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Elevated serum homocysteine level has a positive correlation with serum cardiac troponin I in patients with acute myocardial infarction

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Abstract

The objective of the present study is to find out whether the increased serum homocysteine level is associated with the increased serum troponin I as a surrogate marker of extent of myocardial injury in acute myocardial infarction patients. Elevated homocysteine levels are associated with increased thrombosis. In patients presenting with Acute Coronary Syndrome (ACS), it is not known whether this association is reflected in the degree of myocardial injury. This was a cross sectional study conducted among the patients with acute myocardial infarction in the Department of Cardiology, Dhaka Medical College Hospital during the period of October 2009 to September 2010 and which included 194 consecutive patients with acute myocardial infarction. The mean (±SD) serum homocysteine level was 20.2±14.3 μmol/L with range from 7.4 to 129.1 μmol/L. Mean serum troponin-I level was classified according to normal (<15μmol/L) and high (≥15μmol/L) levels of serum homocysteine values. The mean serum troponin-I level was 8.9±8.6 ng/ml in the patients having normal serum homocysteine level and 18.4±6.5 ng/ml in the patients having high serum homocysteine level. A significant positive correlation (r=0.273; p<0.001) was found between serum troponin-I level with homocysteine level. Patients with moderate hyperhomocysteinemia (≥15 μmol/L) was found to be 7.09 times more likely to have increased serum troponin-I (a surrogate marker of extent of myocardial injury). The main observation of the present study was that elevated serum homocysteine level has a positive correlation with serum cardiac troponin-I in patients with acute myocardial infarction. So serum homocysteine is associated with increased extent of myocardial injury as measured by serum cardiac troponin-I level, a surrogate marker in patients with acute myocardial infarction.

Introduction

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide. Primary risk factors have been identified with the development of atherosclerotic coronary artery disease and MI. These are hyperlipidaemia, diabetes mellitus, hypertension, smoking, male gender and family history of premature coronary artery disease. Other than the primary risk factors hyperhomocysteinemia is on special focus now a days. The detrimental effect of severe hyperhomocysteinemia on the cardiovascular system was first described by Mc Cully[1]. Since then several studies have been conducted in the last four decades regarding the association of hyperhomocysteinemia and cardiovascular disease.

Homocysteine (Hcy) is a sulfydryl aminoacid that lies at an important metabolic branch point of methionine metabolism, between remethylation and transulfuration pathways[2]. This lead to the formation of methionine and cystathionine respectively. Several enzymes regulate these pathways under normal condition in the presence of Vit. B_{12}, B_6 and Folic acid. Abnormality in any of the enzymes or vitamin deficiency may give rise to hyperhomocysteinemia. Hyperhomocysteinemia has been classified as: Moderate (Hcy >15 to 30 μmol/L), Intermediate (Hcy >30 to 100 μmol/L) and Severe (Hcy >100 μmol/L)[3].

The exact mechanism of atherothrombosis associated with hyperhomocysteinemia is not clearly understood. Several studies have pointed to an association with inhibition of thormbomoduline activity**,** reduction of protein c activation, increased platelet aggregation, and predisposition to endothelial injury. Moreover, hyperhomocysteinemia induce smooth muscle proliferation, accelerate oxidation of LDL cholesterol, impair endothelial derived nitric oxide, decrease synthesis of heparan sulphate proteoglycan and also induce proinflammatory changes in the vessel wall[4].

There is a recently reported paper regarding an association between Hcy concentration and plasma markers of thrombosis activation in patients presenting with Acute Coronary Syndrome (ACS)[5]. These results postulate that elevated Hcy

concentration would lead to increased myocardial injury in those patients group. Cardiac Troponin-I is specific for cardiac tissue and is detected in the serum only if myocardial injury has been occurred. Serum troponin-I level can be used as a surrogate marker of extent of myocardial injury.

The present study is intended to see the association between elevated homocysteine level and the extent of myocardial injury measured by cardiac troponin-I in AMI patients. This information would help to focus on the detrimental effect of homocysteine on cardiovascular disease. So measures could be taken to control serum homocysteine along with other risk factors of cardiovascular diseases.

Materials and Methods

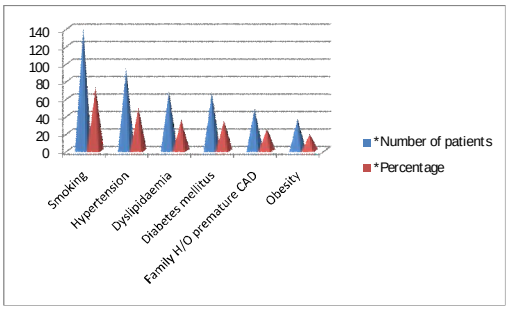
This was a cross sectional study conducted among the patients admitted with acute myocardial infarction in the dept. of cardiology Dhaka Medical College Hospital (DMCH) during the period of October 2009 to September 2010. A total of 194 consecutive patients with AMI were included in the study.

