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Comparison of Serum Homocysteine and Highly Sensitive C- reactive protein Levels in Patients of Acute Coronary Syndrome with and without Type-2 Diabetes

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Abstract

Background: The association of high serum homocysteine concentration and C- reactive protein as a risk factor for the acute coronary syndrome. The aim of study was to evaluate serum homocysteine and hs-CRP level in newly diagnosed ACS patients together with comparison of homocysteine and hs-CRP level in ACS patients with & without type 2 diabetes and also to find out the correlation between serum homocysteine and hs- CRP level among the ACS patient with and without type 2 DM. **Material & Methods:** This was a cross sectional study and total of 260 patients with new onset of ACS admitted in the CCU, Department of Cardiology, DMCH were included in the study during Jan, 2011 to Feb, 2012. Among them 72 ACS patients with type 2 diabetes was considered as group I and 188 ACS patients without diabetes was considered as group II. Serum total homocysteine level, hs-CRP level and traditional risk factors for ACS were documented from all the study population. **Results:** Most of the patients were found in 4th decade in both groups. Acute STEMI was more common clinical feature in both groups. The mean serum homocysteine level in all groups of ACS patients were significantly higher in patients without DM in comparison to type 2 DM. Similarly, the mean hs-CRP level in all groups of ACS patients were significantly higher in patients without type 2 DM. The mean serum homocysteine and hs-CRP level were significantly higher in nondiabetic ACS patients. However, dyslipidaemia was significantly higher in patients with type 2 DM. Hypertension, obesity and family history of ACS were not significant between two groups. There was no correlation found between serum homocysteine with serum hs-CRP in ACS patients with type 2 DM and ACS patients without DM respectively. **Conclusion:** So, both serum homocysteine and hs-CRP level in ACS patients were significantly higher in patients without DM. In ACS, C-reactive protein elevation was a better marker of extension of myocardial damage than homocyesteine. No correlation was found between serum homocysteine with hs-CRP level in ACS patients with and without type 2 DM respectively.

Keywords:- Serum homocysteine, C- reactive protein, hs-CRP level, ACS patients, Type 2 DM.

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INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide, responsible for one-third of death.[1] It has been projected that cardiovascular disease worldwide will climb from the second most common cause of death, with 29 percent of all deaths in 1990, to first place, with more than 36 percent of all deaths in 2020. This is more than twice the percentage of deaths from cancer.[2] Various studies have pointed out that South Asians have a higher prevalence of CAD as compared with other ethnicities, with a higher rate at younger ages.[3] National data on incidence and mortality of coronary heart disease are few in Bangladesh. The prevalence of coronary heart disease was estimated as 3.3/1000 in 1976 and 17.2/1000 in 1986 indicating a 5-fold in the disease in 10 years.[4] In 1975, the incidence of ischemic heart disease in Bangladesh was reported to be 3.3 per thousand. These were commonly seen among the rich and middle class of people in the urban area, the commonest age group being 45-49 years.[5] Then subsequently in 1985, the same authors reported an increased incidence of 14 per thousand.[6] As quoted by Malik, WHO reported the incidence of IHD in Bangladesh as 11 percent among the CVD.[7] In another survey, it was 17.6 percent of cardiac patients in a general hospital.[8] Among the hospitalized patients in the National Institute of Cardiovascular Disease, Dhaka, IHD patients were 56%.[9] Traditionally there are some conventional risk factors like age, male sex, positive family history, hypertension, smoking, hyperlipidemia, metabolic syndrome, diabetes, lack of exercise, obesity, and some emerging risk factors, like C- reactive protein, Homocysteine, Fibrinogen, etc.[10] The most appropriate role for the use of emerging risk factors is in the determination of aggressiveness of therapy and the most advantageous medication for patients with intermediate Framingham risk, a family history of premature CVD without traditional risk factors, or CVD in the absence of traditional risk factors.[11] DM is associated with a higher short-term risk for major adverse cardiovascular and cerebrovascular events and HF and a higher long-term risk for mortality in unselected patients with acute ischemic chest pain.[12] More than 30 years ago, the Framingham Heart Study followed 239 patients with diabetes and observed a 3-fold increase in age-adjusted cardiovascular mortality.[13] Subsequent studies demonstrated, patients with type 2 diabetes without prior myocardial infarction have a risk of death from CAD as patients without diabetes with prior MI.[14] Diabetes is now considered to be a risk equivalent of coronary artery disease for future MI and cardiovascular death.[15,16,17,18,19] Therosclerosis with thrombosis superimposed is by far the most frequent underlying cause.[20] Inflammation plays an important role in all stages of the atherosclerotic process, from the onset of initial lesions to plaque progression and complications.[21] Prognostic studies have shown that C-reactive protein is a strong predictor of cardiovascular events.[21] In particular, in acute coronary syndromes, high concentrations of CRP are a marker of recurrent cardiac events for up to 5 years.[22] Type 2 diabetes mellitus is a strong risk factor for coronary artery disease, which in turn is the leading cause of mortality and morbidity in diabetic patients.[23,24,25] Although this increased risk has been attributed primarily to hyperglycemia, dyslipidemia, and a

