Nutrition Institute. This body is under the control of RIQAS and also comes under the inter-laboratory control of the Centre of Laboratory Quality Control.

Fasting serum insulin and glucose levels were used for calculation of the insulin resistance index HOMA-IR using the formula: HOMA-IR = (fasting insulin [μU/mL] × fasting glucose [mg/dL]) / 0.0555) / 22.5. HOMA-IR < 3.0 was classified as normal [6].

**Statistical analysis**

The results are presented as mean ± SD or numbers and percentages. The t-Student test and logistic regression were used for statistical analysis of the results. For non-normally distributed variables, logarithmic transformation was applied. In the logistic regression model, all independent variables were continuous, except metabolic syndrome which was a dummy variable. Birthweight was expressed in units of 100 g. A p value of 0.05 was considered statistically significant. All calculations were done using SPSS v. 18.0.0.

**RESULTS**

The mean CIMT was 0.62 ± 0.11 mm. The mean and median values of atherosclerosis risk factors in the subgroups of subjects of different CIMT values (> 0.6 mm vs ≤ 0.6 mm)
Carotid intima-media thickness, atherosclerosis risk factors and birthweight in young males

are presented in Table 1. The subgroup with CIMT > 0.6 mm, in comparison with the subgroup with CIMT ≤ 0.6 mm, had significantly lower mean birthweight, lower mean serum HDL-cholesterol level, higher TC/HDL ratio, higher fasting serum glucose level, higher HbA1c, and also, although at borderline statistical significance, higher insulin resistance index HOMA-IR. In the subgroup of subjects with CIMT > 0.6 mm, there was significantly higher prevalence of metabolic syndrome (43.3% vs 22.5%, p = 0.031). Differences in the prevalence of smoking habit were not significant.

Adjustment of the relationship between CIMT and birthweight, either for body mass index (BMI) or waist circumference, and selected risk factors related to the increased CIMT, such as HDL-cholesterol or TC/HDL ratio or fasting glucose or HbA1c or HOMA-IR in the logistic regression model did not remove the effects of lower birthweight on the risk of CIMT > 0.6 mm (Table 2), despite still high odds ratios for coronary risk factors (more than one, data not shown). Adjusting the relationship between CIMT and birthweight for metabolic syndrome revealed that both factors were independently related to the atherosclerosis risk (Fig. 1). The odds ratios for metabolic syndrome was 2.647 (95% CI 1.032–6.790, p = 0.043) and for birthweight it was 0.857 (95% CI 0.776—0.948, p = 0.003).

The subgroup with CIMT > 0.6 mm, in comparison with the subgroup with CIMT ≤ 0.6 mm, had significantly lower mean birthweight, lower mean serum HDL-cholesterol level, higher TC/HDL ratio, higher fasting serum glucose level, higher HbA1c, and also, although at borderline statistical significance, higher insulin resistance index HOMA-IR. In the subgroup of subjects with CIMT > 0.6 mm, there was significantly higher prevalence of metabolic syndrome (43.3% vs 22.5%, p = 0.031). Differences in the prevalence of smoking habit were not significant.

Table 1. Comparison of mean and median values of coronary risk factors in subjects with CIMT ≤ 0.6 mm (n = 80) and with CIMT > 0.6 mm (n = 30)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>CIMT ≤ 0.6 mm (n = 80)</th>
<th>CIMT &gt; 0.6 mm (n = 30)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (mean ± SD)</td>
<td>Median (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight [g]</td>
<td>3,525 (3,556 ± 430)</td>
<td>3,380 (3,224 ± 539)</td>
<td>0.001</td>
</tr>
<tr>
<td>TG [mmol/L]</td>
<td>1.18 (1.42 ± 0.77)</td>
<td>1.39 (1.55 ± 0.91)</td>
<td>0.487**</td>
</tr>
<tr>
<td>TC [mmol/L]</td>
<td>4.73 (4.80 ± 0.79)</td>
<td>4.87 (4.91 ± 0.83)</td>
<td>0.494</td>
</tr>
<tr>
<td>HDL-C [mmol/L]</td>
<td>1.33 (1.36 ± 0.33)</td>
<td>1.21 (1.19 ± 0.27)</td>
<td>0.012</td>
</tr>
<tr>
<td>LDL-C [mmol/L]</td>
<td>2.65 (2.78 ± 0.67)</td>
<td>3.02 (3.00 ± 0.75)</td>
<td>0.152</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.53 (3.71 ± 1.04)</td>
<td>3.88 (4.36 ± 1.40)</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>24.5 (25.4 ± 4.2)</td>
<td>27.2 (26.8 ± 4.2)</td>
<td>0.140</td>
</tr>
<tr>
<td>Waist [cm]</td>
<td>90.0 (92.2 ± 11.3)</td>
<td>95.5 (95.0 ± 12.3)</td>
<td>0.263</td>
</tr>
<tr>
<td>Glucose [mmol/L]</td>
<td>5.28 (5.28 ± 0.44)</td>
<td>5.53 (5.48 ± 0.42)</td>
<td>0.045</td>
</tr>
<tr>
<td>HbA1c [%]</td>
<td>5.36 (5.40 ± 0.50)</td>
<td>5.76 (5.63 ± 0.54)</td>
<td>0.044</td>
</tr>
<tr>
<td>Insulin [µU/mL]</td>
<td>7.30 (9.44 ± 7.61)</td>
<td>9.25 (10.45 ± 5.52)</td>
<td>0.112**</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.72 (2.25 ± 1.88)</td>
<td>2.42 (2.56 ± 1.44)</td>
<td>0.074**</td>
</tr>
<tr>
<td>SBP [mm Hg]</td>
<td>132.5 (136.9 ± 17.5)</td>
<td>132.5 (142.0 ± 24.1)</td>
<td>0.227</td>
</tr>
<tr>
<td>DBP [mm Hg]</td>
<td>85.0 (85.8 ± 12.2)</td>
<td>80.0 (86.8 ± 18.0)</td>
<td>0.734</td>
</tr>
<tr>
<td>Fibrinogen [mg/dL]</td>
<td>222 (229 ± 42)</td>
<td>234 (236 ± 36)</td>
<td>0.432</td>
</tr>
</tbody>
</table>

