ORIGINAL ARTICLE

A relation of serum homocysteine, uric acid and C-reactive protein level in patients with acute myocardial infarction

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ABSTRACT

Aim To determine the relationship of homocysteine (HCY), uric acid (UA) and C-reactive protein (CRP) in serum of patients with acute myocardial infarction (AMI) prior to application of percutaneous coronary intervention (PCI) and their level of correlation in serum of patients with normal and elevated CRP (predictor of worse cardiovascular outcomes).

Methods The study involved 85 patients with diagnosed AMI. Before the PCI, venous blood samples were taken into the vacuum test tubes. The analysis of HCY, UA, inflammatory markers CRP and neutrophil to lymphocyte ratio (NLR) as well as lipoprotein status were performed on a different type of analysers and according to accepted protocols of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

Results Elevated level of both HCY and UA in AMI patients as well as a positive correlation between HCY and UA level was observed. Classification of patients on the basis of mean UA concentration showed significant difference at the level of HCY concentration (p=0.022).

Conclusion Since HCY and UA participate in the atherosclerotic process and their metabolism, as well as the effects on the cardiovascular system show significant overlaps, their serum level should be analysed synchronously with the level of CRP and NLR (indicators of significant inflammatory process in vessels). Considering a potential link between all parameters observed, further research involving a greater number of patients and including the post treatment effects should be conducted.

Key words: ST elevation myocardial infarction, inflammation, atherosclerosis, oxidative stress

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INTRODUCTION

Acute myocardial infarction (AMI), one of the cardiovascular complications, occurs as a result of atherosclerotic plaque rupture and emergence of thrombus. Myocardial tissue becomes inflamed and necrotic, it loses contraction and impulse conducting ability with net result of decreased oxygen distribution (1).

Research done in the last two decades, among other factors, points out amino acid homocysteine (HCY) as an independent risk factor for cardiovascular diseases (CVD) (2-4). A rise of 5 μmol/L in HCY level increases risk of coronary heart disease from 20% to 50% (5). Whatever the cause is, mild and moderate hyperhomocysteinemia (13 to 25 μmol/L) is strongly associated with stroke, coronary artery disease, obstructive CVD (6), restenosis, heart failure and major adverse cardiac events (MACE) (death, reinfarction, restenosis) after percutaneous coronary intervention (PCI) (7) and with all causes of death in that patients (8). In general, the effects of HCY in CVD appear to be a consequence of oxidative process in the vascular endothelium resulting in disturbed NO synthesis and vasodilatation (9). This implies the existence of a potential correlation between measured concentrations of HCY and the status of antioxidants. However, despite ongoing prospective studies involving thousands of patients, methodological difficulties prevent a clear identification of these relations, especially independence or the interaction between the increased level of HCY and traditional risk factors (8). Therefore, the risk of arteriosclerotic coronary lesions occurrence due to increased level of HCY remains mostly unnoticed/unclear, especially in patients with AMI.

Interestingly, research results investigating the association of uric acid (UA) level in serum and cardiovascular risk are unclear and contradictory with insufficient data on UA level in patients with AMI before PCI (15). The UA is the final product of xanthine oxidase activity in purine metabolism. Adenosine, which is synthesized locally in vascular smooth muscle cells of the myocardial heart tissue, is rapidly degraded to UA in the endothelium. The UA is then eliminated by kidneys and through bowels (27). Major effects are observed at the level of increased UA concentrations and elevated xanthine oxidase activity. These two could be used as markers in ischemic cardiac disease. A few papers also show association of increased UA concentrations with increased incidence of CVD (7,10). There is also evidence that UA in serum can promote lipids metabolism impairment (11), and that increased UA concentrations can stimulate the free radical formation as well as the occurrence of atherosclerotic plaque (12). These processes result in tissue damage, a consequence of which may be myocardial infarction. On the other hand, under physiological concentrations, uric acid together with other extracellular antioxidants (e.g. ascorbic acid, α-tocopherol, carotenoids and bilirubin) has an antioxidative effect controlling the rate and activity of free radicals (13). Experimentally induced decrease in serum UA levels caused a decrease in antioxidant capacity, and an increase in markers of oxidative stress (14). Uric acid makes more than half of the antioxidant serum capacity and is the most common antioxidant in the body's water compartment. It improves endothelial function by restoring NO generation which could decrease vascular tone and increase tissue blood flow suggesting its protective role in cardiovascular related diseases (15). Reduced serum concentrations have been reported in some pathological conditions (16).