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prothrombotic state, recent observations have focused attention on low-grade inflammation in the pathogenesis of type 2 DM and its complications.[22] In recent years, a considerable numbers of studies have analyzed that prognostic role of different biomarkers in acute coronary syndromes.[25] Moderate hyperhomocysteinemia defined as total homocysteine concentration between 12 to 30 µmol/L, occurs in about 30% of patients with clinical complications of atherosclerosis. Prospective and genetic studies have shown that moderate hyperhomocysteinemia in healthy persons is only a weak predictor of cardiovascular disease.[22] Contrary to it, in patient with ischemic heart disease, renal failure or diabetes mellitus and in thromboembolic disease, hyperhomocystinemia represents a strong predictor of vascular morbidity and mortality.[23] Both hyperhomocysteinemia and increased inflammatory activities are shown to be associated with atherosclerosis and coronary disease.[23] Over the past decade, atherosclerosis and inflammation have been closely linked and C-reactive protein, as an acute phase reactant and non-specific marker of inflammation has been widely studied.[22] The analysis of biochemical markers particularly C-reactive protein helps to better define the prognosis and may also be helpful in stratifying patients for risks for major cardiac events.[24] Chronic poor metabolic control of diabetes is characterized by elevated plasma homocysteine concentration.[25] In uncomplicated type 2 diabetic patients without nephropathy of have shown that basal level of homocysteine was 35% lower in compared with healthy controls. They concluded that chronic hyperglycemia may affect its renal excretion, or accelerate hepatic trans-sulfuration secondary to insulin disorders. In Bangladesh few studies to evaluate association of homocysteine as a risk factor in ACS patient and correlations of Hs-CRP with angiographic severity of coronary artery disease was done separately, but no study has been done to evaluate the relation between homocysteine and Hs- CRP in acute coronary syndrome patient. The aim of this study is to establish the differences in the behavior of C-reactive protein and homocystine concentrations as well as the relationship between these concentrations in patient of acute coronary syndrome, with and without type 2 diabetes.

OBJECTIVE

General objective

To evaluate the association of high serum homocysteine and hs- CRP with type 2 diabetic patients with acute coronary syndrome (ACS).

Specific objectives

- To measure serum homocysteine level in newly diagnosed ACS patients.
- To measure serum hs-CRP level in newly diagnosed ACS patients.
- To compare the homocysteine and hs-CRP levels between ACS with and without type 2 diabetes.
- To see the correlation between serum homocysteine and hs- CRP level among the ACS patient with type 2 DM.

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MATERIAL AND METHODS

This was a cross sectional study, conducted in the department of Cardiology, Dhaka Medical College Hospital from January 2011 to February 2012. All the patients with new onset ACS (STEMI, NSTMI, and UA), admitted in the CCU, DMCH, Dhaka within the study period. A total of 260 patients were recruited as study population. All the patients were divided into two groups according to the presence or absence of type 2 DM. Group I ACS with type 2 DM= 72 patients and group II ACS without type 2 DM= 188 patients. Data was collected by using a preformed data sheet. Informed consent was taken from all cases or from the legal guardians. Initial evaluation of the study population by clinical history and examination was performed and recorded accordingly. Risk factors of ischemic heart disease (IHD) like hypertension, smoking, dyslipidaemia, diabetes mellitus, family history of premature CAD and obesity was noted from all patients. Drug history was taken regarding anti-hypertensive, anti-diabetic, lipid lowering drugs & vitamins. Blood was collected for fasting "serum homocysteine assay" and Hs -CRP on the morning following the admission day. Necessary laboratory investigations (RBS, S. lipid profile, S. Creatinine, S. Troponin-I, S. Homocysteine, S. Hs- CRP, ECG, Echocardiography etc.) was done and recorded. All the information was properly noted in the preformed data sheet. Laboratory method for determination of serum homosysteine level. Serum homocysteine level was measured by "Fluorescence Polarization Immunoassay (FPIA)" method and recorded in units of µmol/L. Laboratory method for determination of serum hs- CRP level. The CRP test was performed by using DADE BEHRING BN 100, estimated by nephelometric system. Data was analyzed by SPSS Version 16. Test statistics to be used to analyze the data are: Descriptive statistics, Chi square and unpaired t-test and correlation coefficient test. Level of significance was set at 0.05. All the facilities required for this study are available in Dhaka Medical College Hospital, Dhaka except "Serum Homocysteine" and "Hs-CRP" assay which was done from the "Biochemistry Department, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka." The study was approved by the "Research Review Committee" & the "Ethical Committee" of DMCH, Dhaka. All the patients included in this study was informed about the nature, risk and benefit of the study. Proper permission was taken from the department and institution concerned for this study.

RESULTS

[Table 1] showed that the mean age was 50.33±15.50 years ranging from 32 to 72 years in group and 45.86±18.76 years with range from 31 to 80 years in group II. Maximum number was found in the age group of 31-40 years in both group. The mean age difference was not statistically significant between the two groups.

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[Table 2] showed the clinical diagnosis of the study population. Acute STEMI was found 52(72.2%) in group I and 132(70.2%) in group II. Acute NSTEMI was found 8(11.1%) and 24(12.8%) in group I and group II respectively. UA was found 12(16.7%) in group I and 32(17.0%) in group II. There was no statistical significant difference found in both groups regarding the clinical diagnosis in chi square test.

