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Factors associated with C-reactive protein at the early stage of acute myocardial infarction in men

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Abstract

Background: *Elevation of C-reactive protein (CRP) is associated with acute coronary events. CRP is related to cardiovascular risk factors and adipokines. The aim of the study was to reveal the factors associated with elevated CRP levels in patients with ST-segment elevation acute myocardial infarction (STEMI). As there are sex-related differences in plasma levels of CRP and adipokines, our study was designed for males.*

Methods: *Seventy men admitted within the initial 6 hours of STEMI were categorized into 4 groups according to the quartile of CRP. Clinical data and laboratory measurements were analyzed.*

Results: *Anthropometric measurements, glucose at admission, resistin, and leptin were significantly higher, and adiponectin lower with the increase of CRP quartile. A significant positive correlation between CRP and body mass index, waist circumference, glucose at admission, resistin, and leptin and a negative relation of CRP to HDL-cholesterol and adiponectin were observed. In univariate logistic regression analysis, variables associated with a level of CRP above the fourth quartile were history of angina, obesity, diabetes, glucose at admission, resistin, leptin, and adiponectin, and independent predictors were glucose at admission and resistin. To predict the elevated CRP level the optimal cut-off for glucose at admission was 144 mg/dL (sensitivity 84%, specificity 86%) and for resistin was 21.5 ng/mL (sensitivity 79%, specificity 71%).*

Conclusions: *Glucose at admission and resistin are independently associated with elevated levels of CRP in men during the early stage of STEMI.* (Cardiol J 2009; 16: 36–42)

Key words: C-reactive protein, adipokines, myocardial infarction

Introduction

C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP) are recognized as valuable inflammatory biomarkers, but a growing body of evidence supports the active role of CRP in the devolvement of vascular damage. Hyperresponsiveness of the inflammatory system is observed in patients with unstable coronary disease, and this state is further enhanced by CRP [1]. The exact mechanisms that associate CRP with atherosclerosis and its complications are not fully understood. It has been suggested that CRP facilitates a proinflammatory and proatherosclerotic phenotype mostly by the activation of nuclear factor-kappa B signal transduction pathway in peripheral blood monocytes and endothelial cells [2, 3].

Chronic elevation of blood CRP and hs-CRP levels has been observed in individuals with cardiovascular risk factors such as diabetes, smoking,

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obesity, hypertension, and dyslipidemia. White adipose tissue is recognized as an active endocrine and paracrine organ which has an impact on energy balance, glucose and lipid metabolism and is responsible for a low-grade, subclinical inflammatory state [4–6]. There are, however, significant sex-related differences in the location of the adipose tissue, the number of fat cells and fat cell size, plasma levels of CRP and adipokines [7].

The association between adipokines and markers of inflammation have been previously demonstrated in cohorts of healthy subjects, patients with diabetes, and patients with coronary artery disease [5, 8–12]. In the course of acute myocardial infarction, hyperglycemia on admission has been revealed as a new factor associated with increased levels of inflammatory markers [13].

CRP levels within 6 hours of the onset of myocardial infarction reflect the baseline levels of blood CRP and indicate the vulnerability of coronary lesions that follow the plaque rupture, not being affected by the myocardial necrosis [14, 15]. Moreover, in acute coronary syndromes, CRP is predictive of adverse cardiovascular outcome [16].

The associates of the elevated CRP level in male patients with acute myocardial infarction that might have an impact on the instability of the culprit coronary lesion have not been fully elucidated.

The aim of the study was to reveal the factors most significantly associated with blood levels of CRP in male patients at the early stage of ST-segment elevation acute myocardial infarction (STEMI).

Methods

The detailed information concerning methods is presented in our previously published study in which we focused on the relation between obesity and low grade inflammation in acute myocardial infarction [17].

Study population

Seventy male patients successfully treated with primary percutaneous coronary intervention (TIMI flow grade 3, residual stenosis < 30%) within the initial 6 hours of STEMI, aged ≤ 65 years, were categorized into 4 groups according to the quartile of CRP: group I < 2.04 mg/dL, group II ≥ 2.04 mg/dL and < 3.60 mg/dL, group III ≥ 3.60 mg/dL and < 7.00 mg/dL, group IV ≥ 7.00 mg/dL. Clinical data, body mass index (BMI), waist circumference, CRP, lipid profile, and adipokines — leptin, adiponectin, and resistin were analyzed.

