ORIGINAL ARTICLE

Positive correlation between uric acid and C-reactive protein serum level in healthy individuals and patients with acute coronary syndrome

Emina Spahić[1], Sabaheta Hasić[2], Emina Kiseljaković[2], Halima Resić[3], Mehmed Kulić[4]

[1]Primary Health Center Zenica, [2]Department of Medical Biochemistry, School of Medicine University of Sarajevo, [3]Clinic for Hemodialysis, Clinical Center University of Sarajevo, [4]Cardiology Clinic, Clinical Centre University of Sarajevo; Bosnia and Herzegovina

ABSTRACT

Aim To assess serum levels and correlation between uric acid (UA) and C-reactive protein (CRP) in acute coronary syndrome (ACS) and apparently healthy individuals.

Methods The cross-sectional study included 116 examinees of age 44 to 83 years, distributed in two groups: 80 ACS patients including 40 with acute myocardial infarction (AMI), and 40 with unstable angina pectoris (UAP), and 36 apparently healthy (control group) individuals. Patients with ACS were hospitalized at the Cardiology Clinic, Clinical Centre Sarajevo in the period October-December 2012. Laboratory analyses were conducted by standard methods. The accepted statistical significance level was $p<0.05$.

Results Serum levels of CRP and UA were higher in patients with ACS as compared to control group ($p<0.01$). The median serum UA was insignificantly lower, and CRP was significantly higher in patients with AMI compared to UAP ($p=0.118$ and $p=0.001$, respectively). Both CRP and UA correlated positively in both ACS and control groups ($rho=0.246$; $p=0.028$ and $rho=0.374$; $p=0.027$). A positive correlation between serum CRP and UA was noted in patients with AMI, but negative in patients with UAP ($p>0.05$).

Conclusion The correlation between CRP and UA in the patients with ACS indicates the association of oxidative stress and inflammation intensity in damaged cardiomyocytes. Correlation between UA and CRP in apparently healthy individuals indicates a possible role of UA as a marker of low-grade inflammation and its potential in risk assessment in cardiovascular diseases.

Key words: angina, unstable, inflammation, myocardial infarction, oxidative stress

Corresponding author:
Emina Spahić
Primary Health Center Zenica
Fra Ivana Jukića 2, 72000 Zenica, Bosnia and Herzegovina
Phone +387 32 403 418;
Fax; +387 32 242 113;
E-mail: spahca@hotmail.com

Original submission:
14 May 2015;
Revised submission:
20 June 2015;
Accepted:
29 June 2015.

Med Glas (Zenica) 2015; 13(2):

INTRODUCTION

Inflammation plays a significant role in all stages of atherosclerosis from initiation through progression, but also in pathogenesis of acute cardiovascular event (1). Acute inflammatory response is a major characteristic of cardiovascular occlusive event. Significant increase of serum C-reactive protein (CRP) occurs in inflammatory processes of different etiology, as a part of or independently of cardiac etiology (1,2). In healthy individuals, CRP circulates in very low concentrations (2), and individuals who are at the risk of development of cardiovascular diseases show systemic inflammatory response registered by increased serum CRP level. Apart from being a marker of inflammation, CRP contributes to development of atherosclerotic disease, and it is considered as the most powerful predictor of myocardial infarction and stroke (3). The elevated uric acid (UA) levels are related to arterial hypertension, systemic inflammation, and cardiovascular diseases through endothelial dysfunction and pathological remodeling of blood vessels, but physiological UA levels act as a powerful antioxidant (4). One of the mechanisms of elevated level of serum UA that contributes to systemic inflammation is induction of CRP expression in endothelial and smooth muscle cells of blood vessels, which facilitates its increased synthesis and elevated level in circulation (5). The CRP induces proinflammatory cytokine release and forms terminal complement complexes in the intima of the early atherosclerotic lesion which contribute to plaque instability (6).

The study objective was to assess a correlation between the serum UA and CRP levels in apparently healthy individuals and acute coronary syndrome (ACS) patients.