[Table 3] showed the serum homocysteine level with clinical diagnosis. The mean serum homocysteine level in patients with acute STEMI was 14.14±6.6µmol/L in group I and 19.63±18.1 µmol/L in group II. In acute NSTEMI was 15.89±8.02 µmol/L and 18.19±6.0 µmol/L in group I and group II respectively. In UA was 12.75±4.88 µmol/L in group I and 15.21±5.19 µmol/L in group II. The mean serum homocysteine level in acute STEMI, acute NSTEMI and UA were statistically significant between the two groups.

[Table 4] showed the hs-CRP level mg/L with clinical diagnosis. The mean hs-CRP level in patients having acute STEMI was 21.16±17.84 mg/L ranging from 4.82 to 92 mg/dl in group I and 30.6±28.52 mg/L ranging from 1.85 to 126 mg/L in group II. In acute NSTEMI was 14.12±12.37 mg/L ranging from 1.24 to 32.65 mg/L and 39.67±29.53 mg/L ranging from 0.6 to 76.61 mg/L in group I and group II respectively. In UA, it was found 8.12±7.77 mg/L ranging from 6.51 to 21.20 mg/L in group I and 28.51±27.61 mg/L ranging from 4.15 to 97.80 mg/L in group II. The mean hs-CRP level in patients having acute STEMI, acute NSTEMI and UA were statistically significant between the two groups.

[Table 5] showed the serum homocysteine level with acute coronary syndrome. The mean serum homocysteine level in patients with MI was 14.38±6.76 µmol/L in group I and 19.09±16.81 µmol/L in group II. In without MI was 12.75±4.88 µmol/L and 15.21±5.19 µmol/L in group I and group II respectively. The mean serum homocysteine level in with MI and without MI were statistically significant between the two groups in unpaired t-test. Patients with MI has elevated level of homocysteine than patients without MI but the difference was not statistically significant within each group in unpaired t-test.

[Table 6] showed the mean hs-CRP level in patients having with MI was 20.22±17.29 mg/L in group I and 31.54±28.78 mg/L in group II. In without MI was 8.12±7.7 mg/L and 28.51±27.61 mg/L in group I and group II respectively. The mean hs-CRP level in patients with and without MI were statistically significant between the two groups in unpaired t-test. But within each group patients with MI has elevated level of hs-CRP than patients without MI but the difference was statistically significant.

[Table 7] showed the total mean serum homocysteine was 14.11±6.48 µmol/L with range from 3.44 to 28.78 µmol/L in group I and 18.41±15.49 µmol/L with range from 5.48 to

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129.05 µmol/L in group II. In male was 16.25±5.81 µmol/L with range from 8.8 to 27.78 in group I and 19.48±16.68 µmol/L with range from 5.48 to 129.05 µmol/L in group II. In female was found 7.67±3.45 µmol/L with range from 3.44 to 13.7 and 13.69±6.82 µmol/L with range from 8.47 to 38.06 µmol/L in group I and group II respectively. The mean serum homocysteine level difference was statistically significant in total patients and in female patients but was not in male.

[Table 8] showed the mean hs-CRP level was 18.21±16.69 mg/l ranging from 0.51 to 92 mg/l in group I and 31.02±28.54 mg/l ranging from 0.6 to 126 mg/l in group II. In male was found 19.90±17.05 mg/L ranging from 0.75 to 92 mg/L in group I and 32.27±27.37 mg/L ranging from 3.01 to 126 mg/L in group II. In female was found 13.13±14.87 mg/L ranging from 0.51 to 50.5 and 25.36±33.22 mg/L with ranging from 0.6 to 97.8 mg/L in group I and group II respectively. The mean hs-CRP level difference was statistically significant in patients and male but not significant in female. But within each group mean hs-CRP level difference in male and female was not statistically significant in unpaired t-test.

[Table 9] showed the risk factors of the study patients and it 30(41.7%) and 70(37.2%) patients had HTN in group I and group II respectively. Smoker was found 22(30.6%) in group I and 96(51.1%) in group II. Obesity 12(16.7%) and 38(20.2%) in group I and group II respectively. Dyslipidemia 54(75.0%) in group I and 112(59.6%) in group II. Family history was 6(8.3%) in group I and 30(16.0%) in group II. Smoking and dyslipidemia were statistically significant between two groups but others were not significant in chi square test.

[Table 10] showed among the patients with HTN, the mean serum homocysteine level was 10.9±11.05 µmol/L and 31.51±28.85 µmol/L in group I and group II respectively. In smoker was 18.13±21.49 µmol/L in group I and 30.73±29.45 µmol/L in group II. In obese was 11.43±8.56 µmol/L and 25.35±24.97 µmol/L in group I and group II respectively. Patients having dyslipidemia was 18.08±17.61 µmol/L in group I and 30.56±28.22 µmol/L in group II. Similarly, in those with F/H of premature CAD was 13.35±6.91 µmol/L and 26.17±18.46 µmol/L in group I and group II respectively. The mean serum homocysteine differences were statistically significant in HTN and dyslipidemia between two groups, but smoker, obesity and F/H of premature was not statistically significant.