Acute and chronic inflammation or infection, autoimmune diseases, liver, and thyroid and kidney diseases were exclusion criteria. Additional exclusion criteria were applied due to the unreported (in this study) requirements for the acquisition of echocardiographic parameters: atrial fibrillation, atrio-ventricular or bundle branch block, temporary or permanent stimulation, significant valvular heart disease, and technical problems with echocardiographic data acquisition. Only those patients who gave informed consent entered the study.

Anthropometric measurements, clinical definitions, and treatment

Diagnosis of STEMI was based on clinical symptoms, electrocardiographic signs, and elevation of myocardial necrotic markers. All patients received aspirin, and those who underwent stenting were concomitantly treated with an additional antiplatelet agent. Heparin was infused during the procedure. Glycoprotein IIb/IIIa inhibitor was administered in a similar proportion of patients from both groups. The following pharmacological treatment with aspirin, clopidogrel, statins, beta-blockers, inhibitors of angiotensin II, nitrates, and diuretics was similar in both groups. BMI was calculated as body weight divided by height squared (kg/m^2). Weight and height were measured while the subjects were fasting. Waist circumference was measured at the widest diameter between the xiphoid process of the sternum and the iliac crest. Diabetes, hypertension, and dyslipidemia were defined when diagnosed previously or in-hospital.

The study was approved by the Internal Ethics Committee of the Medical University of Łódź, and each patient gave informed consent.

Laboratory measurements and echocardiography

CRP and glucose were determined at admission, as well as fasting lipid profile, resistin, leptin, and adiponectin. Plasma triglycerides (TG) and total cholesterol (TCH) were measured by enzymatic analytical chemistry. HDL-cholesterol (HDL-CH) was precipitated using dextran-sulphate and measured enzymatically. The LDL-cholesterol (LDL-CH) was calculated using the Friedewald equation: LDL-CH = = TCH – (TG/5) – HDL-CH. CRP concentrations were measured with an immunoturbidimetric assay. Fasting blood samples for measurements of adipokines were taken the day after admission and plasma was frozen at –70° until analysis with the quantitative sandwich enzyme immunoassay technique (ELISA) obtained from R&D Systems Inc.

Echocardiographic study was performed on the 2–3rd day after admission. Left ventricular ejection fraction (LVEF) was assessed at 4- and 2-chamber apical views with biplane Simpson's formula to evaluate left ventricular systolic function.

Statistical analysis

Continuous data were expressed as mean ± ± standard derivation (SD). Variables were log--transformed before statistical analysis, if necessary. Differences between groups were compared using one-way analysis of variance (ANOVA), Least Significant Difference method (LSD) was used for the *post-hoc* test. Categorical variables were presented as number and percentage of patients, and comparisons between the analyzed groups were performed with the χ^2 test or Fisher's exact test, as appropriate. The association between CRP level and analyzed parameters (clinical, anthropometric and biochemical) was examined using Pearson's or Spearman's correlation coefficient, as appropriate. The independent predictors of elevated levels of CRP were identified using multivariate logistic regression analysis including variables that were significantly associated with CRP in univariate analysis. The variables included in the univariate logistic regression analysis were: age, history of angina, multivessel disease, smoking, obesity, hypertension, diabetes, glucose at admission, dyslipidemia, resistin, leptin, and adiponectin. The results were expressed as odds ratio (OR) and 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values for hyperglycemia and resistin, which were identified as independent predictors of elevated CRP level in multivariate logistic regression analysis. Results were expressed in terms of the area under the curve (AUC) and 95% CI for this area. Optimal cut-off of the CRP level above the fourth quartile was chosen when the sensitivity and specificity were maximized. A p value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using Statistica software (version 6.0, Statsoft, Tulsa, OK, USA) and MedCalc statistical software (version 7.2.1.0 for Windows; Mariakerke, Belgium).

Results

The clinical characteristics and biochemical parameters of the study group are presented in Table 1. The incidence of obesity, dyslipidemia, diabetes, and history of angina increased in the upper quartiles of CRP. There was no significant difference in mean age, smoking, hypertension, time since the onset of symptoms to admission, localization of myocardial infarction, multivessel disease, and LVEF between the study groups. The assessed anthropometric measurements (BMI and waist circumference), as well as glucose at admission, resistin, and leptin, were significantly higher and adiponectin was significantly lower with the increase of CRP quartile.