EXAMINEES AND METHODS

The cross-sectional study included 116 examinees of both genders (59 males and 57 females), aged 44 to 83. Examinees were distributed into two groups: acute coronary syndrome group (ACS), consisted of 40 acute myocardial infarction patients (AMI) and 40 unstable angina pectoris (UAP), and group consisted of apparently healthy individuals as control group (CG) (the data are drawn from a database). The patients with ACS were hospitalized at the Intensive Care Unit of Cardiology Clinic, Clinical Centre of Sarajevo in the period October- December 2012. Diagnosis of acute coronary syndrome was established on the basis of electrocardiogram changes (ECG), clinical symptoms, and elevated levels of serum cardiac troponin (cTnI). The control group included patients who had normal laboratory values during a routine check.

Results of biochemical analysis obtained within 48 hours of hospital admission were collected from patients' medical histories. Stable angina pectoris patients and those with malignant, liver and kidneys diseases, acute or chronic systematic inflammatory diseases, infectious or septic states, patients treated with allopurinol and chronic alcohol consumption were excluded from the study. Laboratory results of apparently healthy individuals, who were without objective and subjective signs of diseases and underwent routine laboratory testing were used as control group data.

Biochemical analyses were conducted at the Clinic of Chemistry and Biochemistry, Clinical Centre of Sarajevo. The serum cTnI was measured by AxSYM Troponin-I ADV Immunoassay (reference range 0-0.04 ng/mL) using AxSym analyzer (Abbott Laboratories, Abbott Park, IL, USA). Immunoturbidimetric method of CRP (reference range 0-5 mg/L) and spectrophotometric method of uric acid (155-428 μmol/L) were used for analysis on Dimension Xpand Plus (Siemens, Munich, Germany).

The study was performed according to the principles outlined in the Declaration of Helsinki.

This investigation was approved by School of Medicine, University of Sarajevo, Bosnia and Herzegovina.

Normality of distribution of variables analyzed by Shapiro-Wilk test was not satisfied, so the numeric variables were presented by median with interquartile range (25-75 percentiles). The difference between groups was analyzed by Mann-Withney U, non-parametric test. The degree of correlation was examined by the test according to Spearman. Levels $p<0.05$ were considered as statistically significant.

RESULTS

The patients with acute coronary syndrome were slightly older in the comparison to the control group (p>0.05) (Table 1).

Table 1. Demographic characteristics of patients with acute coronary syndrome and controls

	Patient groups			
Variables	CG (n=36)	ACS (n=80)	AMI (n=40)	UAP (n=40)
Age (years)	64 (44-81)*	67 (50-83)	66 (53-81)	67 (50-83)
No (%) of males	17 (47.2)	40 (50)	20 (50)	20 (50)

*NS (not significant) compared to ACS patients (p>0.05) CG, control group; ACS, acute coronary syndrome; AMI, acute myocardial infarction; UAP, unstable angina pectoris;

Median level of serum cTnI in the ACS patients was 0.33 (0.06-18.84) ng/mL and AMI patients had significantly higher cTnI level in the comparison to UAP patients (p<0.01). Levels of CRP and UA were significantly higher in the ACS compared to the control group (p<0.01). Levels of CRP in AMI patients were higher in comparison to UAP group (p=0.001), but UA was lower compared to UAP (p=0.118) (Table 2).

Table 2. Blood levels of cardiac troponin I, C-reactive protein and uric acid in acute coronary syndrome patients

	Variables		
Patient's group	**cTnI (ng/mL)**	**CRP (mg/L)**	**UA (µmol/L)**
ACS	0.33 (0.06-18.84)	21.70 (10.40-63.42)*	364 (312-437.75)
CG	/	1.90 (1.0-4.8)	263 (216-320)
AMI	16.22 (4.38-29.97)†	47.5O (15.60-74.75)†	357.50 (323.25-498.25)‡
UAP	0.06 (0.027-0.12)	13.35 (8.02-31.0)	379 (290.75-414.50)

*p<0.01 between ACS and control group; †p<0.01 between AMI and UAP groups; ‡ no significant difference between and AMI and UAP groups; ACS, acute coronary syndrome; CG, control group; AMI, acute myocardial infarction; UAP, unstable angina pectoris; cTnI, cardiac troponin I; CRP, C reactive protein; UA, serum uric acid

A moderate positive relationship between serum CRP and UA levels (rho=0.374; p=0.027) was observed in the CG patients (Table 3), while weaker relationship between the two observed parameters was noticed in ACS group (rho=0.246, p=0.028). Although the association between CRP and UA was positive in AMI and negative in UAP group, both of them were no significant (p>0.05).