[Table 11] showed among the patients with HTN the mean serum Hs-CRP level was 10.89±11.05 µmol/L and 37.93±38.95 µmol/L in group I and group II respectively. In smoker was 32.03±32.32 µmol/L in group I and 35.33±31.4 µmol/L in group II. Among the obese was 34.82±50.88 µmol/L and 30.39±27.72 µmol/L in group I and group II respectively. Patients with dyslipidemia, the mean was 29.59±33.71 µmol/L in group I and 39.57±43.14

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µmol/L in group II. Similarly, in those with F/H of premature CAD the mean serum hs-CRP level was 13.35±6.91 µmol/L and 30.41±21.63 µmol/L in group I and group II respectively. The mean serum hs-CRP differences were statistically significant in HTN, and F/H of premature CAD, but other risk factors were not statistically significant.

Table 1: Age distribution of the study patients (N=260) Bar chart

Age (in year)	**Group I (n=72)**		**Group II (n=188)**		**P value**
	n	**%**	**n**	**%**	
31 - 40 yrs.	32	44.4	118	62.8	0.073^{ns}
41 - 50 yrs.	12	16.7	24	12.8	
51 - 60 yrs.	18	25.0	20	10.6	
61 -70 yrs.	10	13.9	24	12.8	
>70 yrs.	0	0.0	2	1.1	
Mean ± SD	50.33	±15.50	45.86	±18.76	
Range (min-max)	(32-70) yrs.		(31-80) yrs.		

Table 2: Distribution of the study patient according to different ACS presentation (N=260)

Clinical diagnosis	**Group I (n=72)**		**Group II (n=188)**		**P value**
	n	**%**	**n**	**%**	
Acute STEMI	52	72.2	132	70.2	
Acute NSTEMI	8	11.1	24	12.8	0.928^{ns}
UA	12	16.7	32	17.0	

Table 3: Distribution of the study subjects according to serum homocysteine level, clinical diagnosis (N=260)

	Serum homocysteine (µmol/L)		
Clinical diagnosis	**Group I (n=72)**	**Group II (n=188)**	**P value**
	Mean ±SD	**Mean ±SD**	
Acute STEMI	14.14±6.6	19.63±18.1	0.012^{s}
Range (min-max)	(3.44 - 27.70)	(5.48 - 129.05)	
Acute NSTEMI	15.89±8.02	18.19±6.0	0. 012^{s}
Range (min-max)	(10.32 - 28.78)	(8.50 - 28.29)	
UA	12.75±4.88	15.21±5.19	0.001^{s}
Range (min-max)	(6.09 - 20.03)	(10.40 - 32.54)	

Table 4: Distribution of the study subjects according to hs-CRP level and clinical diagnosis (N=260)

	hs-CRP level mg/L				
Clinical diagnosis	**Group I (n=72)**		**Group II (n=188)**		**P value**
	Mean ±SD	**(min - max)**	**Mean ±SD**	**(min - max)**	

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Acute STEMI	21.16 ±17.84	(4.82 - 92.0)	30.06 ±28.52	(1.85 - 126)	0.038[s]
Acute NSTEMI	14.12 ±12.37	(1.24 - 32.65)	39.67 ±29.53	(0.6 - 76.61)	0.001[s]
UA	8.12 ±7.77	(6.51 - 21.20)	28.51 ±27.61	(4.15 - 97.80)	0.001[s]

Table 5: Levels of serum homcysteine in patients with acute coronary syndrome (N=260)

	Serum homcsteine level (µmol/L)		
Acute coronary syndrome	**Group I (n=72)**	**Group II (n=188)**	**P value**
	Mean ±SD	**Mean ±SD**	
With MI (STEMI+NSTEMI)	14.38 ±6.76	19.09 ±16.81	0.022[s]
Without MI (UA)	12.75 ±4.88	15.21 ±5.19	0.001[s]
P value	0.430[ns]	0.198[ns]	

Table 6: Levels of hs-CRP level in patients with acute coronary syndrome (N=260). (N=260).

	hs-CRP level mg/L		
Acute coronary	**Group I (n=72)**	**Group II (n=188)**	**P Value**
	Mean ±SD	**Mean ±SD**	
With MI (STEMI+NSTEMI)	20.22 ±17.29	31.54 ±28.78	0.005[s]
Without MI (UA)	8.12 ±7.77	28.51 ±27.61	0.001[s]
P value	0.021[s]	0.585[ns]	

Table 7: Mean Serum Homocysteine level (□mol/L) of the study subjects according to sex (N=260)

Serum Homocysteine (µmol/L)	**Group I (n=72)**		**Group II (n=188)**		**P value**
	n	**%**	**n**	**%**	
Mean ± SD	14.11 ±6.48		18.41 ±15.49		0.024[s]
Range (min-max)	(3.44 - 28.78)		(5.48 - 129.05)		
Male					
Mean ± SD	16.25 ±5.81		19.48 ±16.68		0.108[ns]
Range (min-max)	(8.8 - 28.78)		(5.48 - 129.05)		
Female					
Mean ± SD	7.67 ±3.45		13.69 ±6.82		0.001[s]
Range (min-max)	(3.44 - 13.7		(8.47 - 38.06)		
P value	0.001[s]		0.048[s]		