A positive correlation between CRP and BMI ($r = 0.44$, $p < 0.001$), waist circumference ($r = 0.41$, $p < 0.0001$), glucose at admission ($r = 0.29$, $p < 0.05$), resistin ($r = 0.41$, $p < 0.0001$), and leptin ($r = 0.43$, $p < 0.001$) and a negative correlation between CRP and HDL-CH ($r = –0.23$, $p < 0.05$) and between CRP and adiponectin ($r = –0.50$, $p < 0.0001$) was observed (Table 2).

As revealed by univariate logistic regression analysis, predictors of elevated CRP were: history of angina, obesity, diabetes, glucose at admission, resistin, leptin, and adiponectin. In the multivariate model independent variables associated with levels of CRP above the fourth quartile were: glucose at admission (OR = 1.07; 95% CI 1.03–1.11; $p = 0.0003$) and resistin (OR = 1.52; 95% CI 1.09––2.11; $p = 0.0122$) (Table 3).

Figure 1 shows the area under the ROC curves for glucose at admission and resistin, as predictors of elevated CRP level (AUC 0.92, 95% CI 0.83–0.97; AUC 0.76, 95% CI 0.65–0.86, respectively). The optimal cut-off for glucose at admission was 144 mg/dL (sensitivity 84% and specificity 86%) (Fig. 1A) and 21.5 ng/mL for resistin (sensitivity 79% and specificity 71%) (Fig. 1B).

Discussion

The principal finding of our study was the demonstration that at the early stage of STEMI, admission hyperglycemia and resistin are independently related to the elevated CRP level.

Acute hyperglycemia is a phenomenon commonly seen in patients with acute myocardial infarction even when they have never been previously diagnosed with diabetes [18]. In these patients admission hyperglycemia was related to CRP and other markers of the inflammatory immune process [13], and it was recognized as a factor negatively affecting outcome [19]. Close interrelation between glucose metabolism and inflammation has been shown in several studies. Chronic inflammation is involved in an early process in the pathogenesis of diabetes [20], and, conversely, high levels of blood glucose, even in levels within the normal range, promote

Table 1. Baseline characteristics of the study groups.

	Group I (n = 17) I quartile < 2.04	Group II (n = 18) II quartile ≥ 2.04 and < 3.60	Group III (n = 16) II quartile ≥ 3.60 and < 7.00	Group IV (n = 19) IV quartile ≥ 7.00	p	
Age (years)	53.71 ± 5.55	53.83 ± 6.83	55.06 ± 5.66	52.00 ± 8.67	NS	
Smoking	8 (47%)	13 (72%)	12 (75%)	15 (79%)	NS	
Body mass index [kg/m^2]	25.95 ± 3.68	27.79 ± 3.72	28.43 ± 5.00	31.01 ± 3.88	< 0.01	IV *vs.* I — p < 0.0001 IV *vs.* II — p < 0.05
Obesity	5 (29%)	9 (50%)	8 (50%)	15 (79%)	< 0.05	IV *vs.* I — p < 0.01
Waist circumference [cm]	94.53 ± 11.51	101.00 ± 11.15	97.88 ± 16.74	109.74 ± 10.25	< 0.01	IV *vs.* I — p < 0.0001 IV *vs.* II — p < 0.05 IV *vs.* III — p < 0.01
Hypertension	8 (47%)	7 (39%)	11 (69%)	12 (63%)	NS	
Diabetes mellitus	2 (12%)	1 (5%)	6 (37%)	8 (42%)	< 0.05	IV *vs.* II — p < 0.05 III *vs.* II — p < 0.05
Glucose at admission [mg/dL]	109.18 ± 16.76	115.56 ± 20.25	132.44 ± 29.82	194.58 ± 71.86	< 0.01	IV *vs.* I — p < 0.0001 IV *vs.* II — p < 0.0001 IV *vs.* III — p < 0.0001
Total cholesterol [mg/dL]	199.53 ± 49.18	227.89 ± 31.33	227.50 ± 42.81	217.58 ± 55.59	NS	
HDL-cholesterol [mg/dL]	49.18 ± 11.95	51.17 ± 11.80	48.06 ± 10.69	43.42 ± 13.50	NS	
LDL-cholesterol [mg/dL]	125.04 ± 33.08	145.70 ± 27.54	147.11 ± 43.64	142.78 ± 63.09	NS	
Triglycerides [mg/dL]	126.59 ± 38.29	155.11 ± 59.48	161.63 ± 52.30	156.89 ± 63.67	NS	
Dyslipidemia	9 (53%)	15 (83%)	15 (94%)	16 (84%)	< 0.05	III *vs.* I — p < 0.05
Resistin [mg/dL]	17.56 ± 8.64	22.92 ± 12.35	17.81 ± 6.96	31.71 ± 16.45	< 0.01	IV *vs.* I — p < 0.0001 IV *vs.* II — p < 0.05 IV *vs.* III — p < 0.01
Leptin	21.31 ± 20.14	29.30 ± 18.11	34.82 ± 25.25	42.21 ± 20.20	< 0.05	IV *vs.* I — p < 0.01
Adiponectin	11.02 ± 6.47	9.46 ± 7.16	7.70 ± 3.76	5.90 ± 5.14	< 0.05	IV *vs.* I — p < 0.001 IV *vs.* II — p < 0.01
History of angina	2 (12%)	5 (28%)	8 (50%)	12 (63%)	< 0.01	IV *vs.* I — p < 0.01 III *vs.* I — p < 0.05
Time to admission [h]	3.47 ± 1.62	3.61 ± 1.75	4.00 ± 1.32	3.05 ± 1.22	NS	
Anterior myocardial infarction	4 (23%)	6 (33%)	9 (56%)	8 (42%)	NS	
Multivessel disease	4 (23%)	6 (33%)	8 (50%)	11 (58%)	NS	
Ejection fraction (%)	58.65 ± 7.04	59.56 ± 7.56	54.63 ± 10.98	55.84 ± 9.96	NS	