*Student test; **Student test after logarithmic transformation of the data; CIMT — carotid intima-media thickness; TG — triglycerides; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; BMI — body mass index; HbA1c — glycosylated haemoglobin; HOMA-IR — homeostasis model assessment of insulin resistance; SBP — systolic blood pressure; DBP — diastolic blood pressure

Table 2. Relationship between CIMT > 0.6 and birthweight adjusted for selected risk factors of atherosclerosis and different anthropometric indices of body fat mass in studied subjects (n = 110)

<table>
<thead>
<tr>
<th>Model</th>
<th>Without adjustment for body fat</th>
<th>BMI adjusted</th>
<th>Waist adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI for OR</td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>Model 0: no CRF adjusted</td>
<td>0.857</td>
<td>0.776–0.946</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 1: adjusted for HDL-C</td>
<td>0.868</td>
<td>0.784–0.960</td>
<td>0.006</td>
</tr>
<tr>
<td>Model 2: adjusted for TC/HDL-C</td>
<td>0.870</td>
<td>0.786–0.963</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 3: adjusted for glucose</td>
<td>0.868</td>
<td>0.785–0.960</td>
<td>0.006</td>
</tr>
<tr>
<td>Model 4: adjusted for HbA1c [%]</td>
<td>0.858</td>
<td>0.775–0.950</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 5: adjusted for HOMA-IR</td>
<td>0.859</td>
<td>0.777–0.949</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CRF — coronary risk factor; CI — confidence interval; OR — odds ratio; rest abbreviations as in Table 1
DISCUSSION

In the studied group, a strong relationship between CIMT and birthweight was particularly striking. Given that the results of other studies have suggested that low birthweight may influence atherosclerosis risk by increasing intensity of ‘classic’ risk factors [3], an important question arises: is the observed influence of birthweight on CIMT related to the other risk factors investigated in our study? We focused particularly on those that were found to be significantly related to CIMT, such as serum HDL-cholesterol, fasting glucose, and HbA1c levels, TC/HDL ratio, and presence of metabolic syndrome. It seemed reasonable to also take into consideration insulin resistance (IR), as we observed a tendency to higher IR in the subjects with higher CIMT.

To solve this problem we adjusted the relationship between CIMT and birthweight for both parameters of adiposity (BMI, waist circumference), and the risk factors that were related to CIMT in our subjects. The performed analysis revealed that the association of birthweight with CIMT value was not influenced by any of these factors. Neither was it influenced by the presence of metabolic syndrome. Thus, birthweight seems to be an independent atherosclerosis risk factor in the studied males. However, it should be emphasised that our estimation is not definitive because of the relatively small sample size.

Our observation is in accordance with the results of other studies. Martyn et al. [7] showed a strong relationship between birthweight and risk of carotid atherosclerosis measured by ultrasound scan in 181 elderly people. Subjects whose birthweight was 6.5 pounds or less had an odds ratio for extracranial carotid stenosis of 5.3 (95% CI 2.0–14.0) when compared to those who weighed over 7.5 pounds at birth, after adjustment for CV factors and gestational age at birth. In a subsequent study, Gale et al. [8] showed that elderly subjects whose birthweight was ≤ 6.5 pounds had a higher risk of carotid stenosis of above 30% reduction of the lumen diameter, than those whose birthweight was > 7.5 pounds. However, the difference was not significant.

Birthweight was an independent risk factor for atherosclerosis in our studied subjects, but it is not easy to explain the observed relationship. We take into consideration several potential mechanisms: the influence of intrauterine growth retardation (IUGR) on the artery structure, endothelial dysfunction and inflammation processes intensity. It is also possible that lower birthweight is a marker of some other relationships. For example, increased maternal oxidative stress may result in both IUGR and an aggravated atherosclerosis risk in the offspring.

