Original Article

Comparative Assessment of Serum Homocysteine and High Sensitivity C-reactive Protein in type 2 Diabetic and non Diabetic Patients with ACS

Lipi Debnath[1], Abdul Wadud Chowdhury[2], Iftekhar Alam[3], Md. Mamunur Rashid[4], Md. Sadaqul Islam Sikder[3]
Bijan Kumar Nath[5]

Abstract:

Background: Increased level of serum homocysteine (Hcy) and high sensitivity C-reactive protein (hs-CRP) have a proven implication with epithelial injury leading to coronary artery disease ((CAD). These are strongly associated with different metabolic syndrome variables, although different studies have shown both positive and negative responses when correlated with type 2 diabetes malitus (T2DM). In this study we explored the role of these markers of CAD in type II diabetic and non diabetic patients with newly diagnosed acute coronary syndrome (ACS) at a tertiary care hospital among Bangladeshi population.

Methods: We wanted to identify whether Hcy and hs-CRP link positively or negatively with type 2 diabetes in this cross sectional observentional study. A total of 260 patients with new onset ACS were included in the study, out of which 72 patients with T2DM and 188 patients without diabetes were considered as group I and group II respectively. Clinical and biochemical data were compared in between the groups.

Results: The mean age of the study population was 50.33±15.50 years and 45.86±18.76 years in group I and II respectivly. Male female ratio was 4:1 among the whole study subjects. There was significantly higher level of serum homocysteine in group II than group I 18.41±15.49 µmol/L vs. 14.11±6.48 µmol/L respectively (p <0.05). Similarly hs-CRP in group I was 26.84±30.30 mg/L and in group II 37.48±37.99mg/L, higher in group II (p<0.05). Both Hcy and hs-CRP were higher in male and female patients in group II. Dyslipidaemia was significant risk factor in group I and smoking in group II (p<0.05).

Conclusion: In patients with ACS serum Hcy and hs-CRP were significantly higher in non-daibetic patients then in patients with type 2 diabetes. This association may be population or ethenicity specific which provide further scope for future elaborate studies.

Keywords: *Homocysteine (Hcy), high sensitivity C reactive protein (hs-CRP), type 2 Diabetes mellitus (T2DM), acute coronary syndrome (ACS).*

(Bangladesh Heart Journal 2020; 32(2): 114-120)

Introduction:

Various studies have pointed out that South Asians have a higher prevalence of coronary artery disease (CAD) as compared with other ethnicities, with a higher rate at younger ages[1]. Traditionally there are some conventional risk factors like age, male sex, positive family history, hypertension, smoking, hyperlipidaemia, metabolic syndrome, diabetes, lack of exercise, obesity, and some emerging risk factors, like C- reactive protein, Homocysteine, Fibrinogen etc[2].

1. Junior Consultant, Department of Cardiology National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.
2. Professor, Department of Cardiology, Dhaka Medical College and Hospital, Dhaka, angladesh..
3. Assistant Professor, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh
4. Professor, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.
5. Senior Consultant, Department of Surgery, Sadar Hospital, Chottogram, Bangladesh.

Address of Correspondence: Dr. Iftekhar Alam, Assistant professor, Department of Cardiology, National Institute of cardiovascular Diseases, Dhaka, Bangladesh. Tel-8801720056180, e-mail:iftekhar1029@gmail.com.

DOI: https://doi.org/10.3329/bhj.v35i2.52897

DM is associated with a higher short-term risk for major adverse cardiovascular and cerebrovascular events and heart failure and a higher long-term risk for mortality in unselected patients with acute ischemic chest pain[3]. Studies demonstrated that, patients with type 2 diabetes mellitus (T2DM) without prior myocardial infarction (MI) have a risk of death from CAD as patients without diabetes with prior MI[4]. Diabetes is now considered to be a risk equivalent of coronary artery disease for future MI and cardiovascular death[5].

T2**DM** is a strong risk factor for coronary artery disease, which in turn is the leading cause of mortality and morbidity in diabetic patients[6]. Although this increased risk has been attributed primarily to hyperglycemia, dyslipidemia, and a prothrombotic state, recent observations have focused attention on low-grade inflammation in the pathogenesis of T2DM and its complications[7].