Table 8: hs-CRP level (mg/L) of the study subjects according to sex (N=260)

	Group I (n=72)		**Group II (n=188)**		**P value**
hs-CRP level (mg/L)	**n**	**%**	**n**	**%**	
Mean ±SD	18.21 ±16.69		31.02 ±28.54		0.001[s]
Range (min-max)	(0.51 - 92.0)		(0.6 - 126.0)		
Male					
Mean ±SD	19.90 ±17.05		32.27 ±26.37		0.002[s]

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Range (min-max)	(0.75 -92.0)	(3.01 -126.0)	
Female			
Mean ±SD	13.13 ±14.87	25.36 ±33.22	0.145^{ns}
Range (min-max)	(0.51 - 50.5)	(0.6 - 97.8)	
P value	0.138^{ns}	0.202^{ns}	

Table 9: Distribution of the study subjects according to risk factors (N=260)

Risk factors	**Group I (n=72)**		**Group II (n=188)**		**P value**
	n	**%**	**n**	**%**	
HTN					
Present	30	41.7	70	37.2	0.510^{ns}
Absent	42	58.3	118	62.8	
Smoking					
Smoker	22	30.6	96	51.1	0.002^{s}
Non-smoker	50	69.4	92	48.9	
Obesity					
Yes	12	16.7	38	20.2	0.516^{ns}
No	60	83.3	150	79.8	
Dyslipidemia					
Yes	54	75.0	112	59.6	0.020^{s}
No	18	25.0	76	40.4	
Family history					
Present	6	8.3	30	16.0	0.111^{ns}
Absent	66	91.7	158	84.0	

Table 10: Distribution of the study subjects according to mean serum homocysteine level and risk factors for ACS (N=260)

Risk factors for ACS	**Group I (n=72)**	**Group II (n=188)**	**P Value**
	Mean ±SD	**Mean ±SD**	
HTN	10.9 ±11.05	31.51 ±28.85	0.001^{s}
Smoker	18.13 ±21.49	30.73 ±29.45	0.072^{ns}
Obesity	11.43 ±8.56	25.35 ±24.97	0.091^{ns}
Dyslipidemia	18.08 ±17.61	30.56 ±28.22	0.003^{s}
F/H Of Premature CAD	13.35 ±6.91	26.17 ±18.46	0.107^{ns}

Table 11: Distribution of the study subjects according to mean Serum hs-CRP level and risk factors for ACS (N=260)

Risk factors for ACS	**Group I (n=72)**	**Group II (n=188)**	**P value**
	Mean ±SD	**Mean ±SD**	
HTN	10.89 ±35.33	37.93 ±38.95	0.001^{s}
Smoking	32.03 ±32.32	35.33 ±39.36	0.987^{ns}

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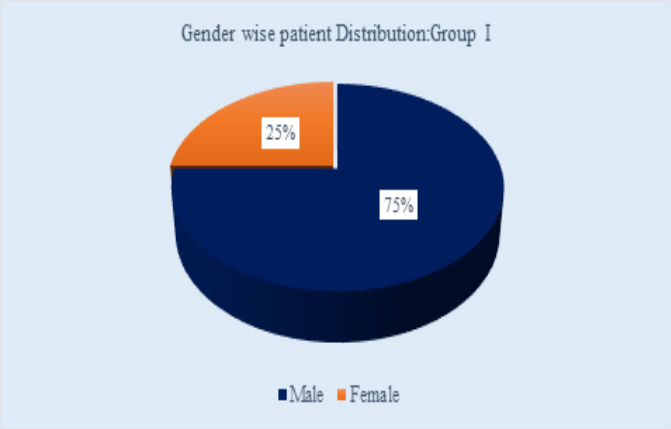
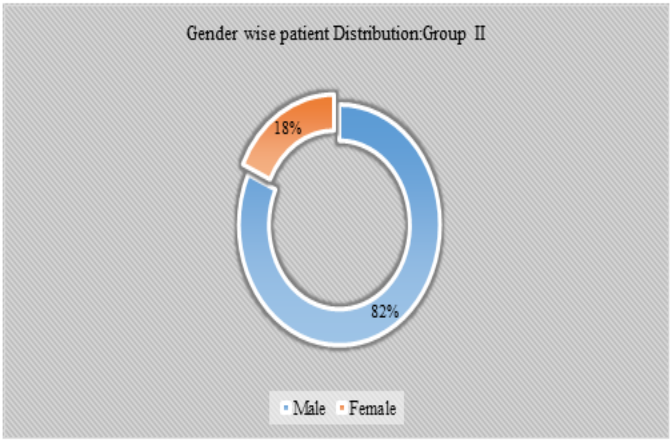
Obesity	34.82 ±50.88	30.39 ±27.72	0.711^{ns}
Dyslipidemia	29.59 ±33.71	39.57 ±43.14	0.137^{ns}
F/H Of Premature Cad	13.35 ±6.91	30.41±21.63	0.001^{s}



