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Plasma Homocysteine Concentration in Acute Coronary Syndromes

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ABSTRACT

Introduction: The high plasma or serum concentrations of total homocysteine are associated with an increased risk of atherothrombotic disease. Aim- a study to assess Plasma Homocysteine Concentration in Acute Coronary Syndromes.

Methods: Total 60 patients with the diagnosis of coronary artery disease and non-hemorrhagic stroke are included in this study.

Results: In the present study, the plasma homocysteine level is significantly elevated in patients with CAD and non-hemorrhagic stroke. The elevated plasma homocysteine level is an independent and traditional risk factor for CAD. This in turn may revolutionise the development of new strategies of treatment for primary prevention of CAD and non-hemorrhagic stroke in those individuals who do not have traditional risk factors. In absence of the established major atherogenic risk factors like hypertension, diabetes mellitus, hyperlipidemia and smoking, atherosclerotic occlusive vascular events are known to occur. This indicates that there may be an additional independent risk factor such as elevated plasma homocysteine. There is increasing evidence that, linked hyperhomocysteinaemia as a risk factor for the pathogenesis of atherosclerosis. To confirm this concept, 60 cases of occlusive atherosclerotic vascular events (45 coronary artery disease and 15 non-haemorrhagic cerebrovascular diseases), without other risk factors are studied, for plasma homocysteine levels.

Conclusion: Homocysteine levels are studied in control subjects without clinical vascular diseases. The data is analysed to demonstrate the correlation of homocysteine levels with vascular events.

Key Words: Homocysteine, Acute coronary syndromes, Non-Haemorrhagic stroke

INTRODUCTION

The first to hypothesise that hyperhomocysteinaemia is a risk factor for atherothrombosis. More recently, many but not all cross-sectional and prospective studies have shown that high plasma or serum concentrations of total homocysteine are associated with an increased risk of atherothrombotic disease. High total homocysteine concentrations can be lowered by treatment with folic acid and vitamin B₁₂. So assessment of whether such treatment lowers the risk of atherothrombosis is important.^{1,2}

Hyperhomocysteinaemia as a Risk Factor

Hyperhomocysteinaemia is an independent risk factor for Coronary Artery Disease (CAD).³ Elevated plasma homocysteine concentration is found in almost one-third of all patients with atherosclerosis. Elevation by 12% above the

upper limit of normal (15 micromoles per litre) is associated with a three-fold increase in the risk of acute myocardial infarction (AMI). Homocysteine concentration is determined by genetic and nutritional factors.⁴ vitamin B₁₂ and folic acid are essential co-factors for the remethylation of homocysteine to methionine and dietary supplementation with these vitamins lowers plasma homocysteine by up to 30 %. These observations have formed the basis of large scale intervention trials that are seeking to determine whether lowering homocysteine concentration through vitamin-B supplementation can improve survival in patients with CAD.²² Increasing evidence suggests that adverse vascular effects of elevated homocysteine are mediated through endothelial dysfunction which is an early manifestation of atherosclerosis.⁴

So, far studies investigating the effects of lowering homocysteine concentrations on vascular endothelial function have yielded conflicting results.⁵ In primates, folate supple-

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mentation is reported to reduce plasma homocysteine concentration but not to affect vascular function.³⁴ In healthy human subjects, folate supplementation is associated with reduced homocysteine concentration and improved vascular endothelial function. Though in these studies there was no relation between homocysteine concentration and endothelial function implying that the effects of B vitamins on endothelial function may not be mediated through homocysteine lowering.⁶

India is on the threshold of an epidemic of cardiovascular disease (CVD). The country is going through an epidemiological transition. Infectious and nutritional diseases are receding as the cause of adult mortality, while non-communicable diseases assume more menacing proportions.⁷

MATERIALS & METHODS

All cases of acute coronary syndromes including acute myocardial infarction and non-hemorrhagic stroke admitted in the Intensive Care Unit, Dept. of Medicine, Krishna Hospital, Karad.

A total of 60 patients with the diagnosis of coronary artery disease and non-hemorrhagic stroke are included in this study.

Exclusion Criteria

The following patients were excluded from the study

1. Diabetes mellitus
2. Hypertension
3. Renal Disease
4. Chronic Smokers
5. Hyperlipidemia

Inclusion Criteria

1. Acute coronary syndromes including acute myocardial Infarction (STEMI, NSTEMI), unstable angina, and cardiac enzyme abnormalities.
Non-hemorrhagic stroke.

