Evaluation of serum homocysteine in young patients presenting with myocardial infarction: a study from rural Maharashtra

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Received: 20 September 2020
Accepted: 05 October 2020

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ABSTRACT

Background: It has been shown that elevated serum homocysteine levels are associated with an increased risk of ischemic heart disease (IHD) and stroke. Also, higher homocysteine 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. Objective of the study was to evaluate the serum homocysteine level in young myocardial infarction patients of rural hospital.

Methods: The present hospital based cross sectional observational study was carried out in Department of Medicine, MIMER Medical College and Hospital, Talegaon Dabhade, Pune. The study population included 45 young patients having acute myocardial Infarction coming to our hospital. The data thus collected was entered in MS excel sheet and analysed by using SPSS 24.0 IBM USA.

Results: Mean age of the study cohort was 36.7 years with 48.9% cases in between the age of 31-40 years and 33.3% were in the age range of 41-45 years. Male predominance was seen in the study cases with 68.9% males and 31.1% females. Prevalence of hyperhomocysteinemia was observed as 64.4% in present study. Mortality rate in our study was 6.67%. Serum homocysteine and all lipid parameters were in positive correlation except High-density lipoprotein which has negative correlation. Homocysteine levels were correlating significantly with level of atherosclerosis as measured by Gensini score.

Conclusions: Coronary heart disease is related to high serum homocysteine concentration. Serum homocysteine levels also correlates well with the severity of MI.

Keywords: Coronary artery disease, Homocysteine, Myocardial infarction

INTRODUCTION

The mortality from coronary artery disease is increasing rapidly in developing countries like India. It is estimated that mortality from cardiovascular diseases in developing countries has doubled from 1970 to 2015. In India alone there had been 1.2 million deaths from coronary heart disease in 1990 and an increase in cardiovascular deaths by 11.1% is predicted by 2020. Multiple risk factors are implicated for this rise, ranging from cigarette smoking, hypertension, diabetes mellitus and obesity to various psychosocial stresses imposed by social dynamics and urbanization.¹

Acute myocardial Infarction (MI) is said to have occurred when there is biochemical evidence of myonecrosis in a patient with chest pain suggestive of coronary ischemia for prolonged period (>30 min). They are classified as ST...
segment elevation MI and non-ST-segment elevation MI. 2 ST segment elevation MI (STEMI) represents the most lethal form of myocardial insult. The thrombus results in total cessation of coronary blood flow in the territory of occluded artery that leads to ST segment elevation on the ECG.2

Although MI is usually the disease of people over 40 years of age, an increasing number of younger patients are being hospitalized with acute coronary syndromes. It brings significant physical and psychosocial morbidity. The increased prevalence in young adults can be partly attributed to the increased prevalence of risk factors for atherosclerosis among the population under the age of 40.3 Besides atherosclerotic coronary artery disease, non-atherosclerotic coronary artery diseases or hypercoagulability should be considered for young cases of myocardial infarction.3

Homocysteine, a sulphur containing amino acid was first described by Vigneaud in 1931. Elevated plasma levels of Homocysteine have been associated with vascular disease. The hallmarks of homocystinuria are Ectopic lentis, Marfanoid appearance, vascular manifestations, musculo- skeletal and CNS manifestations. In blood only about 1% of total Homocysteine is in free reduced form. The major part of Homocysteine in plasma is oxidized and either covalently bound to proteins or occur as disulfides.4

The determinants of total homocysteine in plasma include several genetic enzyme defects especially cystathionine beta synthase and MTHFR polymorphism age and gender, drugs, vitamin status, diabetes, steroid hormones, thyroid disease etc.5,6 Homocysteine has been found to induce vascular injury by multiple mechanisms: Homocysteine promotes leucocyte recruitment by up regulating monocyte chemoattractant protein and interleukin expression and secretion.7,8 It also causes oxidation of LDL which has lipid peroxidation effect. Homocysteine increases smooth muscle cell proliferation and enhances collagen production.8 And it also causes direct endothelial injury.9 Prothrombotic effects of Homocysteine, which have been demonstrated in patients with acute coronary syndromes and stroke, include attenuation of endothelial cell tissue plasminogen activator binding sites, activation of factor VIIa and V, inhibition of protein C and heparin sulphate, increased fibrinopeptide A and prothrombin fragments 1 and 2, increased blood viscosity, and decreased endothelial antithrombotic activity due to changes in thrombomodulin functions. Also prolonged exposure of endothelial cells to Homocysteine reduces the activity of dimethyl arginine dimethylamino hydrolase, the enzyme that degrades asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase; this impairs the production of nitric oxide. This may contribute to impaired endothelium dependent vasodilatation of both conduit and resistance vessels.

