A study on serum homocysteine as an independent risk factor for coronary artery disease

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Abstract

Background: Coronary artery disease (CAD) has become the most common cause of mortality in the entire world. Homocysteine is implicated as an early atherosclerotic promoter. Homocysteine (Hcy) is an essential amino acid in humans. It has been known as a novel and independent risk factor for coronary heart disease (CHD). The prevalence of hyperhomocysteinemia varies between 5% and 30% in the general population.

Aim of the study: To assess whether hyperhomocysteinemia is one of the independent risk factors for coronary artery disease.

Materials and methods: The study was conducted in the Department of General Medicine, Government K.A.P. Viswanatham Medical College, Trichy from 2017-2018. Totally 100 Patients who were presented to our hospital with coronary artery disease of age group 30 to 70 years were included in the study. Diagnosis of coronary artery disease was made based on a history of angina pain, electrocardiography (ECG) changes and cardiac enzyme levels. Diagnosis of acute MI was made according to WHO criteria.

Results: Among the 100 patients, 66 had acute Myocardial Infarction and 34 had angina. Among the 52 patients who had hyperhomocysteinemia, 34 patients (65%) were young with age ≤ 45 years and 18 patients (35%) were with age > 45 years. In our study, 66 patients with MI were included. Among the 28 patients (42.4%) were young with age ≤45 years. In this group of young patients with MI, 21 patients (65.4%) had hyperhomocysteinemia and 7 patients (34.6%) had normal homocysteine level.

Conclusion: Finally, during the last decade, the utility of homocysteine in predicting risk for
atherothrombotic vascular disease has been evaluated in several observational studies in a large number of patients. These studies show that the overall risk for vascular disease is small, with prospective, longitudinal studies reporting a weaker association between homocysteine and atherothrombotic vascular disease compared to retrospective case-control and cross-sectional studies. Furthermore, randomized controlled trials of homocysteine-lowering therapy have failed to prove a causal relationship.

Key words
Homocysteine, Coronary Artery Disease, Atherosclerosis, Angina, Early myocardial infarction.

Introduction
Coronary artery disease (CAD) has become a major health problem and main contributor to mortality in the entire world as well in our country India. India is in epidemiological transition. The emerging threat of non-communicable diseases is a matter of concern in addition to the burden of endemic infections [1]. Previously, CAD was considered to be a result of an urban lifestyle; however, recently published studies have indicated that CAD is also on the rise in rural areas According to the World Heart Federation, 35% of all CVD deaths in India occur in those aged 35–64 years 90–95% of all cases and deaths are due to CAD Approximately, one-sixth of the world’s population lives in India and CAD remains the highest cause of mortality in India [2]. Coronary artery disease is the narrowing or blockage of the arteries and vessels that supply oxygen and nutrients to the heart. Most of the CADs are explained in the presence of traditional risk factors like hyperlipidemia, smoking, hypertension, and diabetes mellitus. Those 15–20% of CAD have no identifiable risk factors and therefore they miss the opportunity for primary prevention. However, despite aggressive control of risk factors in the general population, it is not possible to prevent progression of CAD in all patients [3]. Homocysteine has been recognized as early in the 1990s as a risk factor for the presence of atherosclerotic vascular disease and hypercoagulability states [4]. Homocysteine has emerged as a significant marker of vascular disease, especially in patients of Asian origin Increasing age, male sex, smoking, coffee consumption, high blood pressure, unfavorable lipid profile, high creatinine, and faulty diet are among the factors associated with increased homocysteine levels; physical activity, moderate alcohol consumption, good folate, and vitamin B-12 status are associated with lower homocysteine levels. It has been shown that elevated serum Hcy levels are associated with an increased risk of ischemic heart disease (IHD) and stroke [5]. Also, higher Hcy concentrations in IHD or stroke patients than in controls have been reported. Some prospective and case-control studies with inconsistent results, some with highly significant results and others with no association have been observed [6].

Materials and methods
The study was conducted in the Department of General Medicine, Government K.A.P. Viswanatham Medical College, Trichy from 2017-2018. Totally 100 Patients who were presented to our hospital with coronary artery disease of age group 30 to 70 years were included in the study. Diagnosis of coronary artery disease was made based on a history of angina pain, electrocardiography (ECG) changes and cardiac enzyme levels. Diagnosis of acute MI was made according to WHO criteria.

Exclusion criteria: Coronary artery disease patients with following known risk factors were excluded: Smoking Alcoholism, Diabetes mellitus, Hypertension, Hyperlipidaemia, Chronic kidney disease, Chronic liver disease.

Measurement of serum homocysteine [7, 8] 4 ml of blood was collected in EDTA coated tubes. Samples were stored at 2-8 degrees if
testing is delayed. Then serum was separated by centrifugation. Serum homocysteine was measured using Fluorescence Polarisation Immuno Assay (FPIA). First, the bound homocysteine present in serum was reduced to free homocysteine by the use of dithiothreitol (DTT). Then the free homocysteine was converted to S-adenosyl homocysteine (SAH) by the use of enzyme S-adenosyl homocysteine hydrolase enzyme and adenosine. (SAH – Hydrolase Homocysteine + adenosine SAH + H2O.) This mixture containing SAH, antibody, FPIA diluent buffer and a tracer tagged with a fluorescent chromophore were added to the cuvette. There were competition between SAH from the serum sample and the fluorescent tagged tracer to bind with the antibody. Then the intensity of the polarised fluorescent light was measured using FPIA optical assembly.

**Results**

100 patients were included in the study. Serum homocysteine levels were measured and the results were analyzed. Among the 100 patients, 62 were male and 38 were female. Male preponderance was seen.

