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Original Article

Association of Serum Homocysteine Concentration in Patients with Acute Coronary Syndrome

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Abstract

Introduction: *Coronary artery disease (CAD) has become the most common cause of mortality and morbidity in the entire world. The aim of the study was to find out the association between serum homocysteine level and acute coronary syndrome (ACS).*

Methods: *This was a case control study, conducted in the department of Cardiology, Dhaka Medical College Hospital, Dhaka, during the period of July 2011 to December 2011. In this period, newly diagnosed patients with ACS were taken as cases, and age, sex matched healthy subjects with normal ECG were taken as controls.*

Results: *Total 120 cases were studied. Serum homocysteine level ≤I5 µmol/L was found in 28 (46.7%) cases without CAD and risk factor and in 52 (86.7%) controls. Serum homocysteine level >15 µmol/L was found in 32 (53.3%) caswes with CAD whereas 8 (13.3%) in controls.*

Conclusion: *Serum total homocysteine concentration (tHcy) is recognized as an independent and important risk factor for ACS patients. As a result, we should to plan strategies for reduction of serum homocysteine concentration in both the ACS patients and the high risk population.*

Key words: *Homocysteine, Acute coronary syndrome. High risk population*

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Introduction

Coronary artery disease (CAD) has become a major health problem and is the most common cause of mortality & morbidity in the entire world.[1] Among the coronary artery diseases, acute coronary syndrome is the leading cause of death in the developed countries & second leading cause of death in developing countries. It has been estimated that, by the year 2020, coronary artery disease (CAD) will hold first place in the WHO's list of leading cause of disability.[2] About 7.1 million deaths occurred globally in 1999 due to CAD and it will rise to 11.1 million by 2020. In the United Kingdom (UK), 1.3 million people develops CAD every year while in USA, 0.8 million people suffers from new heart attacks each year. In India 4% rural and 11% urban population suffers from CAD. The progressively increasing trend of the disease in our country shows that the prevalence was 3.3/1000 in 1976 and 17.2/1000 in 1986 indicating a 5 fold increase in 10 years.[4]

Acute coronary syndrome (ACS) constitutes a spectrum of clinical presentations, ranging from unstable angina (UA) through non-ST segment elevation myocardial infarction (NSTEMI) to ST segment elevation myocardial infarction (STEMI). It is a multifactoral disease involving well-known risk-factors such as age, male sex, smoking, hypertension (HTN), diabetes mellitus (DM), obesity, hypercholesterolemia, family history of premature CAD & sedentary lifestyle.[3] An ACS develops when a vulnerable or high risk atheromatous plaque (having a thin fibrous cap and a large lipid core with abundant inflammatory cells accumulation) undergoes disruption of its fibrous cap. Following plaque-rupture, a sufficient quantity of thrombogenic substances are exposed, and the coronary artery lumen may become partially or completely occluded by a combination of platelet-aggregates, fibrin and red blood cells. Completely occlusive thrombus leads to STEMI, while sub-totally occlusive thrombus leads to NSTEMI or UA.[4]

There is a growing recognition that high level of serum homocysteine is associated with atherosclerotic vascular diseases including CAD. This started in the late 1960s when McCully KS et al.[5] a pathologist in Boston, encountered two children with elevated serum homocysteine concentrations and homocystinuria, who, despite being very young, had autopsy evidence of extensive arterial thrombosis and atherosclerosis. Several studies have also demonstrated that the presence of moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis in the coronary, cerebral and peripheral vasculature.[6,7,8]

Several studies have attempted to establish the prevalence of hyperhomocysteinemia in patients with accelerated vascular diseases. In general, case control studies have been robust in confirming the association

between hyperhomocysteinemia and coronary artery disease (CAD). In a meta-analysis, Boushey CJ et al.[9] estimated that an increase of 5 µmol/L in the serum total homocysteine concentration (tHcy) raises the risk of coronary artery disease by as much as an increase of 20 mg/dl (0.52 mmol/L) in the serum cholesterol concentration.

Though, several studies have been undertaken in the past in India and abroad, regarding the association of high serum homocysteine concentration as a risk factor for ACS, this association has not been studied in our country. That's why, we designed this study to evaluate the association of high serum homocystine concentration which can play an important role as a risk factor for ACS.