Even though individual effects of both UA and HCY are relatively well known in AMI patients, data which show their level of interaction with CRP, a major inflammatory marker, are limited and often contradictory and require further research.

The aim of this research was to determine homocysteine, uric acid and CRP levels in patients with AMI before PCI application and more importantly to determine their level of correlation in serum of AMI patients with normal and elevated CRP, which, according to literature is a predictor of the worse cardiovascular outcomes (17,18).

PATIENTS AND METHODS

Patients and study design

This prospective research included 85 patients diagnosed with AMI. Patients were admitted to the Department of Cardiology at the University Clinical Hospital of Mostar, Bosnia and Herzegovina, in the period between October 2016 and December 2017. All research involving human

subjects and material derived from human subjects in this study was done in accordance with ethical recommendations and practices of Mostar University Clinical Hospital and University of Sarajevo, School of Pharmacy.

The AMI diagnosis was established by a cardiologist on the basis of at least two of the three WHO criteria (1). All patients were diagnosed with ST elevation myocardial infarction (STEMI) myocardial infarction, followed by PCI as a treatment method. In all stratified patients, diagnosis of STEMI infarction was confirmed by electrocardiogram (ECG). Detailed medical history including usual CVD risk factors, such as diabetes, hypertension, hyperlipidaemia, smoking, and the existence of a family disease was taken for each patient. Hypertension was defined as systolic arterial pressure ≥140 mmHg and/or diastolic arterial pressure ≥90 mmHg values, or as the use of antihypertensive drugs. Smoking was defined as daily consumption of at least one cigarette. Exclusion criteria were pregnancy, diabetes, the use of antiepileptic, contraceptive therapy, cancer, and vitamin B12 supplementation in the last 6 months.

Due to the simpler interpretation of possible statistically significant results, according to previous studies, patients involved were divided by age and concentration of UA in serum (below and above the mean UA level of 325.77 μmol/L) as well as in tertiles according to different HCY concentration. Patients were also classified on the basis of gender, and measured concentration of CRP and LDL (concentration falling both within and outside the reference range).

Methods

After ECG, and before the PCI, venous blood samples were taken into the vacuum tubes. A serum sample, used to determine the HCY, UA concentrations and other general biochemical assays, was obtained with one anticoagulant-free 7.5 mL test tube (Sarstedt, Germany). Whole blood sample for haematological assays was taken in single 2.6 mL test tube with EDTA as anticoagulant (Sarstedt, Germany). Residual part of the serum and whole blood sample was taken for research after the completion of routine treatment ordered by a cardiologist.

The concentration of the HCY (μmol/L) was measured in serum by non-competitive immunoassay method, e. g. chemiluminescence microparticle immunoassay (CMIA) (Architect ci8200 Integrated System analyser, Abbot, Ilinois, USA). The UA concentration was measured on the AU680 analyser (Beckman Coulter, California, USA) according to the standardized IFCC (International Federation of Clinical Chemistry) method, photometric method (uricase-POX) (19). Other biochemical assays were performed on AU680 analyser also according to standardized IFCC methods, i.e. cholesterol (mmol/L)-photometry (CHOD-PAP), triglycerides (mmol/L) -photometry (GPO-PAP), high-density lipoprotein (HDL) (mmol/L) -photometry IFCC, low-density lipoprotein (LDL) (mmol/L) -photometry IFCC, CRP (mg/L) -immunoturbidimetry.

Haematological parameters (leukocytes, lymphocytes and neutrophil counts) were measured on Sysmex XT2000i analyser (Sysmex corporation, Kobe, Japan) by impedance and VCS (volume, conductivity and scatter) principle. Neutrophil to lymphocyte ratio (NLR) was calculated from the obtained data.