In recent years, a considerable numbers of studies have analyzed the prognostic role of different biomarkers in acute coronary syndromes (ACS)[8]. 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 a weak predictor of cardiovascular disease[9]. Contrary to it, in patient with ischemic heart disease, renal failure or diabetes mellitus and in thromboembolic disease, hyperhomocysteinemia represents a strong predictor of vascular morbidity and mortality[10].

DM is associated with a higher short-term risk for MACCEs and HF and a higher long-term risk for mortality in unselected patients with AICP. DM should be included as a high-risk variable in national acute coronary syndrome guidelines. Top of Form

Bottom of Form

Atherosclerosis with thrombosis superimposed is by far the most frequent underlying cause[11]. Inflammation plays an important role in all stages of the atherosclerotic process, from the onset of initial lesions to plaque progression and complications[12]. Prognostic studies have shown that C-reactive protein (CRP) is a strong predictor of cardiovascular events[13]. In particular, in acute coronary syndrome, high concentrations of CRP are a marker of recurrent cardiac events for up to 5 years[14]. Both hyperhomocysteinemia and increased inflammatory activities are shown to be associated with atherosclerosis and coronary disease[9].

Over the past decade, atherosclerosis and inflammation have been closely linked and hs-CRP, as an acute phase reactant and non-specific marker of inflammation has been widely studied[9]. The analysis of biochemical markers particularly hs-CRP helps to better define the prognosis and may be helpful in stratifying patients at risks for major cardiac events[15]. Also chronic poor metabolic control of diabetes is characterized by elevated plasma homocysteine concentration[10]. In uncomplicated T2DM patients without nephropathy, Mazza et al., 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[16].

In Bangladesh few studies to evaluate association of Hcy 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 ascertain the differences in the behavior of C-reactive protein and homocysteine concentrations as well as their impact in patient of acute coronary syndrome, with and without type 2 diabetes.

Methods:

This cross sectional observational study was carried out in the department of Cardiology of Dhaka Medical College Hospital (DMCH), from October 2010 to September 2011. 260 patients with acute coronary syndrome encompassing STEMI, NON STEMI and UA who were admitted at the CCU of DMCH were the study population. They were divided on the basis of presence of T2DM, group I patients with T2DM and group II patients without T2DM. All consecutive patients who were clinically diagnosed as ACS and undertook measurement of serum serum Homocysteine and high sensitive CRP were enrolled in the study on the basis of inclusion and exclusion criteria. Patients with history of previous UA, STEMI, NSTEMI, percutaneous coronary intervention, coronary artery bypass grafting, cardiomyopathy, Congenital heart disease, vulvular heart disease, severe co-morbid conditions and taking Folic acid, Vit.B-6,Vit.B-12 or statins were excluded from the study.

Informed consent was taken from all patients or from the legal guardians. Initial evaluation of the study population by history and clinical examination was performed and recorded accordingly in the preformed data collection sheet. Demographic variables e.g. Age, sex and personal information were recorded. Risk factors of ischemic heart

disease (IHD) e.g. hypertension, smoking, dyslipidaemia, diabetes mellitus, family history of premature CAD and obesity was noted. Necessary laboratory investigations RBS, fasting lipid profile, S. Creatinine, S. Troponin-I was done and recorded. 12 lead resting ECG was done at a paper speed of 25 mm/s and 10mm/mV standardization at admission. Trans-thoracic echocardiography was done by 2D & M-mode and Doppler echo modalities and left ventricular ejection fraction (LVEF) was measured by Tichoitz's method.

Blood was collected for fasting serum homocysteine assay and hs -CRP on the next morning following the admission day. Serum homocysteine level was measured by Fluorescence Polarization Immunoassay (FPIA) method and recorded in units of ¼mol/L. The serum Hs-CRP was performed by using DADE BEHRING BN 100, estimated by nephelometric system as per instructions of the manufacturer.