Graph 1: Gender distribution of the study patients Group I



Graph 2: Gender distribution of the study Patients Group II

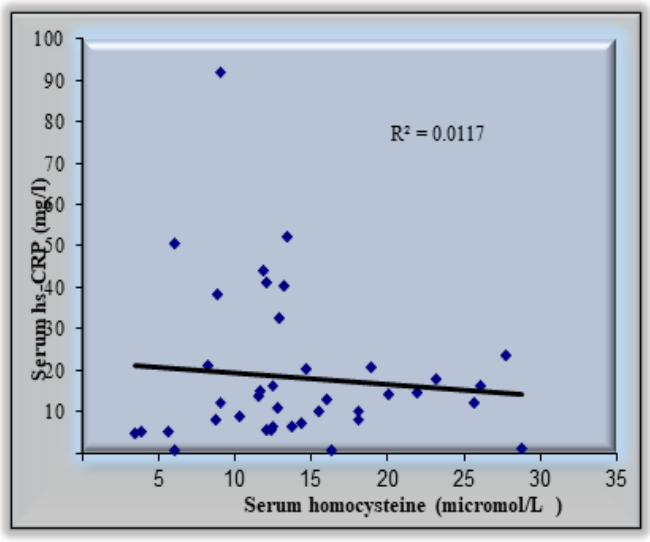


Figure 1: Scatter diagram showing no positive correlation (r=0.1082; p>0.05) between serum homocysteine with Serum hs-CRP in ACS patients with type 2 DM.

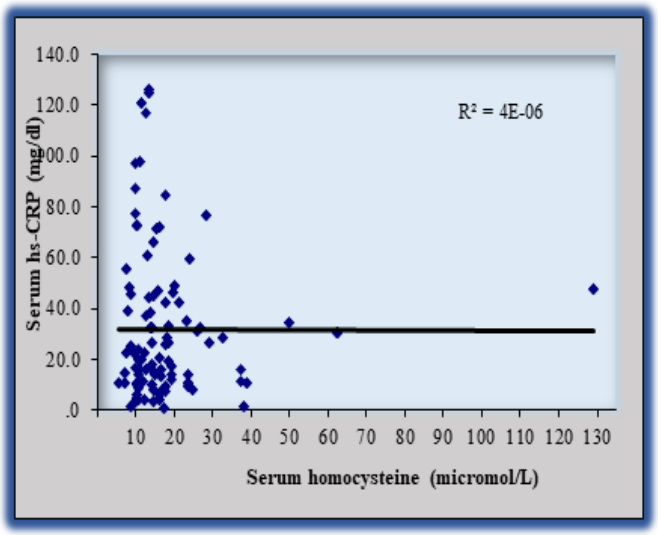


Figure 2: Scatter diagram showing no correlation (r=0.002; p>0.05) between serum homocysteine with serum hs-CRP in ACS patients without DM.

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DISCUSSION

This cross sectional study was carried out with an aim to evaluate serum homocysteine and hs-CRP level in newly diagnosed ACS patients together with comparison of homocysteine and hs-CRP level in ACS patients with & without type 2 diabetes and also to find out the correlation between serum homocysteine and hs- CRP level among the ACS patient with and without type 2 DM. A total of 260 patients with new onset of ACS admitted in the CCU, Department of Cardiology, DMCH were included in the study during Jan, 2011 to Feb, 2012. Among them 72 ACS patients with type 2 diabetes was considered as group I and 188 ACS patients without diabetes was considered as group II. Serum total homocysteine (tHcy) level, hs-CRP level and traditional risk factors for ACS were documented from all the study subjects. In this study it was observed that the mean age was 50.33±15.50 years ranging from 32 to 72 years in group I and 45.86±18.76 years ranging from 31 to 80 years in group II, which was almost similar in both groups. Most of the patients were found in 4th decade in both groups (44.4% vs 62.8%). Similar age range obtained by Al Suwaidi et al.[26] where they found age range 17 to 82 years. Ockenel et al.[27] observed the mean age of patients was 49 years with range from 20-70 years. Gonzalez-Porras et al.[28] observed the mean age of patients was 47 years with range from 26-54 years. They have stated that the higher age range may be due to increased life expectancy, geographical and racial influences. In the current study it was found that male were 75.0% & 81.9% and female were 25% & 18.1% in group I and group II respectively .Male female ratio was almost 4:1 in the whole study patients, which indicates that ACS was more common in male subject which was closely resembled with Gonzalez-Porras et al,[28] where the authors found male female ratio was almost 6:1. Similarly, Puri et al.[29] mentioned that CAD affects male more frequently and severely in male than females that has been attributed to the protective role of oestrogen in premenopausal females. They also suggested that lower female percentage might be due social circumstences that restrict women seeking medical help outside the home even in face of serious illness. In this current study acute STEMI, acute NSTEMI and UA were found in 72.2% vs 70.2%, 11.1% vs 12.8% and 16.7% vs 17.0% in group I and group II respectively, which were similar ($p>0.05$) in both groups regarding the clinical diagnosis. Gonzalez-Porras et al.[28] have shown 57.0% STEMI, 23.0% NSTEMI and 20.0% UA in their study. Regarding the clinical diagnosis and serum homocysteine level it was found that mean tHcy level were significantly higher in patients without DM in all diagnosis. In STEMI it was found (14.14±6.6 vs 19.63±18.1), in NSTEMI (15.89±8.02 vs 18.19±6.0) and in UA (12.75±4.88 vs 15.21±5.19) in group I and group II respectively. Similar findings were observed by Kurowska et al.[30] They concluded that chronic hyperglycemia may affect renal excretion of tHcy by glomerular hyperfiltration or accelerate hepatic trans- sulfuration secondary to insulin disorder. In this study there was increased value of mean hs-CRP level in patients of all clinical diagnosis but this was significantly ($p<0.05$) higher in patients without DM. In acute STEMI it was (21.16±17.84 vs 30.06±28.52), in NSTEMI (14.12±12.37 vs 39.67±29.53) and in UA (8.12±7.77 mg/L vs 28.51±27.61) in group I & II accordingly. It is possible that in diabetic patients with ACS the extent and severity of