It has been shown that elevated serum homocysteine levels are associated with an increased risk of ischemic heart disease (IHD) and stroke.10 Also, higher homocysteine 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.11

So, the present study was aimed to establish correlation between raised level of homocysteine and myocardial infarction among young patients.

Objective

Objective of the study was to evaluate the serum homocysteine level in young myocardial infarction patients of rural hospital.

METHODS

The present hospital based cross sectional observational study was carried out in Department of Medicine, MIMER Medical College and Hospital, Talegaon Dabhade, Pune.

Study population:

The study population included 45 young patients having acute myocardial Infarction coming to our hospital. The study was carried out during July 2018 to June 2020 for a period of two years.

Inclusion criteria

All patients aged upto 45 years who fulfil two out of these three conditions i.e. severe chest pain lasting for> 20 minutes and not responding to sublingual nitroglycerine tablets significantly, presence of pathological Q wave along with ST segment elevation and subsequent T wave inversion and significant rise in CPK-MB and Troponin T on 1st or 2nd day.

Exclusion criteria

Exclusion criteria were patients with chest pain due to non-cardiac causes, myocardial Infarction patients of age older than 45 years.

After admission detailed history and clinical examination was carried out and following investigations were done: 12 lead ECG, serum CPK-MB, serum troponin–T, hemogram, urine examination, lipid Profile, serum homocysteine, serum hs-CRP, serum homocysteine levels and lipid Profiles were measured in a 12-hour fasting blood sample, serum homocysteine–fluorescence polarization immunoassay method by AxSYM Assay system using the principle of conversion of oxidized homocysteine to reduced form and then converting into
Statistical analysis

The data thus collected was entered in MS excel sheet and analysed by using SPSS 24.0 IBM USA. The quantitative data was represented as their mean±SD. Categorical and nominal data was expressed in percentage. The t-test was used for analyzing quantitative data, or else non parametric data was analyzed by Mann Whitney test and categorical data was analyzed by using chi-square test. The significance threshold of p value was set at <0.05.

RESULTS

Mean age of the study cohort was 36.7±4.2 years with 48.9% cases in between the age of 31-40 years and 33.3% were in the age range of 41-45 years (Table 1).

Table 1: Distribution of study cases as per age group.

| Age group (years) | N  | %     |
|-------------------|----|-------|
| ≤ 20              | 1  | 2.2   |
| 21-30             | 7  | 15.6  |
| 31-40             | 22 | 48.9  |
| 41-45             | 15 | 33.3  |
| Total             | 45 | 100.0 |

Male predominance was seen in the study cases with 68.9% males and 31.1% females (Figure 1).

Figure 1: Distribution of study cases as per gender.

Table 2: Distribution of study cases as per prevalence of hyperhomocysteinemia.

| Hyperhomocysteinemia (>15 µmol/l) | N  | %     |
|-----------------------------------|----|-------|
| Yes                               | 29 | 64.4  |
| No                                | 16 | 35.6  |
| Total                             | 45 | 100.0 |

Prevalence of hyperhomocysteinemia was observed as 64.4% in present study (Table 2).

Gensini score of 1 was observed in 24.4% cases while score of 2, 4 and 8 was reported in 48.9%, 20% and 6.7% cases. (Table 3). Mortality rate in our study was 6.67% (Table 4).