The research protocol was approved by the "Research Review Committee" & the "Ethical Committee" of DMCH, Dhaka. The numerical data obtained from the study were analyzed and significance of difference was estimated by using the statistical methods. Data were expressed in frequency, percentage, mean and standard deviation as applicable. Comparison between groups was done by unpaired student's test, chi-square test, and Fisher's exact test as applicable. Data were analyzed by using computer based SPSS program (version 16). Probability less than 0.05 was considered significant.

Results:

There was no significant age difference among the groups. The mean age of the study population in group I was 50.33±15.50 years and in group II the mean age was 45.86±18.76 years. (Table I)

Table I

Distribution of age of the patients

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

In group I 75.0% was male and 25% female and in Group II 81.9% was male and 18.1% was female. Male female ratio was 4:1 among the whole study subjects. (Figure 1)

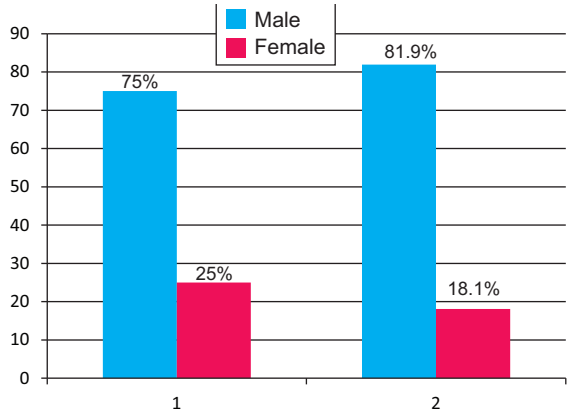

Fig.-1: *Sex distribution of the study subjects (N=260)*

There was similar presentation of ACS in between the groups, no statistically significant difference found in between the study groups regarding the clinical diagnosis. (Table II)

Table-II

Clinical presentation of subsets of ACS among the study groups

Clinical diagnosis	Group II(n=72) n	%	Group II (n=188) n	%	p Value
STEMI	52	72.2	132	70.2	0.460^{ns}
NSTEMI	8	11.1	24	12.8	0.928^{ns}
UA	12	16.7	32	17.0	0.253^{ns}

The table III shows the serum homocysteine level with clinical diagnosis in between the groups. The mean serum homocysteine level was higher in group II patients with diabetis malitus. The mean serum homocysteine level in STEMI, NSTEMI and UA were statistically significant ($p<0.05$) between the two groups.

The mean hs-CRP level in patients having acute STEMI, acute NSTEMI and UA were statistically significant ($p<0.05$) in group II. (Table IV)

Serum Homocysteine level was divided into two sub groups according to sex. The mean serum homocysteine level was statistically significant ($p<0.05$) between male and female patients within each group.(Table V)

The mean hs-CRP level difference in male and female was statistically significant ($p<0.05$) in group I but not significant ($p>0.05$) in group II. (Table VI)

Smoking and dyslipidemia were statistically significant ($p<0.05$) between two groups but others were not significant ($p>0.05$) in chi square test. (Table VII)

The mean serum Homocysteine differences were statistically significant and high in group II in HTN, smoker and dyslipidemia, but obesity and F/H of premature heart disese was not statistically significant. (Table VIII)

The mean serum Hs-CRP differences were statistically significantly high in group II for HTN, and F/H of premature CAD, but other risk factors were not statistically significant between the two groups. (Table IX)

Table-III

Distribution inbetween the groups of serum homocysteine level according to clinical diagnosis of ACS (N=260).