Table 3. Spearman's correlation of serum C-reactive protein and uric acid in patients with acute coronary syndrome and in control group

		Patient groups			
Variables		**CG**	**ACS**	**AMI**	**UAP**
CRP / UA	rho	0.374	0.246	0.244	- 0.150
	p	0.027*	0.028*	0.129	0.355

*p<0.05; CRP, C-reactive protein; UA, serum uric acid; CG, control group; ACS, acute coronary syndrome; AMI, acute myocardial infarction; UAP, unstable angina pectoris; rho-Spearman correlation coefficient;

DISCUSSION

The development of atherosclerosis depends on the balance between proinflammatory stimuli, anti-inflammatory and anti-oxidative defense mechanisms. The range of CRP values in blood of healthy volunteers indicates a low grade inflammation (CRP > 3 mg/L). According to American Heart Association, this category of apparently healthy individuals is at the risk of development of cardiovascular diseases (6,7). Yamada et al. have found that in 94% of the apparently healthy individuals CRP was lower than 2 mg/L with median of 0.12 mg/L (8). In Koenig et al. study, 55-80 % of the individuals had CRP lower than 2 mg/L, which is considered as a level for detection of active inflammation, infection, or tissue damage (9). Investigation of serum UA concentration and its role and importance as an independent risk factor for the development of cardiovascular diseases is complicated by the fact that elevated levels of UA combine with other factors to increase the cardiovascular risk (10). The physiological range of uric acid concentration has been noted in healthy individuals included in the present study. As one of the most powerful antioxidants, uric acid eliminates free radicals from the body, and serum UA elevation could represent a compensatory mechanism against free radicals (10). Uric acid functions in early stages of atherosclerosis as an antioxidant, but it becomes prooxidant in the cell through increased rate xanthine oxidase activity (11). In prospective cohort study which included middle-aged Finish men without cardiovascular diseases, cancer or diabetes, serum UA levels in the lower third of reference range were associated with greater risk of cardiovascular death than those with concentrations of UA in upper third. (12). Consistent with Jalal at al. study (13), we observed a positive association between CRP and UA in the control group. De Carvalho Vidigal study suggested that uric acid is suitable biochemical indicator for detecting changes in hs-CRP and can also predict higher C-reactive protein levels in apparently healthy men improving the assessment of cardiovascular risk (14).

Serum levels of CRP in the present study were significantly higher in ACS subjects compared to the controls, which is in accordance with Baruah et al. and Kushner et al. studies (15,16). Myocar-

dial necrosis leads to inflammatory response, cytokines activation and consequential increase of CRP synthesis. Binding of CRP to necrotic myocardial cells and consecutive complement activation is considered responsible for a further myocardial necrosis expansion (17).

Higher level of serum CRP concentration in the patients with AMI indicates greater myocardial inflammatory response as the consequence of more severe myocardial lesion in AMI than in UAP patients (18). In Munir et al. study, significant increase of serum CRP within 12 to 24 hours has been shown in patients with UAP, myocardial infarction without elevation of ST-segment (NSTEMI), and myocardial infarction with ST elevation (STEMI) (19). Besides the CRP localization in atherosclerotic lesions, it localizes also in ischemic myocardium and promotes complement activation (20). Results of this study have shown that levels of UA in ACS group were statistically significantly higher in comparison with the control group, and insignificantly lower in the AMI group compared to UAP (p=0.118). The similar results were published in Gur et al. study who found increased UA values in AMI and UAP patients compared with controls, but uric acid level was not in relation to the severity of coronary artery disease (21). Higher levels of uric acid indicate greater intensity of oxidative stress in ACS than in control group. Under local ischemia condition and increased synthesis of oxygen radicals, UA becomes prooxidant (22-24).