The inclusion criteria : Patients with AMI admitted in the dept. of cardiology DMCH; whoose serum homocysteine and troponin-I level were measured. The exclusion criteria were patients having cardiomyopathy, congenital heart disease, vulvular heart disease; patients with severe comorbid condition; patients having previous MI, percutaneous coronary intervention, coronary artery bypass grafting; patients already taking folic acid, vit. B_6, vit. B_{12} or any of them and patients unwilling to give consent.

Informed consent was taken from each patient. Patient's name and particulars were recorded in the case record file. Initial evaluation of the patients by history and clinical examination was performed and recorded in the preformed data collection sheet. Demographic profile and Pulse, BP, Body weight, were noted. Risk factors of ischaemic heart disease like hypertension, smoking, dyslipidaemia, diabetes mellitus, obesity and family history of premature CAD were noted. Drug history was taken regarding anti hypertensive, lipid lowering and and vitamin (B_6, B_{12}, Folic acid) supplements. Baseline laboratory investigations e.g. Serum creatinine, lipid profile, RBS, ECG, Echocardiography, were done for each patient. Serum total homocysteine was measured on fasting sample. Cardiac troponin-I (cTI) which reflects the degree of myocardial injury was measured after 10 to 12 hours of onset of symptoms (peak cTI). All the information were properly noted in the preformed data sheet. Serum homocysteine level was measured on fasting sample by Fluorescence Polarization Immuno Assay (FPIA) method and was recorded in units of µmol/L. Cardiac troponin-I (cTnI) was measured by microparticle enzyme immunoassays on a routine AxSYM analyzer . Both the tests were done in the Biochemistry Department of Bangabandhu Sheikh Mujib Medical University (BSMMU)**.** Data was analyzed by Statistical Package For Social Science (SPSS). The statistical tests used to analyze the data were: Descriptive statistics, Correlation coefficient test, Multiple logistic regression test and unpaired t test. Level of significance was set at 0.05. Prior to commencement of this study the respective authority approved the research protocol. All the patients included in this study were informed about the nature, risk and benefit of the study. Proper permission was taken from the department and institution concerned for this study.

Results

The mean age was 42.8±12.1 years with range from 21 to 75 years. Male female ratio was almost 9.8:1. Profession of most of the patients were business (41.2%) and service (18.6%). More than half (56.7%) of the patients had chest pain, 39.2% had breathlessness, 11.3% had chest discomfort and 3.1% had other clinical presentations. Most of the patients had Antero septal MI (44.3%), followed by Anterior MI (32.9%), Inferior MI (19.3%) and Ex. Anterior MI (13.6%). Smoking (72.2%), hypertension (48.5%), dyslipidaemia (35.1%) and diabetes mellitus (34.0%) were the common risk factors in this study patients (Graph 1). The mean (±SD) serum homocysteine level was 20.2±14.3 µmol/L with range from 7.4 to 129.1 µmol/L (Table I). Mean serum troponin-I level was classified according to normal (<15µmol/L) and high (≥15µmol/L) levels of serum homocysteine values. The mean serum troponin-I level was 8.9±8.6 ng/ml in the patients having normal serum homocysteine level and 18.4±6.5 ng/ml in the patients having high serum homocysteine level (Table II). The difference was statistically significant ($p<0.05$) in unpaired t test. A significant positive correlation ($r=0.273$; $p<0.001$) was found between serum troponin-I level with homocysteine level (Figure 1). Serum homocysteine level was significantly ($p<0.05$) higher among smoker and dyslipidemia (Table III), but others risk factors were not significant ($p>0.05$). Serum troponin-I level was significantly ($p<0.05$) higher among the smoker, diabetic and obese patients (Table IV). Multiple logistic regression model test (Table V) showed that patients with moderate hyperhomocysteinemia (≥15 µmol/L) had a 7.09 times more likely to increase serum troponin-I (a surrogate marker of extent of myocardial injury).