Clinical Diagnosis	Group I (n=72)	Group II (n=188)	p Value
	Serum homocysteine (µmol/L)		
	Mean±SD	Mean±SD	
STEMI	14.14±6.6	19.63±18.1	0.012[s]
NSTEMI	15.89±8.02	18.19±6.0	0. 012[s]
UA	12.75±4.88	15.21±5.19	0.001[s]
Group mean	14.11±6.48	18.41±15.49	0.024[s]

Table-IV

Distribution inbetween the groups of hs-CRP level according to clinical clinical diagnosis (N=260)

Clinical Diagnosis	Group I (n=72)	Group II (n=188)	p Value
	Hs CRP level (mg/L)		
	Mean±SD	Mean±SD	
STEMI	30.12±33.11	41.26±43.26	0.049[s]
NSTEMI	14.12±12.32	39.67±29.53	0. 001[s]
UA	8.12±7.77	28.51±27.61	0.001[s]
Group mean	26.84±30.30	37.48±37.99	0.034[s]

Table-V

Mean Serum Homocysteine level (mmol/L) of the study subjects according to sex (N=260)

S. Homocysteine (µmol/L)	Group I (n=72)		Group II (n=188)		P value
	N	%	n	%	
Male					
Mean ± SD	16.25	±5.81	19.48	±16.68	0.108[ns]
Female					
Mean ± SD	7.67	±3.45	13.69	±6.82	0.001[s]

Table-VI

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

hs-CRP level (mg/L)	Group I (n=72) N %	Group II (n=188) n %	P value
Male			
Mean±SD	31.41±32.77	39.97±38.71	0.097[ns]
Female			
Mean±SD	13.13±14.87	26.24±32.75	0.012[s]

Table-VII

Distribution of risk factors among the study groups

Risk factors	Group I (n=72)		Group II (n=188)		P value
	N	%	n	%	
HTN	30	41.7	70	37.2	0.510^{ns}
Smoking	22	30.6	96	51.1	0.002^{s}
Obesity	12	16.7	38	20.2	0.516^{ns}
Dyslipidemia	54	75.0	112	59.6	0.020^{s}
Family history	6	8.3	30	16.0	0.111^{ns}

Table-VIII

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
	Serum homocysteine (µmol/L)		
	Mean±SD	Mean	±SD
HTN	14.86±7.29	19.83±20.30	0.044^{s}
Smoker	15.81±7.12	19.09±11.82	0.028^{s}
Obesity	14.95±10.25	18.65±15.60	0.064^{ns}
Dyslipidemia	14.07±6.10	17.88±14.91	0.036^{s}
F/H Of Premature CAD	14.26±10.09	15.74±5.51	0.132^{ns}

Table-IX

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
	Hs CRP level (mg/L)		
	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}
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}

Discussion:

This cross sectional study was carried out with an aim to evaluate the serum homocysteine and hs-CRP level in type 2 diabetic and non diabetic patients with recently diagnosed ACS.

In this study, 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, difference was not significant (p>0.05). Similar age range was obtained by Ockene et al., observed the mean age of patients 49 years with range from 20-70 years[17]. Gonzalez-Porras et al., observed the mean age of patients 47 years with range from 26-54 years[11].

In the current study, 75.0% and 81.9% were male in group I and group II respectively, which indicates that ACS was more common in male subjects, which closely resembled with Gonzalez-Porras et al., where the authors found male female ratio was almost 6:1[11]. Similarly, Puri et al. observed ACS was more common in male subjects[18].

In this current study, STEMI was found 72.2% in group I and 70.2% in group II. NSTEMI was found in 11.1% and 12.8% in group I and group II respectively. UA was found in 16.7% in group I and 17.0% in group II. Gonzalez-Porras et al., have shown 57.0% STEMI, 23.0% NSTEMI and 20.0% UA[11]. Cusack et al., found that, stable angina with major adverse cardiac event (MACE) in 22.0% and no MACE in 35.0%. Unstable angina was in 24.0% and 35.0% respectively with MACE and no MACE[19].

Regarding the clinical association with serum homocysteine level it was observed that the mean serum

homocysteine level in patients with subsets of ACS were significantly (p<0.05) higher in patients without DM. The observed mean homocysteine was 14±6.48 µmol/L and 18.41±15.49 µmol/L in group I and II respectively. Kurowska et al., showed the mean(±SD) serum homocystieine level in patients having MI 14.7±6.7 µmol/L in patients with type 2 diabetes and 16.9±7.4 µmol/L in patients without diabetes. In UA the investigators showed the mean serum homocystieine level was 13.9±5.6 µmol/L in patients with type 2 diabetes and 13.8±4.2 µmol/L in patients without diabetes, which are similar with the current study[20].