There are data that suggest a relationship between IUGR and an alteration of artery structure. One of the most recent studies [9] has shown that umbilical arteries of newborns with IUGR were thinner, stiffer and narrower than those of newborns appropriate for gestational age (AGA). In another study performed in children aged about eight years [10], it was demonstrated that abdominal aortic stiffness was increased in those with IUGR. Similarly, in an investigation that included 50 year-old adults who had been small at birth [11] it was found that their arterial compliance was reduced.

Several studies have shown that endothelial dysfunction is more prevalent in subjects born with low birthweight. Martin et al. [12] demonstrated impaired acetylcholine induced vascular relaxation in low birthweight infants in comparison with those with normal birthweight. Similar observations were made in young adults. Flow-mediated brachial artery dilatation was reduced in those with a history of low birthweight compared to normal birthweight subjects [13].

Recently published studies have investigated the relationship between low birthweight and inflammation processes. A Swedish study [14] demonstrated that lower birthweight was associated with chronic low-grade inflammation in children and adolescents. Similarly, the ARIC study showed that IUGR predicted enhanced inflammation and endothelial activation in adult life [15].

Oxidative stress seems to play a crucial role in programming endothelial dysfunction and subsequent atherosclerosis. Increased oxidative stress has been reported in small for gestational age (SGA) infants compared to AGA infants [16]. Similarly, Hracsko et al. [17] found that in newborns with IUGR, lipid peroxidation was enhanced and levels of antioxidants and antioxidant enzyme activities were decreased.

Pro-oxidative stress is a feature of many conditions that may lead to SGA, such as pre-eclampsia, gestational hypertension, smoking, malnutrition, infections and inflammation. Maternal overt hypercholesterolaemia is one of the conditions that may result in oxidative stress and increased athero-

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sclerosis risk in the offspring. Rapid progression of atherosclerosis in the offspring of hypercholesterolaemic mothers has been observed even in cases of normocholesterolaemia in their progeny [18].

Limitation of the study
Our study has several limitations. It was based on a relatively small group of 110 participants. A large proportion of the original study group (39%) did not reply to our invitation. The clinical and laboratory data were collected a few years before the ultrasound scans. However, this may exert only a marginal effect on the results, because changes in the arterial wall develop very slowly.

CONCLUSIONS
The CIMT value in young males was independently related both with birthweight and disturbances of carbohydrate and lipid metabolism.

Conflict of interest: none declared

References
Związek między grubością kompleksu błony środkowej i wewnętrznej ściany tętnicy szyjnej a czynnikami ryzyka miażdżycy i masą urodzeniową u młodych mężczyzn

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Streszczenie

Wstęp: U wielu młodych osób badania sekcyjne i ultrasonograficzne wykazują obecność zmian miażdżycowych. Progresja tych zmian wiąże się z obecnością sercowo-naczyniowych czynników ryzyka. Inne badania sugerują, że ryzyko miażdżycy może zależeć także od masy urodzeniowej.

Cel: Celem pracy była ocena związku między grubością kompleksu błony środkowej i wewnętrznej ściany tętnicy szyjnej (CIMT) a czynnikami ryzyka miażdżycy i masą urodzeniową u młodych mężczyzn.

Metody: Badanie przeprowadzono u 110 mężczyzn w wieku 27–32 lat urodzonych po 36. tygodniu czasu trwania ciąży. Wykonano pomiary antropometryczne, badania krwi, zmierzano ciśnienie krwi oraz IMT prawej tętnicy szyjnej.

Wyniki: Grupa z CIMT > 0,6 mm (n = 30), w porównaniu z grupą z CIMT £ 0,6 mm (n = 80), cechowała się znamiennie niższą średnią masą urodzeniową (3224 g vs. 3556 g; p = 0,001), niższym średnim stężeniem w surowicy cholesterolu frakcji HDL (1,19 vs. 1,36 mmol/l; p = 0,012), wyższym stosunkiem TC/HDL (4,36 vs. 3,71; p = 0,009), wyższym stężeniem glukozy w surowicy na czczo (5,48 vs. 5,28 mmol/l; p = 0.045), wyższym HbA1c (5,63 vs. 5,40%, p = 0,044), a także (na pograniczu znamienności statystycznej) wyższą wartość wskaźnika oporności na insulinę HOMA-IR (2,56 vs. 2,25; p = 0,074). W grupie z CIMT > 0,6 mm stwierdzono większy odsetek osób z zespołem metabolicznym (43,3 vs. 22,5%; p = 0,031). Negatywny wpływ obniżonej masy urodzeniowej na ryzyko wystąpienia CIMT > 0,6 mm utrzymał się po uwzględnieniu zarówno aktualnego wskaźnika masy ciała oraz obwodu talii, jak i stężenia cholesterolu frakcji HDL oraz stosunku TC/HDL, a także stężenia glukozy na czczo, HbA1c, i HOMA-IR, jak również obecności zespołu metabolicznego.

Wnioski: Wartość CIMT u młodych mężczyzn niezależnie wiązała się z masą urodzeniową oraz zaburzeniami metabolizmu węglowodanów i lipidów.

Słowa kluczowe: miażdżyca, sercowo-naczyniowe czynniki ryzyka, masa urodzeniowa

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