We have notified that levels of CRP and UA positively correlated in ACS patients. In Baruah et al. study, the similar kinetic of CRP and UA have been registered in post-infarction period. Both markers peak on the 3rd day, and then return to baseline level (15). In the present study a positive correlation between CRP and UA in the serum was established in AMI, and a negative correlation in UAP group, but it was not statistically significant. We consider that a positive correlation between uric acid and C-reactive protein in serum of healthy individuals indicates the importance of serum levels of uric acid in monitoring the intensity of low-grade inflammation. The correlation between the two observed parameters in acute coronary syndrome indicates correlation between intensity of oxidative stress and inflammation in myocardial tissue.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Shrivastava AK, Singh H V, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. The Egyptian Heart Journal 2015; 67:89-97.
2. Matunović R, Stojanović A, Mijailović Z, Rađen G. Importance of determining biomarkers of myocardial necrosis in acute coronary syndrome. Vojnosanit Pregl 2005; 62(Suppl 5): 403-8.
3. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103:1813-18.
4. Rodrigo R, Libuy M, Feliú F, Hasson D. Oxidative stress-related biomarkers in essential hypertension and ischemia-reperfusion myocardial damage. Dis Markers 2013; 35(Suppl 6):773-90.
5. Car S. Serum concentration of uric acid and the outcome of acute coronary syndrome. Medical Faculty, University of Zagreb; 2012; Ph. D. thesis.
6. Silvaa D, Lacerda AP. High-sensitivity C-reactive protein as a biomarker of risk in coronary artery disease. Rev Port Cardiol: 2012; 31(Suppl 11):733-45.
7. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for health care professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107(Suppl 3):499-511.
8. Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N. Distribution of serum C-reactive Protein and Its Association with Atherosclerotic Risk Factors in a Japanese Population. Am J Epidemiol. 2001; 153(Suppl 12):1183-9.
9. Koenig W, Sund M, Frohlich M, Fischer HG, Löwel H, Döring A. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. Augsburg Cohort Study, 1984 to1992. Circulation 1999; 99:237–42.
10. Nieto F, Iribarren C, Gross M, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis. Atherosclerosis 2000; 148(Suppl 1): 131–9.
11. Hayden MR, Tyagi SC. Uric acid: a new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: the urate redox shuttle. Nutr Metab. 2004; 19(Suppl 1):10.
12. Niskanen LK, Laaksonen DE, Nyyssonen K, Alfthan G, Lakka HM, Lakka TA. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med. 2004; 165(Suppl 9): 1546-51.

13. Jalal D, Jablonski K, McFann K, Choncholand M, Seals D. Vascular Endothelial Function Is Not Related to Serum Uric Acid in Healthy Adults. Am J Hypertens. 2012; 25(Suppl 4):407-13.
14. Vidigal F, Rosado L, Rosado GP, Ribeiro C. The high UA levels with increase of CRP and inflammation in the body can contribute to progression of atherosclerotic disease. C. Franceschini Sdo C. Nutr Hosp. 2014; 29(Suppl 4):935-40.
15. Baruah M, Nath C, Chaudhury B, Devi R, Ivvala AS. A study of serum uric acid and C-reactive protein in acute myocardial infarction. IJBMSP 2012; 2(Suppl 1): 21-4.
16. Kushner I, Broder M, Karp D. Control of the acute phase response. Serum C-reactive protein kinetics after acute myocardial infarction. J Clin Invest 1998; 61(Suppl 2): 235–42.
17. Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik A, Navarese EP, Odrowaz-Sypniewska G, Kubica J. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. Mediators Inflamm 2012; 2012:250867.
18. Yildiz HT. High Sensitive C - reactive protein levels in patients with acute coronary syndrome. The Iraqi Postgraduate Medical Journal 2013:643-9.
19. Munir TA, Afzal MN, Ahmed R. C-reactive protein and acute coronary syndrome: correlation with traditional risk factors, diagnostic cardiac biomarkers, and ejection fraction. RMJ. 2009; 34(Suppl 2):154-9.
20. Lagrand WK,Visser CA, Hermens WT, Niessen HWM,Verheught FWA, Wolbink GJ, et al. C-reactive protein as a cardiovascular risk factor; more than an epiphenomenon. Circulation 1999; 96-102.
21. Gur M, Yilmaz R, Demirbag R, Aksoy N. Relation of serum uric acid levels with the presence and severity of angiographic coronary artery disease. Angiology 2008; 59(Suppl 2):166-71.
22. Strazzullo P, Puig JG. Uric acid and oxidative stress: relative impact on cardiovascular risk? Nutr Metab Cardiovasc Dis 2007; 17(Suppl 6):409-14.
23. Sautin YY, Johnson YR. Uric Acid: The oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008; 27(Suppl 6):608–19.
24. Ndrepepa G, Braun S, Haase HU, Schulz S, Ranftl S, Hadamitzky M, Mehilli J, Schömig A, Kastrati A. Prognostic value of uric acid in patients with acute coronary syndromes. Am J Cardiol 2012; 109(Suppl 9):1260-5.