Statistical analysis

An assessment of the normality of data was tested by the Kolmogorov-Smirnov test. Correlations between HCY and UA level, HCY level and age, UA level and gender, age and gender in all subgroups of patients were tested by nonparametric Spearman correlation. The differences between the subgroups of patients based on gender, age, hypertension, CRP, LDL and UA level were tested by the non-parametric Mann-Whitney U test. One sample t-test was used for comparation of HCY and UA with respective reference ranges. In cases of comparison of more than two groups (stratification of patients according to HCY level in tertiles) Kruskal-Wales and $\chi 2$tests were used. $p< 0.05$ was considered statistically significant.

RESULTS

Basic demographic and clinical characteristics of tested groups are summarized in Table 1. The group of 85 patients included in the study comprised (61%) males and (24%) females. A statistically significant difference was observed in the age between male and female patients ($p = 0.026$), i.e. females were older. Age and gender were positively correlated ($rho =0.238$; $p<0.05$).

Table 1. Demographic characteristics of patients and biochemical parameter values

Variable	All patients (n=85)		Males (n=61)		Females (n=24)		p
Age (years) (Mean ±SD)	61.52±11.66		59.78±10.94		66±12.49		p=0.026
Gender (No, %)	-		61 (72)		24 (28)		
Smoking (yes) (No, %)	49 (58)		39 (63)		10 (42)		
Hypertension (yes) (No, %)	59 (70)		43 (71)		16 (67)		
Parameter (Reference range)	**Value interval**	**Mean ±SD**	**Value interval**	**Mean ±SD**	**Value interval**	**Mean ±SD**	
Homocysteine (HCY) (5.46-16.2 µmol/L males; 4.44-13.56 µmol/L females)	4.23-44.99	13.44±5.85	4.23-44.9	13.24±6,22	7.14-26.53	13.96±4.88	
Uric acid (UA) (182-403 µmol/L males; 134-337 µmol/L females	134.0-527.0	325.7±89.05	153.0-527.0	338.4±87.27	169.0-496.0	293.6±81.02	p=0.034
Triglycerides (<1.7 mmol/L)	0.40-11.60	2.49±1.73	0.40-11.60	2.64±1.90	0.80-5.40	2.11±1.13	
Cholesterol (<5 mmol/L)	3.2-11.0	6.43±1.56	3.20-9.9	6.26±1.48	4.10-11.0	6.84±1.69	
High-density lipoprotein(HDL) (>1.0 mmol/L)	0.70-2.40	1.37±1.20	0.70-1.8	1.17±0.24	0.90-2.40	1.44±0.38	p=0.002
Low-density lipoprotein (LDL) (< 3 mmol/L)	2.10-7.90	4.40±1.07	2.10-6.4	4.28±0.98	2.80-7.90	4.70±1.23	
C-reactive protein (CRP) (0.0-5.0 mg/L)	0.20-118.40	7.61±14.25	0.20-118.40	8.56±16.21	0.30-30.9	5.28±7.41	
Neutrophile to lymphocyte ratio (NLR) (0.78-3.53)	0.48-22.75	4.73±3.97	0.48-22.75	4.60±4.21	0.98-14.83	5.09±3.31	

Hypertension was noticed in 59 (70%) and it was almost equal among males and females, 43 (71%) and 16 (67%), respectively. Smoking habit was noticed in 49 (58%), with a difference between males and females, 39 (63%), and 10 (42%), respectively (Table 1).

Hypercholesterolemia (cholesterol>5mmol/L) was observed in 70 (82%) patients. Compared to the upper value of the reference range for each lipoprotein analyte, a deteriorated lipoprotein status was observed in most of the patients of both genders. Only six (7%) patients had lipid levels (cholesterol, triglycerides, HDL, LDL) within the reference range. There was a significant difference in HDL and UA levels between males and females, (p=0.002) and (p=0.034) respectively, while no significant differences were observed at the level of other parameters.

