Association between Plasma Homocysteine Concentrations and Carotid Intima-Media Thickness in Patients with Coronary Artery Disease

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Abstract - Introduction: Although homocysteine has atherogenic and prothrombotic properties, the conflicting results from studies made its role in coronary artery disease unclear.

Objectives: The aim of this study was to evaluate the association between plasma levels of homocysteine and carotid atherosclerosis in patients with angiographically confirmed coronary artery disease.

Methods: This prospective study comprised 201 consecutive patients with angiographically confirmed coronary artery disease (CAD) that were divided in three groups considering the presence of vascular affection: 126 patients with monovascular disease (MONO group), 42 patients with bivascular disease (BI group) and 33 patients with trivascular disease (TRI group). The three groups were compared with a control group formed by 41 apparently healthy subjects. We measured serum lipid profile and serum homocysteine levels in all patients. The carotid intima-media thickness (carotid IMT) was determined by ultrasound imaging according to Manheim consensus.

Results: Patients from TRI group had significantly higher levels of total cholesterol, triglycerides and LDL-cholesterol compared with patients from BI group, MONO group and CONTROL group (all $p<0.001$). We observed statistically significant differences between mean values of HC between TRI and BI groups ($p = 0.03$), TRI and MONO groups ($p < 0.001$) and BI and MONO groups ($p = 0.011$). We observed a moderate significantly correlation between carotid IMT and plasma levels of homocysteine ($r = 0.409$, $p < 0.001$).

Conclusion: The study showed an association between plasma homocysteine levels and carotid IMT in patients with angiographically confirmed coronary artery disease. Future studies are necessary to apprehend the effects of homocysteinemia on vascular endothelium.

Key-Words: homocysteine, intimaxmedia thickness, endothelial dysfunction, oxidative stress

1. Introduction

Homocysteine, a sulfur-containing amino acid and an intermediate catabolic product of methionine, has been identified as an independent risk factor for patients with coronary artery disease [1, 2]. The results obtained by other studies were controversial, finding no relationship to vascular risk [3]. Although oxidative stress and activation of proinflammatory factors were the more important mechanisms proposed to explain the atherogenic effects of hyperhomocysteinemia, recent studies demonstrated that hyperhomocysteinemia induces endoplasmic reticulum stress, leading to activation of the unfolded protein response [4]. Another study suggested that hyperhomocysteinemia initiates atherosclerosis by modulating the cholesterol biosynthesis and by significantly increasing the level of other cardiovascular risk factors and markers, with an important role in initiating atherosclerosis [5]. In order to explain the role of homocysteine in vascular bed, it were proposed four major biochemical mechanisms: autooxidation through the production of reactive oxygen species; hypomethylation by forming SAH, a potent inhibitor of biological transmethylations; nitrosylation by binding to nitric oxide or protein homocysteinylated by incorporating into protein [6]. Homocysteine is a major, independent and graded risk factor for atherothrombotic disease [7]. Endothelial dysfunction has been identified as a key mechanism by which vascular risk factors, including possibly homocysteine, may mediate their effect on vascular disease risk [8]. It seems like a mutation in the gene that regulates methylentetrahydrofolate reductase, which reduces its activity and is present in 12% of adult population, is responsible for moderately elevated serum homocysteine levels [9]. Carotid artery intima-media thickness (carotid IMT), measured noninvasively by high-resolution B-mode ultrasonography, has been associated with the risk of coronary artery disease, stroke, and myocardial infarction, and it predicts the progression of coronary artery disease [10]. Ultrasound is frequently used to monitor the intima-media thickness because it has a high-resolution, is
noninvasive and one of the best methods for the detection of early stages of atherosclerotic disease [11, 12]. The aim of this study was to evaluate the association between plasma levels of homocysteine and carotid atherosclerosis in patients with angiographically confirmed coronary artery disease.

2. Materials and Methods
This prospective study included 201 consecutive patients with angiographically confirmed coronary artery disease (CAD) that were divided in three groups considering the presence of vascular affection: 126 patients with monovascular disease (MONO group), 42 patients with bivascular disease (BI group) and 33 patients with trivascular disease (TRI group). Coronary artery disease (CAD) was classified by its extent (number of major coronary vessels affected by at least one stenosis of 50% or more). The exclusion criteria from the study were patients with excessive alcohol intake, diabetes mellitus, renal failure or serum creatinine level over 1.5 mg/dL. All lipid-lowering therapy was withdrawn at least 14 days before the study start.

The three groups were compared with a control group formed by 41 apparently healthy subjects. We recorded by interview the following risk factors: age, gender, hypertension, smoking, diabetes and family history of coronary artery disease. After informed consent was obtained, clinical evaluation included blood pressure measurement, physical examination, chest radiograph, 12-lead electrocardiogram.

While on their usual diet, a venous blood sample was drawn from an antecubital vein in all subjects after an overnight fast to determine TC, HDL-C and TG using standard enzymatic methods. Using Friedewald’s formula it was calculated low density lipoprotein cholesterol [13]. Homocysteine was measured by using enzyme immunoassay method (Hitachi 912 automated analyser (Roche Diagnostics).

Carotid IMT was measured by high-resolution B-mode ultrasonography with an ultrasonographyc apparatus (ALOKA ProSound 4000, with linear transducer of 7.5 MHz) according to Manheim consensus.

Continuous variables were expressed as means ± SD. The relationship between carotid IMT and plasma homocysteine was tested for all four groups, defined by traditional risk factors (Pearson’s and Spearman’s rank bivariate correlation tests were performed). Statistical significance was defined as two–sided \( p < 0.05 \). All statistical analyses were performed using Excel Microsoft Office 2007.