Graph I: Distribution of the study patients according to traditional risk factors (n=194)

Table I: Distribution of the study patients according to serum homocysteine level (µmol/L) (n=194)

Serum homocysteine level (µmol/L)	Number of patients	Percentage
Normal (<15 µmol/L)	74	38.1
High (≥15 µmol/L)	120	61.9
Mean±SD	20.2±14.3	
Range (min - max)	(7.4-129.1)	

Table II: Mean distribution of serum troponin-I level (ng/ml) according to homocysteine level (µmol/L) of the study patients (n=194)

Serum homocysteine level	Serum troponin I (ng/ml)
(µmol/L)	Mean±SD
Normal (<15 µmol/L)	8.9±8.6
High (≥15 µmol/L)	18.4±6.5

t value =8.72, df =192, p=0.001
P value reached from unpaired t-test

Association between Serum Troponin-I level with homocysteine level of the study patients

Serum Troponin-I level was expressed in ng/ml and homocysteine level was expressed in µmol/L. Significant positive correlation was found between Serum Troponin-I level with homocysteine level. The values of Pearson's correlation coefficient was 0.273 which is significant (p<0.001). Therefore, there was linear positive correlation between Serum Troponin-I level with homocysteine level.

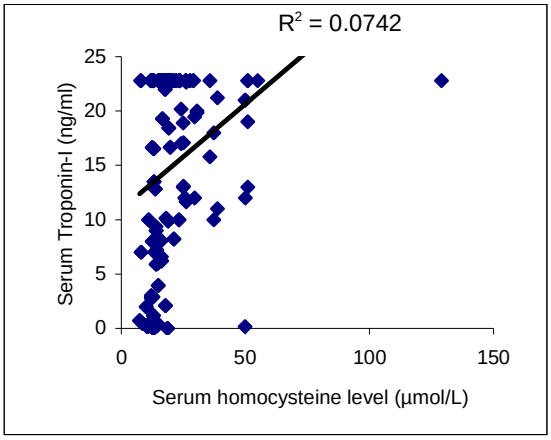


Fig.1: The scatter diagram shows significant relationship (r=0.273) between Serum Troponin-I level with homocysteine level.

Table III: Mean distribution of Serum homocysteine level (µmol/L) according to traditional risk factors in the study patients (n=194)

Risk factors	Serum homocysteine level		t Value	df	P Value
	Risk factor present Mean±SD	Risk factor Absent Mean±SD			
Smoking	21.7±16.2	16.3±5.7	2.40	192	0.017^{s}
Hypertension	18.6±8.8	21.7±17.9	-1.53	192	0.128^{ns}
Diabetes mellitus	17.5±8.0	21.6±16.6	-1.91	192	0.058^{ns}
Family H/O premature CAD	18.7±9.6	20.7±15.5	-.86	192	0.391^{ns}
Dyslipidaemia	23.8±20.4	18.3±9.0	2.60	192	0.010^{s}
Obesity	19.1±9.6	20.5±15.1	-.54	192	0.591^{ns}

ns=not significant, s= significant, df= degress of freedom
p value reached from unpaired t-test

Table IV: Mean distribution of serum troponin-I (ng/ml) according to traditional risk factors in the study patients (n=194)

Risk factors	Serum Troponin-I		t Value	df	P Value
	Risk factor present Mean±SD	Risk factor Absent Mean±SD			
Smoking	15.4±6.1	13.2+7.0	2.16	192	0.031^{s}
Hypertension	15.5±8.3	14.2+8.9	1.06	192	0.292^{ns}
Diabetes mellitus	15.6±6.8	13.1+7.2	2.33	192	0.020^{s}
Family H/O premature CAD	14.4±8.5	14.9+8.7	-.37	192	0.710^{ns}
Dyslipidaemia	14.5±8.6	14.9+8.7	-.34	192	0.733^{ns}
Obesity	17.5±7.7	14.2+8.8	2.06	192	0.040^{s}

ns=not significant, s= significant
p value reached from unpaired t-test

Table V: Association of serum homocysteine and and other risk factors with increase serum troponin-I by multiple logistic regression models (n=194)

	B	S.E	df	Sig	OR	95% CI for OR	
						Lower	Upper
Smoking	2.35	0.858	1	0.006^{s}	1.96	0.39	5.71
Hypertension	1.093	0.672	1	0.104^{ns}	2.90	0.80	11.13
Diabetes mellitus	1.569	0.712	1	0.027^{s}	4.80	1.19	19.3
Family H/O premature CAD	0.715	0.776	1	0.357^{ns}	2.05	0.45	9.36
Dyslipidaemia	0.356	0.714	1	0.618^{ns}	0.70	0.17	2.84
Obesity	0.297	0.827	1	0.719^{ns}	1.35	0.27	6.81
Serum homocysteine level (>15 µmol/L)	1.958	0.726	1	0.001^{s}	7.09	1.71	29.41
Constant	4.920	1.365	1	0.001	0.01		

Discussion

Elevated homocysteine levels are associated with increased thrombosis. In patients presenting with Acute Myocardial Infarction (AMI) it is not known whether this association is reflected in the degree of myocardial injury. In the present series mean serum Troponin-I level was classified according to normal (<15µmol/L) and high (≥15µmol/L) level of serum

homocysteine level. The mean serum troponin-I level was 8.9±8.6 ng/ml in the patients having normal serum homocysteine level and 18.4±6.5 ng/ml in the patients having high serum homocysteine level. The difference was statistically significant ($p<0.05$) in unpaired t test.