Materials and Methods

This was a case-control study which was conducted in the Department of Cardiology, Dhaka Medical College and Hospital, Dhaka, during the period of July 2011 to December 2011. Study population was all the patients with Acute Coronary Syndrome (ACS) within the study period and healthy population within that period. Newly diagnosed patients with ACS admitted in the Coronary Care Unit (CCU) of Dhaka Medical College Hospital, Dhaka, were taken as cases and age & sex matched healthy subjects (doctors, medical students, nurses and other hospital-staffs and patient attendants' from DMCH, Dhaka, with no history of ischaemic heart disease (IHD) and normal ECG was taken as control. In this study, total number of sample was 120, among which cases (patient) 60 and control (normal) were 60.

Selection Criteria:

Inclusion criteria for cases :

Newly diagnosed Acute Coronary Syndrome (ACS) patients having characteristic ischaemic type chest pain with characteristic ECG and cardiac bio-marker (Troponin I) findings of ACS. Those were presenting for the first time in the Coronary Care Unit (CCU) of DMCH, Dhaka is also included.

Inclusion criteria for control:

Age and sex matched healthy subjects having no history of ischaemic heart disease (IHD) and normal ECG

Exclusion criteria:

Study subjects having previous history of myocardial infarction / unstable angina / Percutaneous Coronary Intervention (PCI) / Coronary Artery Bypass Graft Surgery (CABG). Those subjects having cardiomyopathy, congenital heart disease or valvular heart disease and were unwilling to be included in the study, already getting folic acid, vit. B_6 or vit. B_{12} supplementation are excluded.

Data collection procedure: Data were collected by using a preformed data sheet in the following manner:

Informed consent was taken from all cases & controls or from their legal guardians. Initial evaluation of the study population by name, age, sex, height, weight, clinical history and examination were performed and recorded accordingly. Risk factors of coronary artery disease (CAD) like hypertension (HTN), smoking, dyslipida-emia diabetes mellitus (DM), family history of premature CAD and obesity were noted from all cases and controls. Fasting blood samples were collected for serum homocysteine assay on the morning following the admission day from the cases & fasting morning- samples were collected from the controls. Serum homocysteine level was measured by Fluorescence Polarization Immunoassay (FPIA) method and recorded in units of μmol/L from Biochemistry Department of Bangabandhu Sheikh Mujib Medical University. Level of serum homocysteine was grouped as follows:

- Normal homocysteine level: ≤I5 μmol/L.
- High homocysteine level: >15 μmol/L.

Results

After collection, data were checked for consistency, before entry in the SPSS and analysis, the results were presented in tables. The description highlights the main feature. P value calculated using unpaired 't' test.

ns = not significant

The study included 120 subjects and the mean age of the total study subjects was 57.89±38.90 years ranging from 21 to 80 years. Among the cases, the mean age was 57.7±38.80 years and among the controls, the mean age was 58.33±37.79 years. Maximum number was found in the age group of 36-50 years in both cases and controls. P value calculated using chi square test (Table 1)

Table I: Age Distribution of the Study Subjects (n-120)

Age in years	Case (n-60)		Control (n-60)		Total (n-120)		P value
	n	%	n	%	n	%	
21-35	12	20.0	9	15.0	21	17.5	
36-50	23	38.3	25	41.7	48	40.0	
51-65	22	36.7	24	40.0	46	38.3	
66-80	3	5.0	2	3.3	5	4.2	
Mean±SD	57.7±38.80		58.33±37.79		57.89±38.90		0.761^{ns}
Range (min-max)	(21-80)		(21-80)		(21-80)		

Table II: Sex distribution of the study subjects (n-120)

Sex	Case (n-60)		Control (n-60)		Total (n-120)		P value
	n	%	n	%	n	%	
Male	52	86.7	51	85.0	103	85.8	
Female	8	13.3	9	15.0	17	14.2	0.793[ns]

ns = not significant

Among the 120 subjects, 52(86.7%) and 51(85.0%) were male in the case and control respectively. Females were found 8(13.3%) in the cases and 9 (15.0%) in the controls. Male-female ratio was 6:1 in the whole study subjects. The results are shown in the Table II.

Table III: Distribution of the study subjects according to Serum Homocysteine level (μmol/L) (n-120)

S. Homocysteine level (μmol/L)	Case (n-60)		Control (n-60)		Total (n-120)		P Value
	n	%	n	%	n	%	
≤15	28	46.7	52	86.7	80	66.7	0.001[s]
>15	32	53.3	8	13.3	40	33.3	
Mean±SD	19.5±16.3		12.6±3.3		19.5±12.1		0.002[s]
Range (min - max)	(7.3-129.0)		(7.1-31.4)		(7.1-129.0)		

s= significant, p value calculated from Chi square test and from unpaired 't' test

Serum Homocysteine level ≤15 μmol/L was found in 28 (46.7%) cases and in 52 (86.7%) controls. Serum Homocysteine level > 15 μmol/L was found in 32 (53.3%) cases and in 8 (13.3%) controls (Figure 1).