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disease are more important than inflammation in determining the outcome, or the mechanisms not directly related with inflammation are more important in destabilization of atherosclerotic plaques. Evidence of higher platelet reactivity in diabetic patients on antiplatelet treatment might also help to explain our findings; Kurowska et al,[31] stated that in the group without previously diagnosed diabetes, increased intensity of chronic and acute inflammatory reactions could be related to latent long-term metabolic disturbences existing in the great percentage of this patient. Inducing and supporting a non-specific inflammation, they mediate many of the stages of atherosclerosis development. In this current study the mean serum tHcy level in patients having MI was (14.38±6.76 vs 19.09±16.81) and without MI was (12.75±4.88 vs 15.21±5.19) in groupI and II accordingly. tHcy level was signifiacantly raised in nondiabetic group but there was no significant difference of tHcy value according to the presence or absence of myocardial infarction within group. Kurowska et al,[30] showed the mean serum tHcy level in patients having MI (14.7±6.7 vs 16.9±7.4) and without MI (13.9±5.6 vs 13.8±4.2) with and without diabetes. The mean hs-CRP level was elevated in patients with myocardial infarction (20.22±17.29 vs 8.12±7.77) & (31.54±28.78 vs 28.51±27.61) both in group I and group II. The difference in hs-CRP level between patients with myocardial infarction and patients without MI was particularly significant in the group of diabetic patients ($p<0.05$). Kurowska et al,[21] observed the similar findings in their study (24.3±36.6 vs 6.6±6.5) & (29.7±40.8 vs 25.2±49.9) in patients having MI or not with and without diabetes. They also noticed that the difference was more significant in the group of diabetic patients, which support the current study. They stated that this increase of CRP value concerned the acute phase protein to a greater extent and highest CRP concentrations characterized the patient with myocardial infarction confirms the relationship of increment of CRP levels in ACS patients to the extension of myocardial damage (Brunetti et al,[32] In this current study it was observed that the mean serum tHcy level was significantly higher in ACS patients without DM (14.11±6.48 vs 18.41±15.49). Kurowska et al,[30] showed similar findings of mean serum tHcy level (14.4±6.2 vs 15.3±6.2) which was significantly higher in ACS patients without DM. In another study, Deepa et al,[33] observed the mean homocysteine level was 10.1±4.4 vs 12.6±4.6 µmol/ml in diabetes and non diabetis patients respectively. Facila ET al,[34] concluded that homocysteine over 10µmol/l was an independent prognostic factor increasing the long term risk of all-cause mortality after acute coronary syndrome. On the other hand, Akalin et al,[35] reported that both Hcy levels and inflammation markers were all significantly elevated in type 2 diabetic patients with atherosclerotic vascular disease when compared with patients without vascular disease. Impairment of renal function is the key factor that affects both Hcy levels and inflammatory markers. Inflammation is not involved in the process by which homocysteine leads atherosclerosis in type 2 diabetes. These findings also support the current study. Male patients have significantly higher value of serum tHcy level in both diabetic and nondiabetic group (16.25±5.81 vs 7.67±3.45) and (19.48±16.68 vs 13.69±6.82). Similarly, Idzior-Waluś et al,[36] reported that serum homocysteine was significantly higher in men than in women (15.3±4.7 vs 13.3±3.9) in male