Table 2. Correlation between C-reactive protein and analyzed parameters.

	C-reactive protein	
	r	p
Age (years)	0.16	NS
Body mass index	0.44	< 0.001
Waist circumference	0.41	< 0.0001
Glucose at admission	0.29	< 0.05
Total cholesterol	0.07	NS
HDL-cholesterol	–0.23	< 0.05
LDL-cholesterol	0.14	NS
Triglycerides	0.22	NS
Resistin	0.41	< 0.0001
Leptin	0.43	< 0.001
Adiponectin	–0.50	< 0.0001
Ejection fraction	–0.14	NS

inflammation in the vascular cells [21–23]. A possible pro-inflammatory mechanism of action of hypoglycemia is the induction of cytokine secretion by monocytes and adipocytes [24]. Interesting observations from the study of Schillinger et al. [25] show that inflammation is expressed by elevated hs-CRP and hyperglycemia is expressed by elevated glycosylated hemoglobin A_{1c}, which jointly contribute to the cardiovascular risk of patients with advanced atherosclerosis. The present study confirms the association between diabetes and inflammation although their independent relation was not confirmed. Aggarwal et al. [26], in a study group including more than 80% of patients with acute coronary syndrome, revealed that concentrations of CRP in patients with diabetes were more than twice as high as in the rest of the study group, and diabetes was an independent predictor of elevated CRP concentrations.

Although the potential role of resistin as an independent cardiovascular risk factor has not been confirmed [27, 28], it has been shown that this molecule may induce endothelial dysfunction, and upregulate adhesion molecules and chemokines [29]. In contrast to rodents, in which resistin is derived almost exclusively from fat tissue, in humans peripheral blood mononuclear cells seem to be a major source of this molecule [30]. Our study, in agreement with recent data, showed that resistin correlates with inflammatory markers [9, 10] and suggest that resistin is involved in the generalized inflammatory process.

We have shown that leptin and adiponectin are other adipokines which significantly reveal blood levels of CRP, but they are not independent predictors of elevated CRP level. In previously published reports CRP was associated with leptin in healthy subjects [11], but this relation was not confirmed by Yan et al. [31] in patients with acute myocardial infarction and coronary atherosclerosis. Adiponectin, which is downregulated in obesity, is

Table 3. Univariate and final model of multivariate logistic regression analysis for the fourth quartile of blood C-reactive protein level.

	Odds ratio	–95% confidence interval	+95% confidence interval	p
Univariate logistic regression analysis				
Age (years)	1.0417	0.9601	1.1303	0.3263
History of angina	4.1143	1.3561	12.4823	0.0125
Multivessel disease	2.5218	0.8591	7.3979	0.0919
Smoking	2.0455	0.5898	7.0932	0.2593
Obesity	4.9432	1.4386	16.9853	0.0112
Hypertension	1.6484	0.5588	4.8627	0.3652
Diabetes mellitus	3.3131	1.0367	10.5886	0.0433
Glucose at admission	1.0632	1.0321	1.0952	0.0001
Dyslipidemia	1.6410	0.4077	6.6055	0.4857
Resistin	1.0852	1.0310	1.1422	0.0018
Adiponectin	0.8278	0.6952	0.9856	0.0338
Leptin	1.0293	1.0041	1.0551	0.0223
The final model of multivariate logistic regression analysis				
Glucose at admission	1.0728	1.0328	1.1143	0.0003
Resistin	1.5219	1.0961	2.1139	0.0122