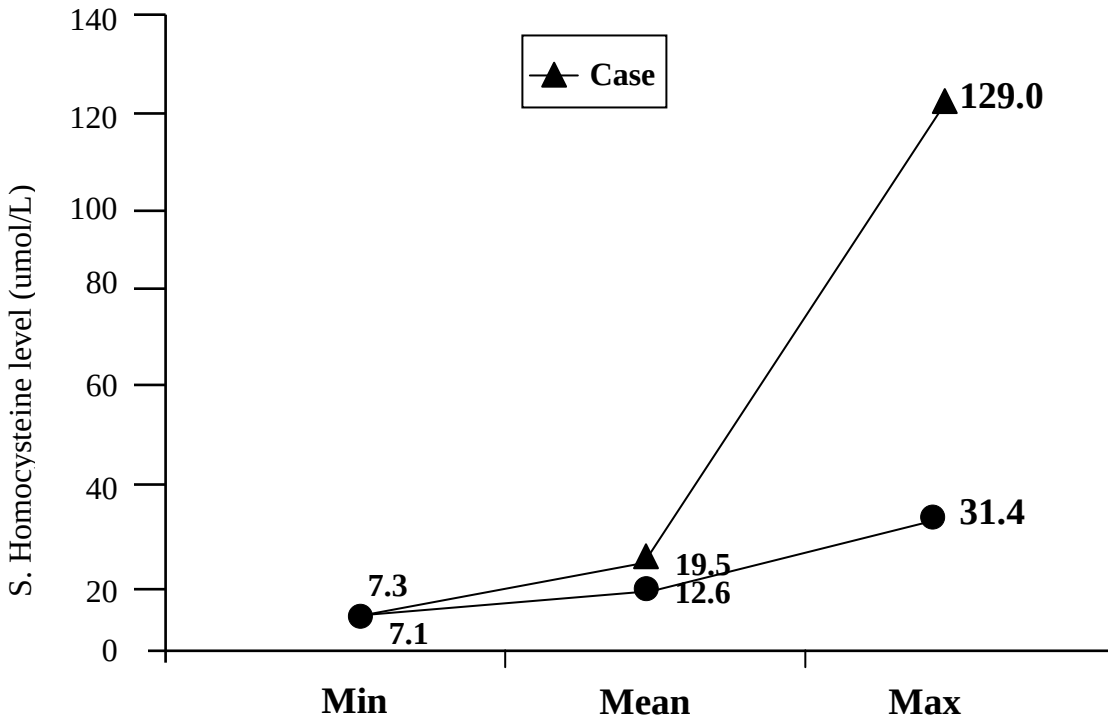

Figure 1: Line diagram showing mean, maximum and minimum distribution of Serum Homocysteine level (μmol/L) of the total study subjects (n-120)

Table IV: Risk-measurement of serum Homocysteine concentration for ACS patients (n-120)

Serum Homocysteine Level (μmol/L)	Case (n-60) [ACS present]		Control (n-60) [ACS absent]		Odds Ratio (OR)	95% CI for OR	P value
	n	%	n	%			
>15	32	53.3	8	13.3	7.43	2.80-20.34	0.001[s]
≤15	28	46.7	52	86.7			

s = significant, p value calculated from Chi square test

Serum Homocysteine level > 15 μmol/L was found in 32 (53.3%) cases and in 8 (13.3%) controls. Serum Homocysteine level ≤15 μmol/L was found in 28 (46.7%) cases and in 52 (86.7%) controls. The difference was statistically significant ($p<0.05$) in chi square test.

Table V: Distribution of the study subjects according to different risk factors for ACS (n-120)

Risk factors	Case (n-60)		Control (n-60)		P Value
	n	%	n	%	
Smoking	26	43.3	14	23.3	0.001[s]
Dyslipidaemia	33	55.0	13	21.7	0.001[s]
HTN	21	35.0	12	20.0	0.065[ns]
DM/IGT	14	23.3	7	11.7	0.093[ns]
F/H of premature CAD	14	23.3	8	13.3	0.609[ns]
Obese/Over-wt.	11	18.3	9	15.0	0.624[ns]

s = significant, ns= not significant, p value calculated from Chi square test.