An analysis of inflammatory markers showed an increased level of CRP and NLR in all subgroups of patients. The mean values for male and female patients were significantly above the reference range for these analytes. Compared to the reference range, HCY levels in both female (p<0.001) and male (p=0.004) subgroup were significantly elevated. There was also a significant increase in UA levels in the male (p<0.001) and female (p=0.002) group compared to the reference range (Table 1).

The distribution of patients in tertiles according to the HCY concentration (Table 2) showed significant differences in CRP concentration among the examined groups, while slightly older patients were characterized with higher homocysteine levels. In subgroups of patients divided by the mean UA concentration on those above and below mean value (325.77µmol/L), a statistically significant difference in HCY (p=0.022) was observed (Table 3).

Table 2. Distribution of patients according to homocysteine (HCY) level

	Group of patients according to HCY level (µmol/L)			
	Group 1 <10.76 (n=28)	**Group 2** 10.76-14.12 (n=28)	**Group 3** >14.12 (n=27)	**p**
Parameter	Mean ±SD	Mean ±SD	Mean ±SD	
Uric acid (UA) (µmol/L)	338.18 ±88.40	326.55 ±89.91	350.47 ±96.34	0.130
Leukocyte (x109/L)	11.43±3.50	10.97±3.04	11.51±2.34	0.507
CRP (mg/L)	11.71±27.72	5.17±6.65	7.83±10.46	0.005
Neutrophile to lymphocyte ratio	4.85±3.74	4.54±3.92	4.79±4.50	0.864
Triglycerides (mmol/L)	2.75±2.52	2.45±1.37	3.06±1.83	0.227
Cholesterol (mmol/L)	6.49±1.23	6.70±1.46	6.40±1.43	0.947
High-density lipoprotein (HDL) (mmol/L)	1.18±0.20	1.33±0.33	1.14±0.24	0.160
Low-density lipoprotein (LDL) (mmol/L)	4.41±0.69	4.49±0.97	4.31±0.96	0.985
Age (years)	59.14 ±10.97	61.85 ±11.01	64.23 ±12.44	0.137
Variable	No (%)	No (%)	No (%)	p
Gender (Male)	25 (89)	18 (64)	21 (78)	0.501
Hypertension (yes)	16 (57)	22 (78)	17 (63)	0.578
Smoking (yes)	17 (61)	14 (50)	18 (67)	0.554

In the group of patients stratified on the basis of LDL concentration (i.e.<3 mmol/L>) and hypertension, no statistical difference was observed at the level of HCY. However, a statistically significant difference in UA levels was observed only in the group of patients divided by gender (p=0.034) (Table 3). In other subgroups, the differences were not statistically significant.

The correlation analysis showed a weak positive correlation between UA and HCY level in the group of all patients (rho = 0.276), in patients with

Table 3. Homocysteine (HCY) and Uric acid (UA) concentrations in different subgroups of patients (mean value with standard deviation)

Patient group (No of patients)	Concentration (µmol/L)	
	Homocysteine (HCY) Mean ±SD	Uric acid (UA) Mean ±SD
C-reactive protein		
<5mg/L (53)	13.41±6.53	321.06±88.82
>5mg/L (32)	13.25±4.50	333.93±87.36
Low-density lipoprotein (LDL)		
<3mg/L (8)	15.34±5.47	338.00±87.41
>3mg/L (77)	13.15±5.94	323.96±89.23
Hypertension		
Yes (59)	13.04±4.16	343.64±93.28
No (26)	14.78±9.32	306.73±73.90
Age (years)		
<55 (22)	12.77±6.34	324.86±87.76
55-65 (36)	13.49±6.85	333.89±90.24
>65 (27)	13.92±3.83	315.70±85.62
Gender		
Male (61)	13.24±6.22	338.41±87.27
Female (24)	13.96±4.88	293.66±81.02
p		p=0.034
Uric acid (UA)		
<325.77µmol/L (47)	12.14±4.29	-
>325.77µmol/L (38)	15.06±7.08	-
p	p=0.022	

CRP<5mg/L (rho = 0.271) and LDL>3mmol/L (rho=0.242). In the group of patients below 55 years of age, a slightly higher positive correlation was observed (rho=0.480), while in patients between 55 and 65 years of age a weak positive correlation between the HCY and UA concentrations (rho =0.330) was observed. A weak positive correlation was observed also between the HCY concentration and the age of patients, in group with LDL >3 mmol /L (rho=0.238), hypertension (rho=0.338), and UA below mean value of 325.77µmol / L (rho=0.329). All these correlations were at the level of significance p<0.05 (Table 4).