Diagnostic Criteria

The diagnosis of coronary artery disease was based on clinical history, ECG change (ST-elevation according to nomenclature, ST depression with enzyme abnormalities), cardiac enzyme estimation, and two Dimensional Echocardiography.

The diagnosis of non-hemorrhagic stroke patients was based on clinical history, clinical findings, and CT scan of the head.

OBSERVATIONS AND RESULTS

In the Department of Medicine, Krishna Hospital, Karad 133 patients were diagnosed as CAD.

Total of 358 patients presented with stroke out of which 263 patients were diagnosed as non-hemorrhagic stroke patients.

A total of 45 patients of CAD and 15 patients of non-hemorrhagic stroke fulfilled the criteria for the present study.

Randomly selected, age-matched 25 patients of other medical problems were taken as a control for this study.

SEX DISTRIBUTION

Out of a total of 60 patients with coronary artery disease and cerebrovascular disease, 34 (56.67%) are male and 26 (43.33%) are female shown in **table 1**

Out of 26 patients with acute myocardial infarction, 12 (46.12%) have antero-septal MI, 6 (23.08%) have inferior wall MI, 2 (7.69%) have trans-ant MI, 2 (7.69%) have trans-ant + inf MI, 1 (3.85%) has antero-septal + Hi lat MI and 3 (11.54%) have extensive anterior MI.

Out of total 19 patients with the acute coronary syndrome, 9 (47.37%) have antero-septal MI, 8 (42.11%) have inferior MI, 1 (5.26%) has trans-ant + inf MI, 1 (5.26%) has extensive anterior MI and none in trans-ant MI as well as in antero-septal + hi lat MI. (**Table 2**)

Disease distribution location of non-hemorrhagic infarctions

Out of a total of 15 patients with non-hemorrhagic stroke 7 (46.67%) have RMCA area infarction and 8 (53.33%) have LMCA area infarction.

- In this group, there were no patients of vertebrobasilar territory infarction.

Plasma homocysteine levels in the study group

Out of a total of 60 patients of the study group 2 (3.3%) have normal Hcy level, 13 (21.66%) have moderate Hcy level, 16 (26.66%) have intermediate Hcy level and 29 (48.33%) have severe Hcy level.

Plasma homocysteine levels in different MI groups

Out of a total of 12 patients with antero-septal MI 1 (8.33%) has a normal Hcy level, 1 (8.33%) has a moderate Hcy level, 6 (50.00%) have intermediate Hcy level and 4 (33.33%) have severe Hcy level.

Plasma homocysteine levels in different MI groups

Out of a total of 6 patients with an inferior wall, MI 2 (33.33%) have moderate Hcy level, 2 (33.33%) have intermediate Hcy level, 2 (33.33%) have severe Hcy level and none has normal Hcy level.

Plasma homocysteine levels in different MI groups

Out of 2 patients with transanterior MI 2 (100%) have severe Hcy level and none has normal, moderate, and intermediate Hcy level.

Plasma homocysteine levels in different MI groups

Out of a total of 2 patients with transanterior + inferior wall, MI 2 (100%) have severe Hcy level and none has normal, moderate, intermediate Hcy level.

Plasma homocysteine levels in different MI groups

Out of a total of 1 patient with anteroseptal + high lateral MI 1 (100%) has a moderate Hcy level and none has normal, intermediate, severe Hcy level.

Plasma homocysteine levels in different MI groups

Out of a total of 3 patients with extensive anterior MI 3 (100%) have severe Hcy level and none has normal, moderate, intermediate Hcy level.

Plasma homocysteine levels in different acute coronary syndrome groups

None of the patients had transanterior myocardial ischemia.

Plasma homocysteine levels in different acute coronary syndrome groups

Out of a total of 1 patient with transanterior + inferior MI 1 (100%) has an intermediate Hcy level and none has normal, moderate, severe Hcy level.

Plasma homocysteine levels in different acute coronary syndrome groups

None of the patients had anteroseptal + high lateral myocardial ischemia. (Table 20)

Plasma homocysteine levels in different acute coronary syndrome groups

Out of a total of 1 patient with extensive anterior MI 1 (100%) has a severe Hcy level and none has a normal, moderate, intermediate Hcy level.

Cardiac Enzymes

Out of a total of 45 patients with coronary artery disease, 18 (40%) have CPK-MB elevated in the range of 20-40 IU/It and 27 (60%) have CPK-MB elevated by more than 40 IU/It.