Smoking, dyslipidaemia and HTN were more common risk factors in both cases and controls. However, Smoking and dyslipidaemia were significantly ($p<0.05$) higher in case group in Chi square test. Other risk factors like- HTN, DM/IGT, Family history (F/H) of premature CAD and Obese / Over-wt. were higher in number in cases than in controls

Table VI: Risk factors analysis for ACS (multiple logistic regression models) (n-120)

		95.0% CI for OR			
	OR	Lower	Upper	R^2	P value
HTN	2.71	0.98	7.47	0.17	0.054[ns]
DM/IGT	1.68	0.54	5.22	0.11	0.371[ns]
Smoking	4.19	1.61	10.85	0.41	0.003[s]
Obese/Over-wt.	1.29	0.44	3.79	0.09	0.646[ns]
Dyslipidaemia	5.94	2.16	16.35	0.35	0.001[s]
F/H of premature CAD	3.95	1.11	14.02	0.29	0.033[s]
S. Homocy steine level	6.70	2.48	18.06	0.44	0.001[s]
Constant	0.129				0.000

A smoker compared to a non smoker was 4.19 (95% CI 1.61 to 10.85) times more likely to have ACS. A dyslipidemic subject compared to a non dyslipidemic subject was 5.94 (95% CI 2.16 to 16.35) times more likely to have ACS. A subject with F/H of premature CAD was 3.95 (95% CI 1.11 to 14.02) times more likely to have ACS than those with no F/H of premature CAD. Smoking, dyslipidaemia, F/H of premature CAD and Serum Homocysteine level were found to be significantly ($p<0.05$) associated with ACS-risk; other risk factors (HTN, DM/IGT & obese/over-wt.) were not found to be significantly ($p<0.05$) associated with ACS-risk.

Discussion

This observational case-control study was carried out with an aim to find out the association between serum homocysteine concentration and acute coronary syndrome (ACS) and to assess the strength of association of serum homocysteine level with ACS patients as well as with the traditional risk factors of ACS. In this study, maximum number 48 (40.0%) was found in the age group of 36-50 years in both cases and controls. Males were predominant in this study and male female ratio was 6:1. In this study both cases & controls were divided into two sub groups according to serum homocysteine level which were ≤15 μmol/L and >15 μmol/L. Serum homocysteine level ≤15 μmol/L was found in 46.7% cases and in 86.7% controls. Serum homocysteine level >15 μmol/L was found in 53.3% cases and 13.3% in controls.

In our study it was observed that smoking (43.3% Vs 23.3%) and dyslipidaemia (55.0% Vs 21.7%) were significantly ($p<0.05$) higher in case group. However other risk factors like- HTN (35% vs. 20%), DM/IGT (23.3% vs. 11.7%), F/H of premature CAD (23.3% vs. 13.3%) and Obese/Over-wt. (18.3% vs. 15%) were higher in number in cases but not significantly ($p>0.05$) higher than controls. In Bangladesh, almost similar findings were also observed by Majumder et al.,[10] Siddique et al.[11] and Haque et al.[12]

In the present study, it was found that smoking (25.0% vs. 50.0%) and F/H of premature CAD (12.5% vs.30.0%) were significantly ($p<0.05$) higher in >15 μmol/L homocysteine level in the total study subjects. Other risk factors like HTN, DM/IGT, dyslipidaemia and obese/over wt. were not significantly ($p>0.05$) associated with high serum homocysteine level. Serum homocysteine level was significantly higher among the smokers, dyslipidaemics and those with family history of ischaemic heart disease ($p<0.05$), but no statistically significant association of serum homocysteine level was found with DM and HTN ($p>0.05$). The findings of this study were almost consistent with another study reported by Puri et al.[1]

Conclusion

This observational case-control study has conferred that, a high serum homocysteine concentration is an important & modifiable risk factor for acute coronary syndrome (ACS). As a result, although it was a single centre based study involving limited number of study-subjects, which may provide the basis of large future studies aimed at risk factor analysis in ACS patients as well as identification of the high risk population. The current study will also pave the way of planning strategies for reduction of serum homocysteine concentration in both the ACS patients and the high risk population by life-style modification, B-vitamins supplementation (Vit-B_6, Vit- B_{12} & Folic acid), food-fortification or newer methods in the coming days.

Contribution of the Authors

First author was the main researcher. Other authors helped in data collection, processing, statistical analysis and computer composing.

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