Table 4. The correlation analysis between uric acid (UA) and homocysteine (HCY) level in patient groups

Patient group (No of patients)	Spearman correlation (p)			
	HCY/UA	HCY/Age	UA/Gender	Age/Gender
All patients (85)	rho=0.276 (p=0.011)	p=0.075	rho=0.276 (p=0.033)	rho=0.238 (p=0.025)
C-reactive protein				
<5mg/L (53)	rho=0.271 (p=0.049)	p=0.277	rho=-0.334 (p=0.01)	rho=0.3 (p=0.006)
>5mg/L (32)	p=0.143	p=0.082	p=0.890	p=0.945
Low-density lipoprotein (LDL)				
<3mg/L (8)	p=0.094	p=0.482	p=0.127	rho=0.791 (p=0.034)
>3mg/L (77)	rho= 0.242 (p=0.037)	rho=0.238 (p=0.040)	rho=-0.298 (p=0.009)	rho=0.229 (p=0.047)
Hypertension				
Yes (59)	p=0.285	rho=0.338 (p=0.019)	p=0.260	p=0.552
No (26)	p=0.099	p=0.668	p=0.100	p=0.079
Uric acid (UA)				
<325.77 µmol/L (47)	p=0.119	rho=0.329 (p=0.024)	p=0.331	p=0.102
>325.77 µmol/L (38)	p=0.734	p=0.780	p=0.875	rho=0.339 (p=0.037)
Age (years)				
<55 (22)	rho=0.480 (p=0.024)	p=0.217	p=0.066	p=0.594
55-65 (36)	rho=0.330 (p=0.050)	p=0.531	p=0.348	p=0.896
>65 (27)	p=0.318	p=0.411	p=0.281	p=0.586

DISCUSSION

This research reveals a positive correlation between the HCY and UA level in the group of all patients tested, in the subgroup of patients with CRP levels within the reference range, as well as in patients with increased LDL. A positive correlation was also observed in different age subgroups.

The increased level of HCY in AMI compared to a group of healthy subjects was observed in several studies (6,20,21) which is in accordance with our research results. However, studies related to association of hyperhomocysteinemia and coronary arterial disease are contradictory, some of them indicating an association (22,23), while in other studies, such an association is not observed and is explained by high homocysteine level in healthy population (24). Contradictory results are as well due to different criteria for inclusion and exclusion of patients in research, different numbers of patients, methods of analysis, genetic background and different eating habits (25). Genetic background, sufficient intake of vitamins B6, B12, and folic acid, as well as preserved renal function, are factors that directly affect HCY serum concentration (9) and all should be taken into consideration when assessing HCY concentration in any case. Our research results are consistent with those of Cohen et al., who also found a positive association between homocysteine serum level and uric acid serum level (26). Similar results have been obtained by other researchers as well (8,27). The correlation between HCY and UA is explained by the fact that hydrolysis of S-adenosyl homocysteine leads to adenosine, which is further degraded to UA (25), meaning that an increase of HCY concentration results in an increase in UA concentration. This correlation between these two biochemical parameters in AMI points out the need for a joint observation of these two variables in AMI patients. Interestin-

gly, this correlation was expressed in the group of patients with CRP concentration within the reference range. As already noted, CRP is a marker of low grade vascular inflammation, and atherosclerosis development (28), and it is useful in the complete assessment of cardiovascular risk. It is considered as an indicator of poorer cardiovascular outcome in patients with AMI or angina pectoris. It also reflects the degree of myocardial damage (29). Patients with hs-CRP<1mg/L have a low risk of developing cardiovascular diseases, patients with hs-CRP 1mg/L-3mg/L are in the middle-risk group, while ones with hs-CRP>3mg/L represent a high-risk group for the development of cardiovascular diseases. Taking these risk factors into consideration, it was of no surprise that correlations of HCY and UA were both expected and confirmed in the group of patients with CRP level within the reference range. Patients with CRP level of 5mg/L-10mg/L, 10mg/L-20mg/L, or even more, are at the highest risk group, regardless of the cause of significantly increased level (30). The distribution of patients in tertiles according to HCY level revealed elevated CRP values in all groups of patients. Considering the fact that there are other factors which can cause elevation of CRP levels besides atherosclerosis or AMI, future research should take those factors into consideration.