Plasma homocysteine levels in different Non-hemorrhagic stroke groups

Out of a total of 8 patients with LMCA area infarction, 2 (25%) have moderate Hcy level, 1 (12.50%) has intermediate Hcy level, 5 (62.50%) has a severe Hcy level and none has a normal Hcy level. (Table 23)

Plasma homocysteine levels in different Non-haemorrhagic stroke groups.

Out of a total of 7 patients with RMCA area infarction, 3 (42.86%) have moderate Hcy level, 1 (14.26%) has intermediate Hcy level, 3 (42.86%) have severe Hcy level and none has a normal Hcy level. (Table 24)

Plasma homocysteine levels in the control group.

Out of the total of 25 patients in the control group, 24 (96%) have normal Hcy level, 1 (4%) has moderate Hcy level and none has intermediate, severe Hcy level.

DISCUSSION

Out of total 45 patients are with CAD and 15 patients with non-hemorrhagic stroke are included in this study.

Age and sex distribution

The age group of the male is 23-70 yrs. Age group of the female is 35-70 years. Male to female ratio in this study is 1.3:1. After the age of 45 years, there is no significant gender difference in the prevalence of vascular events. In the younger (<45 years) patients, males appear to have a higher prevalence. Stamfer, Nygard, and Graham et al also noted similar male Predominance.⁸

In the present study, 1 person is in the age group 20-25 years (1.67%), 1 person is in the age group 26-35 years (1.67%), 10 people 36-45 years (16.67%). The majority are in the age group 46-55 years (35%) in the age group 56-65 (30%) and 66-70 years (15%).

In the study by Stamfer, the majority are in the age group of 40-45 years (41%). In the Perry study, 54% of the patients were in the age group of 60-70 years.⁹ Anterior (its variants) MI is the predominant in the present study (69.23%) followed by inferior MI (23.08%), combined (7.69%). Similar results are found in Graham and Nygard. Anterior (its variants) MI is predominant in the present study (52.63%) followed by inferior MI (42.11%) and combined (5.26%). Similar results are found in Graham and Nygard et al.

In the present study both right middle cerebral artery territory infarction (RMCA) and left middle cerebral artery territory infarction (LMCA) are approximately equal in number. In this group there are no patients of vertebrobasilar territory

infarction as the total number of non-hemorrhagic stroke in this study is small.

Homocysteine levels in anterior (and its variants) MI are normal in 5.56%, moderate in 11.11%, intermediate in 33.33%, and severe in 50.00% of patients. In inferior MI the Hcy levels are normal in None, moderate in 33.33%, intermediate in 33.33%, severe in 33.33%. In combined MI the Hcy levels are severe in 100%.

Homocysteine levels in anterior (and its variants) MIsc are normal in 10.00%, moderate in 40.00%, intermediate in 10.00%, severe in 40.00%. In inferior MIsc, the Hcy levels are normal in None, moderate in 12.50%, intermediate in 37.50%, severe in 50.00%. In combined MIsc the Hcy levels are moderate in 100.00%.

Homocysteine levels in LMCA area infarction are normal in None, moderate in 25.00%, intermediate in 12.50%, severe in 62.50%. In RMCA area infarction Hcy levels are normal in None, moderate in 42.86%, intermediate in 14.26%, severe in 42.86%.

Abnormal homocysteine levels are found in all categories of ACS and cerebral infarction.

The level of hyperhomocysteinemia does not seem to reflect the area of infarction in the brain.

It appears to be a linear, severity dependent correlation of the vascular episodes with plasma homocysteine levels.

More extensive myocardial infarctions such as transanterior or combined (anterior + inferior) reflect the severity of the disease and appear to have a significantly elevated level of homocysteine.

In our present study, the mean value of homocysteine from the study group is 78.7 micromol (SD \pm 40.94) and from the control group 9.5 micromol (SD \pm 3.10), which is statistically significant ($P < 0.05$)

The evidence for the role of elevated homocysteine in the causation of CVD is still inconclusive. Even in the event of availability of such evidence from studies in the West, extrapolation to the Indian population will be precluded by the latter's distinct risk factor profile which mandates a study of independent and interactive risk contributions. For new hazard components to be significant in infection avoidance in any populace, they should either be liable for a generous extent of the malady trouble, or their adjustment must tangibly affect sickness pervasiveness in that populace. The major known modifiable risk factors explain at least 75% of new cases of cardiovascular disease even in the western world. Doctors and their patients should hence not dismiss the way that way of life changes consolidating smoking end, a heart sound eating regimen, weight decrease, and ordinary physical movement along with sedate treatment for dyslipidemia,

remain the foundations of CVD avoidance in our populace. The normal estimation of plasma homocysteine and the utilization of explicit treatments coordinated at diminishing raised levels aren't yet suggested.

