Relation between Serum Homocysteine and Carotid Intima-Media Thickness in Obese Egyptian Children


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Relation between Serum Homocysteine and Carotid Intima-Media Thickness in Obese Egyptian Children

M. E. Kandil1, G. M. Anwar2, A. Fatouh1, N. Salama2, A. Ahmed3, E. Elabd2, E. Aly1

Background: Childhood obesity is increasing dramatically worldwide at an alarming rate, but very little is known about its association with atherosclerotic vascular changes and carotid intima in children. Measuring carotid intima-media thickness (CIMT) as a non-invasive marker of early arterial wall alteration is more widely used in adult clinical research but its value in children and adolescents is not clear. Objective: To assess CIMT and serum homocysteine levels in obese children and their relation with serum lipids and anthropometric parameters. Patients and Methods: This study included 41 healthy obese children compared with 41 healthy non-obese children matched in age, gender, and pubertal stage. We determined anthropometric parameters of obesity and sub-clinical atherosclerosis by CIMT measurement using high-resolution ultrasound, in addition to serum levels of homocysteine and lipids. Results: Higher values of CIMT, serum homocysteine, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) were found in obese children compared to controls (p < 0.05). No correlation was documented between homocysteine and CIMT. Significant positive correlations were found between homocysteine/CIMT and anthropometric measurements as well as systolic and diastolic blood pressures. CIMT correlated negatively with HDL-C. Conclusion: Obese children presented increased CIMT, homocysteine, total cholesterol, and LDL-C, indicating a high-risk of endothelial dysfunction and early signs of atherosclerosis. So, these items should be monitored in obese children with emphasis on prevention of obesity and weight reduction. J Clin Basic Cardiol 2010; 13 (online): 8–11.

Key words: obesity, carotid intima-media thickness, homocysteine, lipids, children

The prevalence of obesity in children has at least doubled over the past 25 years with a major impact on health and tends to persist into adulthood [1–6]. Obesity results from a complex combination of factors that act at many stages throughout a person’s life [7].

Thickening of the carotid artery intima-media layer (CIMT) as ultrasonographic marker of early atherosclerosis has been extensively studied over the past decade [8]. Recent data show an acceleration of intima-media thickening and impaired endothelial function in obese children and adolescents [9]. The measurement of CIMT by high-resolution sonar is a feasible, reliable, valid, noninvasive, and cost-effective method [10].

Hyperhomocysteinemia is now regarded as an independent risk factor for atherothrombotic and thromboembolic vascular disease [11]. The exact mechanism remains speculative; there are several plausible mechanisms including endothelial dysfunction, impaired flow-mediated vasodilatation, increased proliferation of vascular smooth muscle cells, enhanced coagulability and inflammatory effects and its angiotoxicity seems to involve the nitric oxide system by inducing oxidant stress [12].

Few pediatric studies can be found to clarify the relation between pediatric obesity and early atherosclerosis as measured by CIMT. Therefore, the aim of our study was to assess serum homocysteine levels and CIMT in obese Egyptian children and their relation with anthropometric parameters and serum lipid profiles.

Patients and Methods

This study included 41 children with exogenous obesity and BMI ≥ 95th percentile on Egyptian growth curves (22 males, 19 females) covering an age range from 5–14.5 years, who were recruited from the Outpatient Clinic of the Diabetes Endocrine and Metabolism Pediatric Unit, Cairo University. Children having endocrinological or genetic causes of obesity, or having any disease affecting homocysteine levels such as renal and liver diseases, or taking medications affecting homocysteine levels such as vitamins and antiepileptic drugs were excluded from the study.

They were compared with 41 healthy age- and sex-matched children (21 males, 20 females) as a control group, with an age range from 5–14 years and with a normal BMI according to Egyptian Growth Charts. All children were subjected to full medical history-taking and thorough clinical examination after parental consent for all participating children. Anthropometric measurements were collected including weight, height, waist, hip, and abdominal circumferences using non-stretchable measuring tapes and skin fold thickness (triceps and subscapular) using the Harpenden caliper. The Body Mass Index (BMI) was calculated as kilograms per meter squared as the ratio of body weight (kg) and squared height (m²) (BMI = body weight [kg]/height² [m²]).

Pubertal development was established according to Tanner’s stages [13]. Young children who had not reached puberty were given the lowest value (stage 1 = preadolescence). The values ranged from 1 = preadolescence to 5 = fully mature.