The procedures followed were in accordance with the ethical standards of the Hospital Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2000.

3. Results
The baseline characteristics of the subjects, the mean values of homocysteine, and carotid IMT are summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRI group (n=42)</th>
<th>BI group (n=42)</th>
<th>MONO group (n=126)</th>
<th>CON group (n=41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.0±8.1</td>
<td>59.1±9.6</td>
<td>59.1±9.8</td>
<td>56.3±5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex M/F (%)</td>
<td>85/15</td>
<td>62/38</td>
<td>69/31</td>
<td>44/56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive history of CVD (%)</td>
<td>16.7</td>
<td>13.5</td>
<td>53.1</td>
<td>16.7</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>14.7</td>
<td>19.4</td>
<td>55</td>
<td>10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholestero l (mg/dL)</td>
<td>251.2±7.4</td>
<td>242.9±8.0</td>
<td>237.8±3.6</td>
<td>180.5±8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>197.0±8.4</td>
<td>184.0±6.4</td>
<td>170.1±22.9</td>
<td>122.8±7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL–cholesterol (mg/dL)</td>
<td>167.8±0.08</td>
<td>159.3±2.55</td>
<td>149.5±23.35</td>
<td>107±6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL–cholesterol (mg/dL)</td>
<td>40±6.68</td>
<td>42.5±7.47</td>
<td>47.1±5.74</td>
<td>49.2±5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>16.9±1.89</td>
<td>15.7±2.63</td>
<td>14.4±2.92</td>
<td>9.4±1.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>1.1±0.12</td>
<td>1.0±0.12</td>
<td>0.9±0.13</td>
<td>0.6±0.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

We obtained statistically significant differences when we compared the mean CT between MONO group and control group (\( p < 0.001 \)), between the BI group and control group (\( p < 0.001 \)) and between TRI group and control group (\( p < 0.001 \)). Also, we obtained statistically significant differences between mean values of CT between TRI and MONO groups (\( p = 0.007 \)) and TRI and BI (\( p = 0.049 \)) and between BI and MONO groups (\( p = 0.023 \)). There were significant statistically differences when we compared the mean values of TG between MONO group and control group (\( p < 0.001 \)), between
the BI group and CONTROL group (p <0.001) and between TRI group and CONTROL group (p <0.001).

It were obtained statistically significant differences between mean values of TG between TRI and BI groups (p = 0.043), TRI and MONO (p <0.001) and BI, and MONO (p = 0.001).

There are statistically significant differences when were compared the mean LDL-C values between MONO group and CONTROL group (p <0.001), between BI group and control group (p <0.001) and between TRI group and CONTROL group (p <0.001).

There were also been obtained statistically significant differences between mean values of LDL-C between TRI and BI groups (p = 0.048), TRI and MONO groups (p = 0.008) and BI and MONO groups (p = 0.019).

We obtained statistically significant differences when we compared the mean HDL-C values between MONO group and control group (p <0.001), between BI group and CONTROL group (p <0.001) and between TRI group and CONTROL group (p<0.001). It were obtained statistically significant differences between mean values of HDL-C between TRI and BI groups (p = 0.039), TRI and MONO (p = 0.005) and BI and MONO (p = 0.043) groups.

We observed statistically significant differences between mean values of homocysteine between TRI and BI groups (p = 0.03), TRI and MONO groups (p <0.001) and BI and MONO groups (p = 0.011).

Statistically significant differences were found when we compared the mean HC values between MONO group and CONTROL group (p<0.001), between the BI group and CONTROL group (p<0.001) and between TRI group and CONTROL group (p <0.001).

We observed a moderate significantly correlation between carotid IMT and plasma levels of homocysteine (r=0.409, p<0.001) (Fig.4).
4. Discussion
Our study showed there is an association between plasma homocysteine and mean IMT in patients with coronary artery disease patients being in concordance with previous studies that showed that plasma homocysteine was associated with the extent of cardiovascular disease. In two Japanese cross-sectional studies, it was reported that plasma homocysteine was associated with carotid IMT [14, 15]. One study showed that 17% of patients with coronary artery disease and 28% of patients with premature vascular disease have hyperhomocysteinemia [16]. Another meta-analysis of numerous studies clearly confirmed the association between blood levels of homocysteine and risk for coronary heart disease or stroke [17]. A meta-analysis demonstrated that a 25% reduction of homocysteine level was associated with an 11% decrease of coronary heart disease risk and a 19% lower stroke disease risk, and yet there is no evidence that lowering homocysteine levels by additional folic acid and/or vitamin B<sub>6</sub>/B<sub>12</sub> is associated with lower cardiovascular risk [18].

Another study analyzed the association between homocysteine metabolism and carotid IMT in patients with vascular events and concluded that elevated homocysteine levels were causally involved in cerebrovascular disease [19]. Other studies failed to detect a correlation between homocysteine and carotid intima-media thickness in ischemic stroke patients [20].

Another recently meta-analysis of MTHFR case-control studies between Homocysteine and Coronary Heart Disease showed that lifelong moderate homocysteine elevation has little or no effect on CHD [21].

Our study could be clinically important, because, by correction of hyperhomocysteinemia by vitamin supplementation, it may be corrected also atherosclerosis. Considering the fact that hyperhomocysteinemia has not been accepted yet as an established cardiovascular and the association between blood homocysteine concentration and the risk of cardiovascular disease remains controversial, future studies are necessary the mechanisms responsible.

5. Conclusion
The study showed an association between plasma homocysteine levels and carotid IMT in patients with angiographically confirmed coronary artery disease. Future studies are necessary to apprehend the effects of homocysteinemia on vascular endothelium.

References: