CRP i polne razlike kod bolesnika sa akutnim infarktom miokarda

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APSTRAKT

Cilj. Inflamacija predstavlja osnovu za nastanak ateroskleroze počevši od endotelne disfunkcije do akutnog koronarnog sindroma. Važan marker inflamacije je C reaktivni protein (CRP). Pokazano je da polni hormoni, estrogen i testosterone modifikuju inflamatorni odgovor ekspresijom inflamatornih citokina u humanim makrofagima.

Metod. Naša retrospektivna studija obuhvata 147 pacijenata (73 pacijenta sa STEMI i 44 pacijenta sa NSTEMI) i 30 zdravih ispitanika (kontrola). Informacije o demografskim karakteristikama i vrednostima CRP-a dobili smo iz kliničkih protokola. Rezultati su obradjeni Student-ovim, t-testom i binarnom logističkom regresijom. Vrednost $p < 0.05$ smatrana je statistički značajnom.

Rezultati. Vrednost CRP-a se razlikuje kod 117 pacijenata koji su imali akutni minfarkt miokarda (73 pacijenta sa STEMI i 44 pacijenta sa NSTEMI) i 30 zdravih ispitanika (kontrola) i statistički je značajna. Takodje se vrednost razlikuje između muškaraca i žena kod STEMI i statistički je značajna ($25,14 \pm 29,23$ nasuprot $13,16 \pm 17,05$, $p = 0,038$). Upotrebom binarne logističke regresije posmatrajući CRP, pol, godine utvrdili smo da na nastanak AMI ima samo CRP uz $OR = 1,952$.

Zaključak. CRP je veći u pacijenata sa akutnim infarktom miokarda, pokazuje razliku među polovima jer su veće vrednosti su kod žena sa STEMI.

Ključne reči: infarkt miokarda; C-reaktivni protein; pol.

CRP and gender differences in patients with acute myocardial infarction

ABSTRACT

Objective. Inflammation appears to be pivotal in all phases of atherosclerosis from the endothelial dysfunction to acute coronary syndromes. An important marker of inflammation is C-reactive protein (CRP). The sex hormones estrogen and testosterone have been shown to modify the inflammatory response by influencing cytokine expression in human macrophage cells.

Method. Our retrospective study included 147 patients (73 patients with STEMI, 44 with NSTEMI) and 30 controls. Information about demographic characteristics, CRP values (at admission) we collected using clinical files. All results were carrying out using Student T test and binary logistic regression. P values ≤ 0.05 were considered statistically significant. Results. CRP difference in 117 patients with acute myocardial infarction (73 patients with STEMI and 44 patients with NSTEMI) and 30 healthy individuals (controls) is statistically significant ($p = 0.001$). CRP difference between male and female is statistically significant in patient with STEMI ($25,14 \pm 29,23$ versus $13,16 \pm 17,05$, $p = 0,038$), but not in NSTEMI patients. Observing CRP, gender and age in binary logistic regression, only CRP increases risk for acute myocardial infarction, $OR = 1,952$.

Conclusion. CRP value is higher in patients with acute myocardial infarction and shows gender difference, higher values are in women with STEMI.

Key words: myocardial infarction; C-reactive protein; sex.

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INTRODUCTION

Atherosclerosis is considered as inflammatory disease, and its acute manifestations are associated with more intense expression of blood-borne inflammatory markers and mediators.¹ Initial event is endothelial dysfunction which is characterized primarily by deficiency of nitric oxide and prostacyclins and increased angiotensin II and plasminogen activator inhibitor-1. Mononuclear cells adhere to the endothelium by selectins, cell adhesion molecules, vascular cell adhesion molecule-1 and integrins. Using chemokines and IL-8 these cells proceed to subendothelial space, monocytes differentiate to macrophages, and incorporate lipids becoming foam cells. Smooth muscle cells migrate to intima, proliferate and form a fibrous cap.² During apoptosis and necrosis macrophages release metalloproteinases which cause a rent in the endothelium, also releasing tissue factor which comes in contact with circulating platelets forming thrombus formation which is a base of acute coronary syndrome. Inflammation appears to be pivotal in all phases of atherosclerosis from the endothelial dysfunction, through fatty streak lesion to acute coronary syndromes.³ After being considered as marker of acute inflammation for several decades, recently C reactive protein has been considered as a potential contributor to inflammatory disease including atherosclerosis as well as marker of cardiovascular risk.⁴

C- reactive protein (CRP) is the first acute phase protein described in literature. It is a non-glycosylated protein in humans, a member of the pentraxin family and the gene has been mapped to chromosome 1. Production is predominantly under the control of IL-6.⁵ However, IL-1 and tumor necrosis factor may also contribute to hepatic synthesis and secretion of CRP. CRP has a half-life of 19 hours and this appears to be constant in health and disease.⁶ The classic dogma that CRP is produced exclusively in liver is challenged by recent data on the extrahepatic production of CRP in different cells including atherosclerotic lesions (especially by smooth muscle cells and macrophages), the kidney, neurons, and alveolar macrophages.⁷ The sex hormones, estrogen and testosterone have been shown to modify the inflammatory response by influencing cytokine expression in human macrophage cells.⁸ Many studies showed high levels of CRP in patients with acute coronary syndrome (STEMI, NSTEMI, unstable angina). But in these studies, patients had other risk factors for acute coronary syndrome (adiposity, diabetes mellitus, hypertension, smoking, sleep apnea, inadequate physical activity etc).⁹⁻¹¹ Also high levels of CRP are found to be increased in this group of patients without ACS. Considering these results we decided to exclude these patients and patients with acute and chronic inflammation, trying to indicate that CRP directly influence on presence of acute myocardial infarction (AMI), especially in women.

Aim of our study was to establish is there a statistical difference between CRP value in patients with acute myocardial infarction and healthy individuals, and STEMI versus NSTEMI patients. Is there a gender difference, and its influence on ACS.

PATIENS AND METHODS

Design for our study was made using a previous study which included 60 patients with acute myocardial infarction and 29 patients as controls. In this study lipid levels, troponin T, CK, AST, LDH and CRP (at admission, peak levels at 36-48 hours and follow up levels after 4-6 weeks), gender, BMI, age and blood pressure were analyzed and compared between groups.¹²

Information about demographic characteristics, routine laboratory tests: troponin I and CRP values (at admission) we collected using clinical files in Coronary unit Cardiology department Clinical Centre Kragujevac.

CRP immunoturbidimetric test for the quantitative determination of C reactive protein in human serum and plasma on OLYMPUS analyzers. When a sample is mixed with R1 buffer and R2 latex suspension, CRP react specifically with anti-human CRP antibodies coated on the latex particles to yield insoluble aggregates. The absorbance of these aggregates is proportional to the CRP concentration in the sample.

The VIDAS Troponin I Ultra assay principle combines a one step immunoassay sandwich method with a final fluorescent detection (ELFA). The measurement values of the VIDAS Troponin I ultra kit range from 0,01 to 30 microg/L. The analytical detection limit, defined as the smallest concentration of cardiac Troponin I which is significantly different from the zero concentration with a probability of 95 %, is < 0,01 mcg/L.

Results were carry out using Student T test and binary logistic regression. P values <0.05 was considered as statistically significant.

Our retrospective study included 147 patients divided into three groups: first group were 73 patients with STEMI, second group were 44 patients with NSTEMI and third group were controls (30 patients). Patients with acute myocardial infarction (STEMI/NSTEMI) were hospitalized in Coronary Unit of Cardiology Department Clinical Centre Kragujevac during 2008 (july-october), and the study protocol was approved by the Research Ethics Committee of Clinical Centre Kragujevac. Control group were healthy individuals. The inclusion criteria were a diagnosis of acute MI (AMI) according to the redefined ESC / ACC Committee criteria. Diagnostic Criteria for STE-ACS and NSTEMI-ACS: Patients with ST segment elevation at the J point in 2 or more consecutive leads (with the cut-off point being > 0.2 mV in leads V1, V2, or V3, and > 0.1 mV in the other leads) were defined as having STE-ACS. Patients with ST segment depression, T wave inversion, or no ECG abnormalities were defined as having NSTEMI-ACS. In both groups troponin I value > 0.16 ng/ml.

We excluded patients who had diseases in which is confirmed, in other studies, increased value of CRP: acute and chronic inflammation, metabolic syndrome, hypertension, diabetes mellitus, sleep apnea.

RESULTS

The study included 147 patients, 117 (61 male and 56 female) in group with AMI, and 30 controls (15 male, 15 female), aged $65,5 \pm 12,6$. In AMI group 73 (62,4%) patients had STEMI and 44 (37,6%) patients had NSTEMI (Table 1).

Table 1. Patients in study

	No			gender	
				Male	Female
Acute myocardial infarction	117	STEMI	73	36	37
		NSTEMI	44	25	19
Controls	30			15	15

Troponin I value was higher in STEMI patients (3.6 microg/L versus 2.4 mcg/L). (Figure 1) CRP value on admission was significantly higher in the acute myocardial infarction (STEMI/NSTEMI) patients when compared with controls ($20,17 \pm 24,56$ versus $3,43 \pm 3,39$; $p=0.000$) (Figure 2).

Figure 1. Median Troponin I value in STEMI/NSTEMI patients

* Median value 3,6/3,4 microg/L

Figure 2. MCRP value in patients with AMI and controls

* Student T test ; $p=0.000$

On the other hand, CRP difference in acute myocardial infarction between patients with STEMI and NSTEMI is not statistically significant ($19,07 \pm 24,44$ versus $21,99 \pm 24,92$; $p=0.536$) (Figure 3).

Figure 3. CRP value in patients with acute myocardial infarction (STEMI/NSTEMI)

* Student T test, $p=0.536$

When we examined STEMI patients, significantly higher CRP value were in women ($25,14 \pm 29,23$ versus $13,16 \pm 17,05$; $p=0,038$), but we did not found statistically significant difference in NSTEMI patients. ($17,75 \pm 20,06$ versus $25,20 \pm 28,02$; $p=0,332$). (Figure 4.)

Figure 4. CRP/Gender difference in patients with AMI(STEMI/NSTEMI)

* Student T test, STEMI: $p=0,038$, NSTEMI: 0,332

Considering CRP, age, gender as influencing factors for AMI, using binary logistic regression, only CRP increase risk for AMI ($p=0.01$). Odds ratio is 1,952 for CRP. It means, if CRP increases for 1, risk for acute myocardial infarction is doubling. Using binary logistic regression for type of AMI, odds ratio is 1,032 for age. It means, if we add 1 year to age, risk for STEMI/NSTEMI ratio is increasing for 3,2 %.(Table 2.)

Table 2. CRP , gender , age on AMI

Parameter	CRP, gender and age on AMI		CRP, gender and age on type of AMI	
	p	Exp (B)	p	Exp (B)
CRP	0.001	1.952	0.650	0.980
Gender	0.531	0.701	0.146	0.807
Age	0.392	1.018	0.001	1.032

* binar logistic regression, $p=0.01$

DISCUSSION

The pathogenesis of atherosclerosis is influenced by inflammatory mechanism and different plasmatic markers, and its acute manifestation, acute coronary syndrome which consists of acute myocardial infarction (STEMI/NSTEMI) and unstable angina, is also marked with high levels of CRP.¹³⁻¹⁵ Many studies showed that not only CRP, but also other inflammatory cytokines as TNF- α , IL-6, and IL-1 β are present in higher concentration in these patients.^{16,17} CRP is localized in tissue macrophages and monocytes which are present in necrotic core of lesions prone to plaque rupture. Leukocytes derived myeloperoxidases primary hosted in polymorph nuclear cells are also present in human atherosclerotic cells, and CRP stimulates myeloperoxidases (MPO) release providing further proinflammatory effects of CRP.¹⁸ CRP induce matrix myeloperoxidases (MMPs) which induce plaque instability.

Also, it attenuate progenitor endothelial cell survivor, differentiation and function via inhibiting nitric oxide and prostacyclin, promote atherothrombosis and increases plasminogen activator inhibitor -1, cell adhesion, endothelin -1. 4,6. In monocyte -macrophages, CRP induce tissue factor secretion, proinflammatory cytokines release, promotes monocyte chemotaxis and adhesion 6, and promote uptake of oxidized but not native LDL because of unexposed phosphorylcholine epitopes on oxidized low density lipoprotein.^{19,20} In vascular smooth muscle cells it upregulate angiotensin 1 receptor resulting in increased reactive oxygen species and cells proliferation.⁶

Our study showed that CRP values in patients with STEMI and NSTEMI is not statistically different, which is in correlation with other studies,¹² but there is statistically significant difference between patients with acute myocardial infarction and healthy controls, also in correlation with other studies.¹⁵

Nakanishi et al. reported that CRP levels are much higher in Westerners than in Japanese, and in women compared with men.²⁰ In addition, gender differences have been reported to be consistent across all ethnic subgroups even after multivariable adjustment.⁸ Our results showed the same in STEMI, greater values were in female, but this difference is not present in NSTEMI. A study showed that physiological and supraphysiological concentrations of testosterone reduce the expression and secretion of TNF- α and reduce the expression of IL-1 β , but did not affect IL-6 or CRP expression. Estrogen does not modify the expression of TNF- α , IL-6, and IL-1 β . Estrogen cause a variable response in CRP expression that is positively associated with the donor's plasma small dense LDL cholesterol concentration. It means that testosterone may exert anti-inflammatory effects by reducing macrophage TNF- α expression while the effects of estrogen on macrophage CRP expression may depend upon the extracellular lipid environment.¹⁶ Another study showed that CRP is predictive marker in women with AMI.¹⁴

Our study also showed in binary logistic regression, if we observe CRP, gender and age only CRP increase a risk for acute myocardial infarction ($p = 0.001$). If CRP value increases for 1, risk for myocardial infarction is doubling. On the other hand, if age increase for 1 year, risk for STEMI versus NSTEMI increase for 3.2%, also shown in study of Corrado and colleagues.²¹

CRP levels is increased in patients with acute coronary syndrome, especially in women with STEMI, and now he should be used not only as a marker of inflammation but also marker of myocardial ischaemia. CRP is a risk factor for acute myocardial infarction compared with age and gender.

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