Table 3: Distribution of study cases as per Gensini score.

| Gensini Score | N  | %     |
|---------------|----|-------|
| 1             | 11 | 24.4  |
| 2             | 22 | 48.9  |
| 4             | 9  | 20.00 |
| 8             | 3  | 6.70  |
| 16            | 0  | 0.00  |
| 32            | 0  | 0.00  |
| Total         | 45 | 100.0 |

Table 4: Distribution according to mortality.

| Mortality | N  | %     |
|-----------|----|-------|
| Yes       | 3  | 6.67  |
| No        | 42 | 93.33 |
| Total     | 45 | 100.0 |

Serum homocysteine and all lipid parameters were in positive correlation except high-density lipoprotein (HDL) which has negative correlation. Homocysteine levels were correlating significantly with level of atherosclerosis as measured by Gensini score (r=0.59; p<0.01) (Table 5).

Table 5: Pearson correlation of serum homocysteine with lipid parameters.

| Homocysteine | R value | P value |
|--------------|---------|---------|
| TC           | 0.39    | 0.08    |
| TG           | 0.31    | 0.19    |
| LDL          | 0.28    | 0.23    |
| HDL          | -0.19   | 0.44    |
| Gensini Score| 0.59    | <0.01   |

Mean homocysteine in less than 30 years age was 17.59±7.08 whereas in 31-45 years it was 17.67±6.41. The difference in the mean homocysteine was found to be statistically not significant (p>0.05). Mean homocysteine in males was 17.5±6.18 whereas in females it was 17.68±7.13. The difference in the mean homocysteine was found to be statistically not significant (p>0.05). Mean homocysteine with Gensini score ≤ 2 males was 13.34±6.83 whereas it was 21.12±6.85 with Gensini score more than 2. The difference in the mean homocysteine was found to be statistically significant (p<0.05). Mean homocysteine in death patients was 15.45±7.08 whereas it was 23.43±11.2 in survived patients. The difference in
the mean homocysteine was found to be statistically highly significant (p<0.001) (Table 6).

Table 6: Comparison of serum homocysteine with demographic variables.

| Variables       | N  | Mean Hcy | SD  | P value |
|-----------------|----|----------|-----|---------|
| Age (years)     |    |          |     |         |
| ≤ 30            | 8  | 17.59    | 7.08| 0.97    |
| 31-45           | 37 | 17.67    | 6.41|         |
| Sex             |    |          |     | 0.933   |
| Male            | 31 | 17.5     | 6.18|         |
| Female          | 14 | 17.68    | 7.13|         |
| Gensini score   |    |          |     | 0.01    |
| ≤ 2             | 33 | 13.34    | 6.83|         |
| >2              | 12 | 21.12    | 6.85|         |
| Mortality       |    |          |     | 0.0001  |
| No              | 42 | 15.45    | 7.08|         |
| Yes             | 3  | 23.43    | 11.2|         |

DISCUSSION

Demography

Mean age of the study cohort was 36.7 years with 48.9% cases in between the age of 31-40 years and 33.3% were in the age range of 41-45 years. Male predominance was seen in the study cases with 68.9% males and 31.1% females (Table 1 and Figure 1).

Studies performed on ischemic stroke among the 15-45 years age group from India also reported a male preponderance.12,13

Similar findings had been reported from Denmark in cases of thromboembolic stroke.14

A higher proportion of males was found among cases of ischemic stroke in studies outside India.15

Homocysteine levels in myocardial infarction

Homocysteine has been found to induce vascular injury by multiple mechanisms: homocysteine promotes leucocyte recruitment by up regulating monocyte chemoattractant protein-I and interleukin-8 expression and secretion.7 It also causes oxidation of LDL which has lipid peroxidation effect. Homocysteine increases smooth muscle cell proliferation and enhances collagen production.8 And it also causes direct endothelial injury.9

Prothrombotic effects of homocysteine have also been demonstrated in patients with acute coronary syndromes and stroke. Also prolonged exposure of endothelial cells to Homocysteine impairs the production of nitric oxide, which in turn contribute to impaired endothelium dependent vasodilatation of both conduit and resistance vessels.