Findings of the current study are consistent with Obaidi et al.'s[5] study where the authors observed that the rise in cardiac troponin-I most notably occurred in homocysteine level >16.5µmol/L in AMI patients. In this study, a positive correlations ($r=0.273$; $p<0.001$) was found between serum Troponin-I level with homocysteine level, which is comparable with Obaidi et al.'s (2000) study[5].

Regarding the risk factors of cardiovascular disease it was observed that the mean (±SD) serum homocysteine level (µmol/L) were significantly ($p<0.05$) higher in smoker (21.7 vs 16.3; $p=0.017$) and in dyslipidemia (23.8 vs 18.3; $p=0.010$) but other risk factors were not significantly ($p>0.05$) associated. These findings are consistent with the reports from Sadeghian S[7] and Dey[8] where the author found that serum homocysteine level was significantly higher among the subjects of smoking, dyslipidaemic and family history of ischaemic heart disease ($p<0.05$), but no statistically significant association of serum homocysteine level was found with Diabetes Mellitus (DM) and Hypertension (HTN) ($p>0.05$). However the European Concerted Action Project[9,10] has observed stronger association between serum total homocysteine level and hypertension.

In the current study it was observed that the mean (±SD) serum troponin-I (ng/ml) was significantly higher in obese patients (17.5 vs 14.2; $p = 0.040$), smokers (15.4 vs 13.2 $p=0.03$), diabetic patients (15.6 vs 13.1 $p=0.020$) but other risk factors were not significantly associated ($p>0.05$). Obaidi et al.[5] showed that serum troponin-I level was significantly ($p=<0.0001$) higher in obese patients along with higher age group of patients. Obaidi et al. also showed that smoking ($p=0.210$) and dislipidaemia ($p=0.379$) were not significantly associated with increased serum troponin- I level.

In this study by multiple logistic regression model it was found that among the risk factors hypertension ($p=0.104$), family H/O premature CAD ($p=0.357$), dislipidaemia ($p=0.618$) and obesity ($p=0.719$) were not significantly ($p>0.05$) associated with increased serum troponin-I level. However patients with hyperhomocysteinemia (≥15 µmol/L) were 7.09 times more likely to have increased serum troponin-I level. Smoking ($p=0.006$) and diabetes mellitus (DM) ($p=0.027$) were also significantly associated with increased serum troponin-I level.

Like the present study Obaidi et al. showed that patients having higher homocysteine level (>16.5 µmol/L) 7.32 times more likely to have increased serum troponin-I level. Page et al.[11] & Souissi et al.[12] found independent association between high serum homocysteine and increased risk of myocardial infarction.

In the present study dyslipidaemia was not significantly associated with increased serum troponin-I. Most of the dislipidaemic patients in the study were used to take lipid lowering drugs. These drugs have non lipid or pleiotropic benefits beyond the regression of atheromatous plaque[13]. The pleitropic effects are maintained by improving endothelial function, stabilizing platelets, reducing fibrinogen, inhibiting the inflammatory response associated with atherogenesis and by stabilizing vulnerable atheromatous plaque[14]. Probably for this reason dyslipidaemia was not significantly associated with increased serum troponin-I.

In the present series serum troponin-I was comparatively higher in obese patients but the number of those patients were small (18.6%). May be due to this reason obesity was not significantly associated with increased serum troponin-I by multiple logistic regression models.

Elevated levels of serum homocysteine may result from geographical variations, racial and ethnic differences, genetic causes, different lifestyle, inadequate intake of B vitamins and folate, inaccurate cooking of vegetables and not implementing fortification of grain products with folic acid. The results of the study may have important implications for prevention of mortality and morbidity from AMI in Bangladeshi population.

The results of the current study suggest further studies are required to assess the effect of homocysteine lowering treatment during AMI on the extent of myocardial injury.

Conclusion: The main observation of the present study was that elevated serum homocysteine level has a positive correlation with serum cardiac troponin-I in patients with acute myocardial infarction. So serum homocysteine is associated with increased extent of myocardial injury as measured by serum cardiac troponin-I level, a surrogate marker in patients with acute myocardial infarction.

Study limitation: Although the result of this study support the hypothesis, there are some facts which might affect the result

- Number of study population was limited.
- It was a single center study

- In “Abbott AxSYM SYSTEM”, to quantitate the serum troponin-I value > 22.78 ng/ml, futher procedure called “Automated Dilution Protocol” is needed. But that Protocol was not available while conducting this study.

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