Measurement of Carotid Intima Media Thickness (CIMT)

Measurement of CIMT by means of non-invasive ultrasound examinations were done for all participants by a single sonographer using a Vivid Three (GE Healthcare, USA) ultrasound scanner with a high-resolution B-mode system with a linear array transducer of 10 MHz frequency, superficial with zooming for maximum magnification. The ultrasound system was connected to a computer system that calibrated the ultrasound images and converted them to numerical data [14].
Homocysteine & CIMT in Obese Children

J Clin Basic Cardiol 2010; 13 (online): 9

Table 1. Demographic, anthropometric, and laboratory data between obese children and control group

<table>
<thead>
<tr>
<th>Items</th>
<th>Obese children (n = 41)</th>
<th>Controls (n = 41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female (%)</td>
<td>22:19 (53.7:64.3)</td>
<td>21:20 (51.2:48.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.25 ± 2.63</td>
<td>10.07 ± 2.28</td>
<td>0.13</td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>0.19 ± 1.4</td>
<td>0.6 ± 1.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Weight (SDS)</td>
<td>11.1 ± 2.2</td>
<td>0.7 ± 1.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>3.6 ± 0.8</td>
<td>0.3 ± 1.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Triceps SFT (SDS)</td>
<td>6 ± 2.4</td>
<td>0.8 ± 1.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Subscapular SFT (SDS)</td>
<td>7 ± 3.2</td>
<td>1.1 ± 1.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.93 ± 0.04</td>
<td>0.88 ± 0.04</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>181.00 ± 31.19</td>
<td>155.12 ± 36.12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>73.39 ± 31.97</td>
<td>79.15 ± 35.64</td>
<td>0.44</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>43.61 ± 12.16</td>
<td>48.17 ± 14.53</td>
<td>0.13</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>122.95 ± 28.96</td>
<td>92.66 ± 26.83</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Serum homocysteine (μmol/l)</td>
<td>11.49 ± 3.80</td>
<td>9.44 ± 2.24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.62 ± 0.12</td>
<td>0.52 ± 0.10</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Data were expressed as mean ± SD except for numbers between parentheses; *p-value is significant if < 0.05. BMI: Body Mass Index; SFT: skin fold thickness; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CIMT: carotid intima-media thickness.

Table 2. Correlations between serum homocysteine, CIMT, and other variables

<table>
<thead>
<tr>
<th>Items</th>
<th>Serum homocysteine</th>
<th>CIMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.202</td>
<td>0.07</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.320*</td>
<td>0.003</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.385*</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.237*</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>0.076</td>
<td>0.64</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.339*</td>
<td>0.002</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>0.352*</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.114</td>
<td>0.31</td>
</tr>
<tr>
<td>Triceps SFT (mm)</td>
<td>0.280*</td>
<td>0.01</td>
</tr>
<tr>
<td>Subscapular SFT (mm)</td>
<td>0.346*</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal SFT (mm)</td>
<td>0.337*</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.226*</td>
<td>0.04</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.266*</td>
<td>0.02</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0.019</td>
<td>0.87</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>0.139</td>
<td>0.21</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>-0.07</td>
<td>0.53</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>0.009</td>
<td>0.93</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.107</td>
<td>0.34</td>
</tr>
<tr>
<td>Serum homocysteine (μmol/l)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*p-value is significant if < 0.05. BMI: Body Mass Index; SFT: skin fold thickness; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CIMT: carotid intima-media thickness.

Samples from Patients and Controls
Fasting venous blood samples (5 ml) were collected from all children on plain tubes after 12 hours’ fasting and were centrifuged, then serum was separated and stored at –20 °C until analysis.

Laboratory Investigations
Lipid profile: total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured by standard methods and ACTH, cortisol, TSH were assessed as well to exclude endocrine causes of obesity.

Assessment of Total Serum Homocysteine (tHcy)
Determination of tHcy in blood was done by Axis® Homocysteine Enzyme Immunoassay (EIA). Protein-bound Hcy had normal levels of cortisol, ACTH, cortisol, and TSH according to our laboratory reference range.

Table 1 shows a comparison of data between obese and non-obese control children was < 90th percentile. Acanthosis nigricans was found in 24.4 % of obese children.

Results

The mean age of obese children included in the current study was 9.26 ± 2.62 (range from 5–15 years). Duration of obesity ranged from 2–8 years with a mean of 4.15 ± 1.68 years, all obese children had a waist circumference (WC) > 90th percentile according to Fernández et al [16], while that of the non-obese control children was < 90th percentile. Acanthosis nigricans was found in 24.4 % of obese children.

Twelve patients (29.2 %) were hypertensive, their systolic (SBP) and diastolic blood pressures (DBP) were above the 90th percentile for age and sex, whereas none of the controls had hypertension, 21.9 % of obese children were pubertal. 68 % of obese children had a family history of obesity, while 22 % had a family history of coronary heart disease.