Pozitivna korelacija između mokraćne kiseline i C-reaktivnog proteina u serumu zdravih osoba i pacijenata s akutnim koronarnim sindromom

Emina Spahić[1], Sabaheta Hasić[2], Emina Kiseljaković[2], Halima Resić [3], Mehmed Kulić[4]

[1]Dom zdravlja Zenica, [2]Katedra za medicinsku biohemiju, Medicinski fakultet, Univerzitet u Sarajevu, [3]Klinika za hemodijalizu, [4]Klinika za srce i reumatizam; Klinički centar Univerziteta u Sarajevu; Bosna i Hercegovina

SAŽETAK

Cilj Ispitati serumske vrijednosti i odnos između mokraćne kiseline (MK) i C-reaktivnog proteina (CRP) kod naizgled zdravih osoba i kod pacijenata s akutnim koronarnim sindromom (AKS).

Metode U presječnu studiju bilo je uključeno 116 ispitanika, starosne dobi između 44 i 83 godine, distribuiranih u dvije grupe: 80 ispitanika s AKS-om i to 40 s akutnim infarktom miokarda (AIM) i 40 s nestabilnom anginom pektoris (NAP), te 36 naizgled zdravih ispitanika (kontrolna grupa, KG). Ispitanici s AKS-om bili su hospitalizirani na Klinici za bolesti srca i reumatizam Univerzitetskog kliničkog centra u Sarajevu u periodu od oktobra do decembra 2012. godine. Laboratorijske analize su urađene korištenjem standardnih metoda. Prihvaćeni nivo statističke značajnosti iznosio je $p<0.05$.

Rezultati Vrijednosti CRP-a i MK-a u serumu bile su više u ispitanika s AKS-om u odnosu na KG ($p<0.01$). Vrijednost MK-a u serumu nije bila značajno niža, dok je vrijednost CRP-a bila značajno viša kod pacijenata s AIM-om u poređenju s pacijenatima s nestabilnom anginom pektoris ($p=0.118$; $p=0.001$). Pozitivna, značajna korelacija je utvrđena između serumskih vrijednosti CRP-a i MK-a i kod ispitanika s AKS-om i kod KG-a. ($rho=0.246$; $p=0.028$ i $rho=0.374$; $p=0.027$). Utvrđen je pozitivan odnos CRP-a i MK-a u serumu ispitanika s AIM-om, a negativan u NAP-u, ali nije bio statistički značajan ($p>0.05$).

Zaključak Odnos CRP-a i MG-a u serumu oboljelih od AKS-a ukazuje na povezanost intenziteta oksidativnog stresa s intenzitetom inflamacije zahvaćenog dijela kardiomiocita. Povezanost vrijednosti MK-a i CRP-a u serumu naizgled zdravih ispitanika ukazuje na moguću ulogu MK-a kao markera intenziteta hronične inflamacije niskog stepena te predstavlja potencijal u procjeni rizika za razvoj kardiovaskularnih bolesti.