Mean age group of patients included in the study was 49.11 years. Among the 100 patients, 47 patients were young with age <45 years. The mean age of this group of patients was 38.13 years. 53 patients were of age group >45 years. The mean age of this group of patients was 58.85 years (Table 1).

**Table 1:** Age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 45 years</td>
<td>47</td>
</tr>
<tr>
<td>Age &gt;45 years</td>
<td>53</td>
</tr>
</tbody>
</table>

Among the 100 patients, 66 had acute Myocardial Infarction and 34 had angina (Table 2).

Among less than 45 years of age, 72.3% had elevated levels of homocysteine compared with only 34% among above 45 years age (Table 3).

This difference was statistically significant using a Chi-square test (Chi-square value: 14.7, P values <0.001).

**Table 2:** Type of CAD.

<table>
<thead>
<tr>
<th>Type of CAD</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>34</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>66</td>
</tr>
</tbody>
</table>

**Table 3:** Age categorized homocysteinemia.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Normal</th>
<th>Hyperhomocysteinemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 45 years</td>
<td>13 (27.7%)</td>
<td>34 (72.3%)</td>
<td>47</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>35 (66.0%)</td>
<td>18 (34.0%)</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>52</td>
<td>100</td>
</tr>
</tbody>
</table>

In our study, 66 patients with MI were included. Among the 28 patients (42.4%) were young with age <45 years. In this group of young patients with MI, 21 patients (65.4%) had hyperhomocysteinemia and 7 patients (34.6%) had normal homocysteine level (Table 4).

**Discussion**

This study showed a male preponderance of coronary artery disease. This is similar to the observation found in Framingham heart study. This can be attributed to the protective effects of estrogen in premenopausal females. It also showed that myocardial infarction is common than unstable angina among the elderly age group. This is also in accordance with the observation seen in American Heart Association study [9]. In our study, the mean age of patients was years. In the group with age <45 years, the mean age is 38.13 years. In Indian sub-continent CAD occurs about a decade earlier as compared to the western world. The role of homocysteine as an independent risk factor of coronary artery disease has not been extensively studied in India.
Due to dietary and other ethnic differences, the results found in western studies cannot be applicable to our population [10]. Recent studies on homocysteine suggest that it is an independent predictor of vascular disease including stroke and CAD. In a study conducted by Mizrahi EH, et al., ‘hyperhomocysteinemia an independent risk factor for vascular disease’, they concluded that ‘hyperhomocysteinemia is an independent risk factor for vascular disease, including coronary disease’ [11]. Patil SS, et al., they concluded that ‘hyperhomocysteinemia is an emerging and important risk factor for thromboembolic and cardiovascular disease’ [12]. Smith SC, et al. in their study analyzed the results of various epidemiological studies regarding the role of homocysteine in coronary artery disease. In our study, the mean homocysteine in patients was 26.35 ± 18.1. This is in accordance with that study. Most of the above studies included patients with coronary artery disease and coexisting known risk factors like diabetes, hypertension, smoking, alcoholism, hyperlipidemia, etc. and compared the hyperhomocysteinemia with the conventional risk factors to find out whether hyperhomocysteinemia is a risk factor for CAD [12]. In our study, we excluded patients with conventional risk factors and included only patients without those risk factors and evaluated whether hyperhomocysteinemia has a role independent of other conventional risk factors in the development of CAD. We found that the significant number of patients had hyperhomocysteinemia and it is also found to be statistically significant with P value < 0.001. Thus hyperhomocysteinemia is emerging as an independent risk factor of CAD in our study [13].

Also in our study, the incidence of hyperhomocysteinemia is found to be higher in patients with age ≤ 45 years presenting with CAD. When compared to patients with age >45 years within the study group, this difference is found to be statistically significant with P value <0.001. So, hyperhomocysteinemia is found to be an important risk factor in patients with younger age presenting with CAD [14]. This also found in a study, ‘Homocysteine and lipid levels in young patients with coronary artery disease’ by Ueland PM, et al. They found that plasma homocysteine emerged as a significant independent risk factor for young CAD patients [15]. In our study, 66 patients with MI were included. Among these 66 patients, 28 (42.4%) were young patients with age <45 years. In this group of young patients with MI 21 patients (65.4%) had hyperhomocysteinemia and 7 (34.6%) had normal homocysteine level. Hence in young patients with MI hyperhomocysteinemia is a significant risk factor. This association between hyperhomocysteinemia and young MI was studied by so many authors [16]. In a study by Verhoef P, et al. conducted in Aligarh, India, they found that the prevalence of homocysteine in young MI patients was 83.3% and homocysteine has emerged as a significant risk factor for young MI [17]. This is also found in a study conducted by Wall RT, et al. They studied the levels of serum homocysteine in young patients with MI and concluded that in patients presenting with normal cholesterol level, coronary artery disease was triggered by increased serum homocysteine level [18]. Wang H, et al. also confirmed this association of serum homocysteine concentration in young with acute MI and recommended the evaluation of serum homocysteine in young patients presenting with MI [19]. In our study among the 48 patients who had normal homocysteine level, 13 patients had age ≤ 45 years and 35 patients had age > 45 years. These patients did not have any conventional risk factors but developed cardiovascular disease [20].

**Conclusion**

It has been established that lowering the markedly elevated circulating homocysteine concentrations found in patients with the inborn error of homocysteinuria due to CBS deficiency, even to suboptimal concentrations, greatly reduces cardiovascular risk. The results of the many ongoing homocysteine-lowering trials with folic acid in vascular patients may certainly clarify whether folate therapy is relevant to
cardiovascular risk in the general population and will provide much important information. Finally, during the last decade, the utility of homocysteine in predicting risk for atherothrombotic vascular disease has been evaluated in several observational studies in a large number of patients.

References