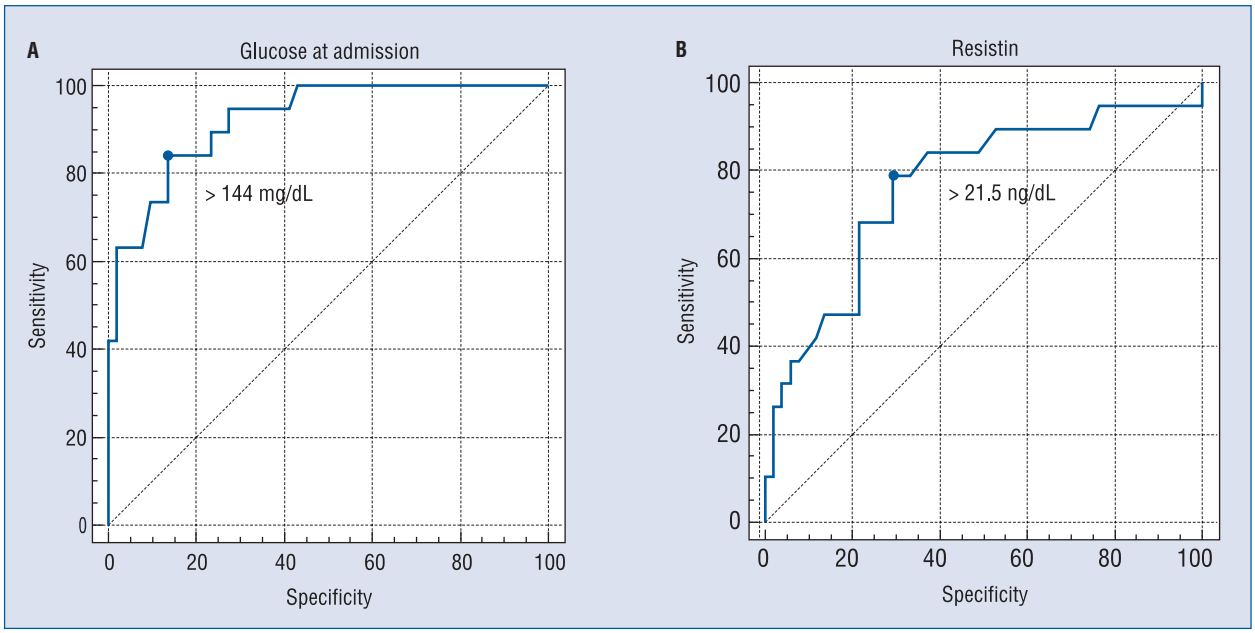

Figure 1. Receiver operated curve for glucose at admission (**A**) and resistin (**B**) for prediction of elevated C-reactive protein level.

an adipokine which is considered to be a protective cardiovascular factor [32–34]. Several published reports have demonstrated that there is an inverse relationship between plasma adiponectin levels and CRP [12, 35], and this observation was confirmed in our group of patients. The association of adipokines and measures of obesity (BMI and waist circumference as shown in the present study) supports the idea that excess body fat results in enhanced systemic inflammation [6, 36].

In the present study, a higher incidence of diabetes, dyslipidemia, and obesity and the trend of a higher incidence of smoking in the upper quartiles of CRP were observed. Values of the measures of obesity were significantly higher and blood levels of HDL-CH lower in the first quartile of CRP than in the fourth quartile. These results show that clustering of risk factors, mostly in a configuration known as metabolic syndrome, is another important low-grade inflammatory state associated with atherosclerosis and its clinical consequences [35, 36].

Limitations of the study

Our study was designed for males, so the results can not be generalized for the female population.

Unfortunately we did not measure glycosylated hemoglobin A_{1c}, which is an indicator of long-term glycemic control and is related to systemic low-grade inflammation. Such information could give further insight into the impact of glucose metabolism on the pro-inflammatory action in acute coronary syndrome.

More precise history of smoking, including the number of cigarettes smoked per day and period of active smoking might have shown the previously revealed [37] significant association between this factor and CRP levels.

Conclusions

Glucose at admission and resistin are independently associated with elevated blood levels of CRP in patients at the early stage of ST-segment elevation acute myocardial infarction.

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