When patients were stratified on the basis of their mean concentration of UA on those below and above 325.77μmol/L, significant difference in the concentration of HCY was observed between the two groups. However, significant difference in HCY level between males and females was not observed, probably due to the weakness of the estrogenic protective effect in the female group, which is according to age (66 ± 12.49 years) in post menopause. Although younger women have lower HCY levels than men, this difference seems to disappear with aging (31). A weak positive correlation was observed between the age and HCY level in different subgroups of patients, which is in accordance with other research (32) and is probably due to the changes in HCY metabolism or renal function disorders. Recent studies associate increased HCY level with more rapid development of thrombotic states (21), which explains the level in patients with AMI, but clear mechanisms are still not fully clear. Hyperhomocysteinemia is considered to cause the reduction of carotid intima media (33) and because of its prothrombotic effect is associated with platelet reactivity, explaining observed increased level in patients with AMI. Because of this, it might be the target of aspirin therapy (34). Homocysteine increases arterial stiffness (35), reduces the possibility of methylation, leading to endothelial dysfunction and proliferation of smooth muscle cells in blood vessels, oxidative stress occurrence, NF-κB activation, inflammation, and inhibition of nitric oxide synthesis in the endothelium (25). It has also been confirmed that the joint effect of hyperhomocysteinemia and hyperuricemia has a stronger effect on the aforementioned epithelial changes (26), which again points out synergistic effect of HCY and UA in CVD.

The reported increased UA concentration in patients with AMI in relation to the healthy control group (36) is confirmed in this research. The UA level in the serum of male and female patients is greater than the reference range levels, which are usually associated with a positive antioxidative effect of UA. Recent studies have shown increased UA level in patients with coronary artery disease compared to patients without this disease but no correlation between UA level and the degree of coronary artery disease was observed (37). Increased UA level promotes emergence of free oxygen species and state of oxidative stress (10), inducing apoptosis of cardiomyocytes, thereby promoting myocardial remodelling. Furthermore, AMI causes tissue hypoxia and hypoperfusion leading to the activation of xanthine oxidase and oxidative stress, resulting with an increase of UA levels. All these changes create a vicious circle in which the function of the heart is continuously deteriorating (38).

Inflammation plays a significant role in all stages of the atherosclerotic changes, starting from the beginning until the end result - AMI. The levels of both inflammatory markers (CRP and NLR) measured in this research are increased when compared to the reference ranges, as previously noted in other research papers (39). Kalay et al. found that high levels of NLR in acute coronary syndrome are independent predictors of coronary atherosclerosis development (40), and CRP is also considered to be a strong predictor of AMI (13). Being strong systemic inflammatory mar-

kers in CVD, CRP and NLR are also used as potential predictors of harmful cardiovascular events (17,18). More recently, the emphasis is on the simultaneous use of both markers in predicting adverse outcome of the disease (41).

In conclusion, this research has shown a correlation between increased HCY and UA levels in serum of patients with AMI who had not yet made PCI. Since both parameters are participants in the atherosclerotic process, our results seem to suggest that their serum levels should be analysed and interpreted simultaneously. This is also true for the levels of CRP and NLR, indicators of a significant inflammatory process and a worse outcome before appropriate therapeutic treatment is applied. To our knowledge, this is one of the first studies addressing the diagnostic value of HCY, uric acid and CRP, taken together in a clinical setting in Bosnia and Herzegovina, the country with very high prevalence of CVD. Considering potential link between them, further research involving a greater number of patients and including the post treatment effects should be done.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare

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