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and female respectively, which is closely resembled with the current study. However, Kurowska et al,[26] showed that serum homocysteine level was almost similar between male and female patient in ACS patients with diabetes and without diabetes, which differ with the current study, that may be due to racial influences may have significant impacts on serum homocysteine level in their ACS patients. In this study, mean hs-CRP level was significantly higher in group without DM (18.21±16.69 vs 31.02±28.54), when considerd as a whole and in man ($p<0.05$). Within each group the mean CRP concentrations did not differ considerably in woman and man. Similar findings observed by Kurowska et al,[30] where the authors found mean hs-CRP level in patients with and without diabetes were (17.0±29.5 vs 27.3±45.2), which was significantly higher in ACS patients without DM. In male patient the level was significantly higher in ACS patients without DM but did not differ considerably in diabetic group. Thus partly support the current study. Idzior-Waluś et al,[36] showed that CRP levels was significantly higher in women with diabetes than in men (4.7±3.2 vs 4.1±7.2) in female and male respectively. Regarding the risk factors of the study subjects HTN was found (41.7% and 37.2%), smoker was (30.6% and 51.1%), obesity was (16.7% and 20.2%), dyslipidemia was (75.0% and 59.6%), family history of premature CAD was (8.3% and 16.0%) in group I and group II respectively.[37] Smoking was significantly higher in nondiabetic group but dislipidemia was significantly higher in diabetic patients. Puri et al,[29] showed that hypertension, smoking, positive family history and dyslipidaemia were the most common risk factors in patients with ACS. Similarly, Schoenenberger et al,[36] Yildirim et al,[38] & Avezum et al,[39] reported that HTN, smoking, obesity, dyslipidemia and family history of CAD were most frequent risk factors in patients with ACS. Some prospective observational studies Maron et al,[40] indicated that obesity was an independent risk factor for coronary and cardiovascular mortality in men and women. Regarding the risk factors, the mean serum tHcy level with HTN was (10.9±11.05 vs 31.51±28.85), In smoker (18.13±21.49 vs 30.73±29.45), in dyslipidemia (18.08±17.61 vs 30.56±28.22), in obese subjects (11.43±8.56 vs 25.35±24.97) and in those with F/H of premature CAD (13.35±6.91 vs 26.17±18.46) in group I and group II respectively. The tHcy level were levated in all risks factor but significantly higher in HTN, smoker and dyslipidemia in patients without DM. Puri et al,[29] showed the mean homocysteine level has a little higher value than the current study. It was (23.93±10.94 and 25.41±11.88) in hypertensive and smoker patients, (27.49±14.41) in family history of CAD. Similarly, there was significant difference of mean serum Hs-CRP level in patients with HTN and positive family h/o CAD between diabetic and nondiabetic ACS patients (10.89±35.33 vs 37.93±38.95) and (13.35±6.91 vs 30.41±21.63). But in case of smoking, obesity and dyslipidemia mean value of hs- CRP were elevated in both diabetic and nondiabetic patients at a similar level without any significant difference. (18.13±21.49 vs 30.73±29.45), (11.43±8.56 vs 25.35±24.97) & (18.08±17.61 vs 30.56±28.22) respectively. In this present series it was observed that there was no correlation between serum homocysteine with serum hs-CRP in ACS patients with type 2 DM and ACS patients without type 2 DM respectively. This is consistent with the findings

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done by Akalin et al. [23] that show inflammatory activity and tHcy levels are increased in type 2 diabetic patients with atherosclerotic vascular diasease, but there was no correlation between Hcy and inflammatory markers except TNFα. They have stated that inflammation is not involved in the process by which tHcy leads to atherosclerosis in type 2 diabetes. Inducing and supporting a nonspecific inflammation, homocysteine mediates many of the stages of atherosclerosis development mentioned by Conaway et al,[41] Mazza et al,[25] demonstrated that homocysteine levels shown poorly correlated with the severity of coronary artery disease, but had a strong predictor of acute coronary syndrome recurrence. Kurowska et al,[30] reported that the patients without previously diagnosed diabetes, the increased homocysteine level and the intensity of chronic and acute inflammatory reactions could be related to latent, long-term metabolic disturbances existing in the great percentage of these patients. Ahmed et al,[42] observed that high CRP level was significant predictor of multivessel disease, high stenosis score, more complex leision & reduced TIMI flow in the culprit vessel in settings acute coronary syndrome. Thus can be used as a new and even simplar tool for risk stratification in acute coronary syndrome. CRP can be used as a marker to identify those subsets of patients of acute coronary syndrome who may need to undergo invasive or conservative strategies. The result of the current study suggest that further studies are required for the assessment of relationship of plasma homocysteine to atherosclerotic vascular disease and inflammatory markers in type 2 diabetic patients and implication of lowering blood hcy and CRP level on the prognosis of acute coronary syndrome patients.

CONCLUSIONS

This cross sectional observational study was done to compare the homocysteine and hs-CRP levels in ACS patients with and without type 2 diabetes as well as to find out the correlation between serum homocysteine and hs- CRP level among ACS patient. Majority of the patients were found in 4th decade and male was predominantly involved. Acute STEMI was more frequent clinical feature in both groups and homocysteine levels was significantly higher in male patients. Both serum homocysteine and hs-CRP level in ACS patients were significantly higher in patients without DM. The difference of homocysteine level was significantly higher in patients having HTN, smoker and dyslipidemia but almost similar in obesity and F/H of premature CAD between two groups. Similarly, the serum hs-CRP differences were significantly higher in HTN and F/H of premature CAD but almost consistent in smoker, dyslipidemia and obesity between two groups. In ACS C-reactive protein elevations was a better marker of extension of myocardial damage than homocyesteine. No correlation was found between serum homocysteine with hs-CRP level in ACS patients with and without type 2 DM respectively. However, future analysis should be done recruiting large number of patients in a multicentre study to reach a conclusive decision.

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Limitations of the Study

There are some facts which might affect the result. It was a single center study. Number of study population was limited.

Only two emerging risk factors (serum homocysteine and hs- CRP) was studied due to lack facility. Although deficiency of vit- B6, vit- B12 & Folic acid may lead to hyperhomocysteinemia, serum concentration assay of these vitamins could not be done due to lack of facilities and financial constraints.

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