On the other hand, Mc Culley hypothesized that elevated plasma homocysteine could cause atherosclerosis. Abundant epidemiologic evidence from more than 20 case-control and cross-sectional studies involving 2000 patients has validated this relation.

The Arnesen et al.⁹ study found that 26%, 26%, 2% of patients were in the moderate intermediate and severe category of Hcy respectively.⁹ In another study by Perry, the incidence was 23%, 6%, and 1% respectively.

Boers and colleagues screened 75 patients with the premature atherosclerotic vascular disease for hyperhomocysteinemia using methionine challenge and found that yearly 1/3rd of all patients with cerebrovascular and peripheral vascular disease had hyperhomocysteinemia.¹⁰

Clark and colleagues subsequently measured homocysteine concentration after methionine loading in a cohort of men with premature vascular disease and demonstrated that 30% of patients with CAD, 42% with cerebrovascular disease, 28% with the peripheral vascular disease had hyperhomocysteinemia.¹¹

Two large prospective studies have assessed the risk of CAD in patients with hyperhomocysteinemia. In the physician's health study 14916 male physicians without known atherosclerosis had an initial homocysteine measurement and were prospectively followed for an average of 5 years. Men with plasma homocysteine concentrations that were 12% above the upper limit of normal had approximately a three-fold increase in the risk of myocardial infarction as compared with those with lower levels even after correction for other risk factors. They estimated that 7% of 271 observed myocardial infarctions could be attributed by hyperhomocysteinemia.¹²

A prospective TROMSO study reported similar results and several other studies have consistently indicated that hyperhomocysteinemia is an independent risk factor for vascular disease.

Graham and coworkers recently measured plasma homocysteine concentration in 750 patients with atherosclerosis and 800 normal subjects. There was a statistically significant difference in plasma homocysteine concentration during fasting between patients and controls (11.25 micromoles / Ltr Vs 9.73 micromoles /Ltr.) and a methionine challenge revealed an additional 27% of patients had hyperhomocysteinemia. Elevated plasma homocysteine conferred an independent risk factor for vascular disease similar to that of smoking or hypercholesterolemia and also had a multiplicative effect as risk amongst smokers and patients with hypertension. The

author suggested that controlling hypertension and smoking might be particularly important with hyperhomocysteinemia.

Nygard and colleagues recently reported a prospective study involving 587 patients with angiographically documented CAD. Baseline homocysteine measurements were obtained and patients were followed for a median of 4.6 years during which time 1.9% of them died. These investigators found a strong association between homocysteine concentrations and overall mortality.¹³

In a recent meta-analysis, Boushey and colleagues estimated that 10% of the risk of CAD in the general population was attributed to elevated homocysteine. They reported that an increase of 5 micromoles per ltr. in plasma homocysteine concentration, raises the risk of CAD by as much as an increase of 20 mg per deci ltr. in the cholesterol concentration.¹⁴

In the present study, in patients with CAD and cerebrovascular atherosclerotic disease, where the major risk factors were excluded, an elevated homocysteine level is obvious. Though the number of patients is small, it may be inferred as an independent risk factor, as only **two** of the cases had normal homocysteine levels.

CONCLUSIONS

Elevated plasma homocysteine levels are seen in 95.5% of patients with coronary artery disease and cerebrovascular disease in this study. There is a statistically significant association between the level of plasma homocysteine and occlusive atherosclerotic vascular disease in the present study and linear correlation of the number of cases with the severity of plasma homocysteine levels. The elevated plasma homocysteine appears to be an independent risk factor for occlusive atherosclerotic vascular disease.

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Table 1: Disease Distribution, Location of Acute Myocardial Infarction (STEMI)

Location of MI	No. of Patients	Parentage
Anteroseptal MI	12	46.12
Inferior wall MI	6	23.08
Transanterior MI	2	7.69
Trans ant + Inf MI	2	7.69
Anteroseptal + Hi lat MI	1	3.85
Extensive anterior MI	3	11.54
Total	26	

Table 2: Disease distribution location of acute coronary syndromes (NSTEMI+UNSTABLE ANGINA)

Location of Ischaemia	No. of Patients	Parentage
Anteroseptal MIsc	9	47.37
Inferior MIsc	8	42.11
Transanterior MIsc	0	00
Trans ant + Inf. MIsc	1	5.26
Anteroseptal + Hi lat. MIsc	0	0
Extensive anterior MIsc	1	5.26
Total	19	