Similarly, the mean hs-CRP level in patients with subsets of ACS was significantly (p<0.05) higher in group II. The mean hs-CRP level of group I and group II was 26.84±30.30 mg/L and 37.48±37.99 mg/L respectively. In the study by Kurowska et al., mean hs-CRP level in patients with MI was 24.3±36.6 mg/l in patients with type 2 diabetes and 29.7±40.8 mg/l in patients without diabetes[20]. In case of UA the hs-CRP level was 6.6±6.5 mg/l in patients with type 2 diabetes and 25.2±49.9 mg/l in patients without diabetes, which were significantly (p<0.05) higher in patients with out DM, which support the findings of current study. Facila et al., concluded that homocysteine over 10µmol/l was an independent prognostic factor increasing the long term risk of all cause mortality after acute coronary syndrome[21].

In this present series it was observed that the mean serum homocysteine level was higher in male and female ACS patients without DM. This finding is supported by Kurowska et al., who showed that the mean serum homocystieine level was 14.4±5.5 µmol/L in male patients with T2DM and 15.4±6.4 µmol/L in male patients without diabetes[20]. Kurowska et al., showed the mean(±SD) serum homocystieine level was 14.4±7.1 µmol/L in female patients with T2DM and 15.2±6.0 µmol/L in female patients without diabetes, which was statistically significant (p<0.05) and support the findings of the current study[20].

Similarly the mean hs-CRP level was higher in male and female ACS patients without DM in this syudy. Kurowska et al., showed lesser hs-CRP level in male patient, which was 17.0±19.8 mg/l in patients with type 2 diabetes and 31.0±50.1 mg/l in patients without diabetes, that was significantly (p<0.05) higher in ACS patients without DM[20]. Thus support the current study. Kurowska et al showed, the mean hs-CRP level was 17.0±38.3 mg/l in female patients with type 2 diabetes and 20.5±33.6 mg/l in female patients without diabetes, which was significantly (p<0.05) higher in ACS patients without DM, which is consistent with the current study[20]. On the other hand, Idzior-Walu[et al. CRP levels was significantly higher in women with diabetes than in men which was 4.7±3.2 mg/l vs 4.1±7.2 mg/l in female and male respectively[22].

Regarding the risk factors dyslipidaemia and smoking was statistically singnificant risk factor in group I and group II respectively. Puri et al. showed that hypertension, smoking, positive family history and dyslipidaemia were the most common risk factors in patients with ACS[18]. The mean serum Homocysteine differences were significantly (p<0.05) higher in HTN, smoker and dyslipidemia in patients without T2DM. But obesity and F/H of premature CAD was almost comparable in both groups. Puri et al. showed the mean homocysteine was 23.93±10.94 nmol/ml and 25.41±11.88 nmol/ml in hypertensive and smoker patients respectively. The mean serum hs-CRP differences was significantly (p<0.05) higher in HTN and F/H of premature CAD in patients without DM, but other risk factors was not significant (p>0.05) between the two groups[18].

This is consistent with the finding done by Akalin A et al., that show inflammatory activity and Hcy levels are increased in type 2 diabetic patients with atherosclerotic vascular diasease, but there was no correlation between Hcy and inflammatory markers except TNF±. Inflammation is not involved in the process by which Hcy leads atherosclerosis in type 2 diabetes[10]. Mazza et al. demonstrated that homocysteine levels poorly correlated with the severity of coronary artery disease, but had a strong predictor of acute coronary syndrome recurrence[16]. A study done by Kurowska et al. 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[20].

Conclusion:

This cross sectional observational study was done to compare the serum homocysteine and hs-CRP levels in ACS patients with and without T2DM. The result of the current study suggests that further studies are required for the assessment of relationship of plasma homocysteine to atherosclerotic vascular disease and inflammatory markers in T2DM patients and implication of lower blood Hcy and hs-CRP level on the prognosis of acute coronary syndrome patients to reach a conclusive decision.