Ten patients (24.3 %) had a high total cholesterol, 15 patients (36.5 %) had a high LDL-C, 6 (14.6 %) had a low HDL-C and 1 (2.4 %) showed high triglycerides. All obese children had normal levels of cortisol, ACTH, and TSH according to our laboratory reference range.

Table 1 shows a comparison of data between obese and non-obese children.

There were no gender-related differences in serum homocysteine concentrations and CIMT.

Table 2 shows the correlations between serum homocysteine, CIMT, and other anthropometric and laboratory data.

Discussion
The results of this study reveal that there is a significant increase in serum homocysteine levels and CIMT in obese Egyptian children compared to healthy non-obese controls, and that serum homocysteine and CIMT are significantly associated with weight, BMI, W/H ratio, skin fold thickness, and blood pressure. Also, CIMT shows a significant negative correlation to HDL-C (Figure 1). The higher tHcy and CIMT in obese children indicate early vascular burden, which is in agreement with other studies [8, 17–19].

Exposure to cardiovascular risk factors (hypertension, hyperlipidemia) in obese children may induce changes in the

ORIGINAL PAPERS, CLINICAL CARDIOLOGY
Although a causal relation between homocysteine levels and impaired vessel wall morphology is related to the known risk factors obesity, hypertension, and dyslipidemia [8], the current study did not show a significant correlation between the homocysteine levels and CIMT, which coincides with many investigators who reported no association between homocysteine and CIMT [8, 14]. Conversely, Ozguven et al [20] showed a significant correlation between homocysteine and CIMT, which may be attributed to the older age of obese children included in their study and also might be due to the larger sample size of participants.

There were no gender-related differences in serum homocysteine concentrations in children, which coincides with Zhu et al [8].

Our study demonstrated significant positive correlations of the CIMT with anthropometric parameters. Higher CIMT was significantly associated with BMI ≥ 95th percentile on Egyptian growth curves. Obesity and CIMT may share common genetic factors [21].

This coincides with the results of previous investigators who demonstrated that a higher BMI was strongly associated with increased CIMT [10, 22–25]. On the other hand, Giannini et al [26] did not find such a relation.

Such an association of CIMT was not observed in overweight patients in a longitudinal follow-up study by Friedman et al [27], who found that CIMT were not increased among overweight children, which was against the findings demonstrated by other investigators who observed impaired endothelial function in healthy overweight children compared to controls as assessed by BMI and expressed by increasing left CIMT [28].

Our study also revealed that homocysteine correlated with BMI in our obese group which is consistent with previous studies [8, 29].

Regarding blood pressure, hypertension was found in 29.2 % of the obese children. Systolic and diastolic blood pressures showed a significant correlation with CIMT. Our results coincide with other investigators who reported a significant association of CIMT to SBP and DBP [24, 30].

Also, BP correlated positively with weight and BMI, which confirms the previously described relationship between higher BP and increasing BMI [3, 31, 32]. However, studies in children with high cardiovascular risk have shown that normalization of blood pressure and metabolic abnormalities led to a regression of arterial changes and decrease of CIMT [33].

Our study demonstrated no correlation between CIMT and total cholesterol, triglycerides, and LDL-C; however, there was a significant negative correlation to HDL-C. These results coincide with those of Oren et al [22] and Thomas et al [30] who found lipids not to be significantly correlated to CIMT except for HDL-C. However, Li et al [34] reported that LDL-C is a consistent predictor of CIMT in young adults.

We did not find any significant correlation between homocysteine and lipid profiles in obese children, which is in agreement with other studies [12, 35].

Our study revealed that 68 % of obese children had a history of excessive food intake and/or less exercise activities and 68 % of them stem from obese families whereas at least one of the parents or grandparents was obese and 22 % of those children came from families in whom at least one of the parents or grandparents had coronary heart disease, which coincides with the results of Huang et al [36].

Makimattila et al [37] showed that the positive family history of cardiovascular disease was a predictor of CIMT in the offspring. Also, Wang et al [38] reported an association between parental premature coronary heart disease (CHD) and offspring CIMT in their large, prospective family study. Another study performed by O’Donnell et al [39] reported that the associations between CIMT and premature parental CHD are significant even after adjusting for other traditional risk factors, suggesting that there are genetic causes behind the subclinical atherosclerosis.

**Conclusion**

Obese children have an increased CIMT, serum homocysteine, total cholesterol and LDL-c, indicating a high risk for endothelial dysfunction and early signs of atherosclerosis. So, these items should be monitored in obese children with emphasis on prevention of obesity and weight reduction.

The results of the current study support the hypothesis that changes in CIMT, as an early marker of atherosclerosis, can be detected in obese children and adolescents non-invasively using high-resolution ultrasound, to screen those at higher risk of premature atherosclerosis, thus decreasing cardiovascular morbidity and mortality.

**References:**


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