In present study, prevalence of hyperhomocysteinemia was observed as 64.4% in present study (Table 2 and 3)

Gosh et al aimed to observe the prevalence of plasma hyperhomocysteinaemia in a cohort of patients with acute myocardial infarction.16 Sixty-three (52.5%) out of 120 patients showed hyperhomocysteinaemia.

Ramesh et al in their study aimed to assess whether hyperhomocysteinaemia is one of the independent risk factors for coronary artery disease.17 Among the 28 patients of MI with age<45 years, 21 patients (65.4%) had hyperhomocysteinaemia and 7 patients (34.6%) had normal homocysteine level.

In a study, Verhoeef et al 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.18

Shanoli et al and Chauhan et al also observed high levels of serum homocysteine in patients of myocardial infarction.19,20

Homocysteine as a predictor of CAD

Hyperhomocysteinemia was reported as an independent risk factor for vascular disease. Authors concluded that ‘hyperhomocysteinemia is an independent risk factor for vascular disease, including coronary disease’ Patil et al, concluded that hyperhomocysteinemia is an emerging and important risk factor for thromboembolic and cardiovascular disease.21

Ramesh et al in their study observed the incidence of hyperhomocysteinemia to be higher in patients with age ≤ 45 years presenting with CAD.17 When compared to patients with age>45 years within the study group, this difference is found to be statistically significant with P value<0.05. So, hyperhomocysteinemia is found to be an important risk factor in patients with younger age presenting with CAD.

In present study, homocysteine levels were correlating significantly with level of atherosclerosis as measured by Gensini score (r=-0.59; p<0.01). Mean homocysteine levels were significantly higher among cases with significant atherosclerosis (Gensini score>2.21.12 vs 13.34 µmol/l; p<0.01) and in cases with poor outcome (Mortality: 23.43 vs 15.45 µmol/l; p<0.01).

Schaffer A et al aimed to investigate the association of Homocysteine with the prevalence and extent of CAD. A significant relationship was found between Hcy levels and the extent of coronary artery disease (71.8% vs 77.8% vs 77.4%, or [95% CI]=1.18 [1.11-1.252], p<0.001 and severe CAD (23.6% vs 29.5% vs 32.1%, or [95% CI]=1.275 [1.209-1.344], p<0.001). Elevated Hcy was significantly associated with increased risk of CAD.
Homocysteine levels are responsible for elevated serum homocysteine. J Vascul Biol.

Cholesterol, the higher levels of Serum homocysteine induces development of atherosclerosis. 1.

Institutional Ethics Committee: Ethical approval: The study was approved by the Institutional Ethics Committee.

In present study, we also observed that lipid profile was correlated significantly with atherosclerosis as measured by Gensini score (p>0.05) (Table 6).

Similar findings were also reported by Chauhan et al who concluded that low levels of LDL-C and high levels of HDL-C did not protect the patients against the Homocysteine induced coronary artery disease. Also, it shows that in patients who did not have high levels of total cholesterol, the higher levels of Serum Homocysteine triggered the coronary artery disease.20

Similar results were also confirmed by Ramesh N et al where patients who did not have any conventional risk factors, developed cardiovascular disease.17

Thus, to summarize, high serum homocysteine concentration was observed in young myocardial infarction cases. Serum homocysteine levels also correlates well with its severity. Also, it has been shown that in patients who did not have dyslipidemia, the higher levels of serum homocysteine levels are responsible for triggering the mechanism for coronary artery disease.

CONCLUSION

Our study results support the hypothesis that coronary heart disease is related to high serum homocysteine concentration. Serum homocysteine levels also correlates well with the severity of MI. From the above findings, it has been shown that low levels of LDL-C and high levels of HDL-C did not protect the patients against the homocysteine induced coronary artery disease. Also, it shows that in patients who did not have high levels of total cholesterol, the higher levels of serum homocysteine levels are responsible for triggering the mechanism for coronary artery disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Khedkar SV, Kumar S, Patil P, Takalkar AA. Evaluation of serum homocysteine in young patients presenting with myocardial infarction: a study from rural Maharashtra. Int J Adv Med 2020;7:1635-40.