References :

1. Raj B. What is the risk of coronary heart disease in South Asians? A review of UK research. J Pub Health Med 2000; 22: 375-385.
2. Maron DJ, Rider PM, Grundy SM, Prevention Strategies for Coronary Heart Disease. In: Fuster

V, Walsh RA, O'rourke RA, Wilson PP, editors, Hurst's, the heart, 12th edn, Mc Graw Hill, New York, USA, 2008; pp. 1235-1244.

3. Farkouh ME, Aneja A, Reeder GS et al, Usefulness of Diabetes Mellitus To Predict Long-Term Outcomes in Patients with Unstable Angina Pectoris, American Journal of Cardiology, 2009; 104(4):492-497.

4. Haffner SM, Lehto S, Ronnemaa T, PyorLa K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Eng J Med. 1998; 339 (4); 229 – 234.

5. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel 111). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel 111) final report. Circulation; 2002; 105 (25): 3143-3421

6. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med 1993; 328:1676-1685.

7. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004; 27:813-823.

8 Bodi V, Sanchis J, Llacer A. et al; Risk stratification in non- ST elevation acute coronary syndromes; predictive power of troponin I, C – reactive protein, fibrinogen and homocysteine. Int. J. Cardiol, 2006; 109, 248.

9 Zak A. ZemanM. ; Consequences of moderate hyperhomocysteinemia in internal medicine. Lek. Cesk.; 2004; 143, 367.

10 Akalin A. Alatas O, Colak o. :Relation of plasma homocysteine levels to atherosclerotic vascular disease and inflammation markers in type 2 diabetic patients. Eur. J. Endocrinol.; 2008; 158, 47.

11 Gonzalez-Porras JR, Martin-Herrero F, Garcia-Sanz R, et al. Hyper- homocysteinemia is a risk factor of recurrent coronary event in young patients irrespective to the MTHFR C677T polymorphism. Thrombosis Research 2007; 119: 691-698.

12 Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999; 340:115- 126.

13 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, Aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336:973- 979.

14 Mueller C, Buettner HJ, Hodgson JM, Marsch S, Perruchoud AP,Roskamm H, Neumann FJ. Inflammation and long-term mortality after Non-ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. Circulation 2002; 105:1412-1415.

15 Brunetti N. D., T roccoli R, Correal M. et. Al.: C-reactive protein in patients with acute coronary syndrome : correlation with diagnosis, myocardial damage, ejection fraction and angiographic findings. Int. J. Cardiol. , 2006: 109, 248.

16 Mazza A., Bossone E., Mazza F. et. al.: Reduced serum homocysteine levels in type 2 diabetes. Nutr. Metab. Cardiovasc.Dis., 2005; 15, 118.

17 Ockene IS, Matthews CE, Rifai N, Ridker PM, Reed G, Stanek. E. Variability and classification accuracy of serial high- sensitivity C- reactive protein measurements in healthy adults. Clin Chem 2001; 47: 444-50.

18 Puri A, Gupta OK, Dwivedi RN, et al. Homocysteine and Lipid levels in young patients with coronary artery disease. JAPI. 2003; 51:681-685.

19 Cusack MR, Marber MS, Lampiase PD, Bucknall CA, Redwood SR. Systemic inflammation in unstable angina is the result of myocardial necrosis. J Am Coll Cardiol 2002; 39:1917-23.

20 Kuruowska M., Kaznowska- Bysetryk I., Dudzinska M., Tarach J., Malicka J. et al. Comparison of homocysteine and C - reactive protein levels determined at the moment of hospitalization in patients with acute coronary syndrome (ACS) with and without type 2 diabetes. ANNALES UNIVERSITATIS MARIAE CURIE- SKLODOSKA LUBLIN- POLONIA 2008; Vol. XXI, N1, 60.

21 Facila L., Nunez J. et al. :Early determination of homocysteine levels in acute coronary syndroms, is it an independent prognestic factor? In. J. Cardiol. 2005: 100, 275.

22 Idzior- Walus B, Cieslik G. et. al.: Homocysteine and C- reactive protein concentrations in serum of diabetic patients. Prazeg . Lek., 2003: 60, 778.51.