Relation of C-reactive protein to obesity, adipose tissue hormones and cardiovascular risk factors in men treated with early percutaneous intervention in course of acute myocardial infarction

Katarzyna Piestrzeniewicz [1], Katarzyna Łuczak [1], Jan Komorowski [2], Joanna Jankiewicz-Wika [2] & Jan Henryk Goch [1]

1. 1st Department of Cardiology, Medical University of Łódź, Poland.
2. Department of Endocrinology, Medical University of Łódź, Poland.

Correspondence to: Katarzyna Piestrzeniewicz, MD., PhD.
1st Department of Cardiology and Cardiosurgery,
Medical University of Lodz,
1/3, Sterling St., 91-425 Lodz, Poland
PHONE: +48 42 636 44 71
FAX: +48 42 637 44 71
EMAIL: kpiestrzeniewicz@gazeta.pl

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Abstract

Adipose tissue appears to be a key regulator of CRP levels. C-reactive protein (CRP), a marker of systemic inflammation, predicts the occurrence of diabetes, the metabolic syndrome and atherosclerotic diseases. Adipokines, the proteins produced by adipocytes are additional factors thought to be involved in the chronic, subclinical inflammatory state of adiposity.

AIM: The aim of the study was to assess the impact of obesity on the blood CRP levels and the relation of CRP to coronary risk factors and adipokines in men with acute myocardial infarction (AMI).

METHODS: The study was performed in 37 obese (BMI≥30) and 33 lean patients (BMI<25) with first AMI treated with percutaneous coronary intervention within the initial 6 hours of AMI. Clinical data, anthropometric measurements, biochemical parameters and blood adipokines concentration were analyzed.

RESULTS: Values of the following parameters were significantly higher in obese than in lean patients: CRP, fasting glucose, glucose at admission, leptin and resistin, whereas HDL-cholesterol and adiponectin levels were lower. In univariate regression analysis CRP was related to obesity, HDL-cholesterol, fasting glucose, glucose at admission and adipokines but only glucose at admission and resistin were the independent positive factors and adiponectin an independent negative factor associated with CRP levels (R^2= 51.1%).

CONCLUSIONS: In the early stage of AMI inflammation is more pronounced in obese than in lean patients. The pleiotropic association between CRP and obesity, adipokines and cardiovascular risk factors might prove it to be an important link between inflammatory reaction and atherogenesis in which adipose tissue hormones are involved.

ORIGINAL ARTICLE

Abbreviations

CRP - C-reactive protein,
TCH - Total cholesterol
TG - Triglycerides
HDL-CH - High density lipoprotein-cholesterol
LDL-CH - Low density lipoprotein-cholesterol
AMI - Acute myocardial infarction
BMI - Body mass index
SD - Standard deviation

INTRODUCTION

Previous studies have established a fundamental role of inflammation in mediating all stages of atherosclerosis [24] and determined low-grade inflammation as a factor involved in the pathogenesis of hypertension and type 2 diabetes relatively early in life [16,41]. It has also become apparent that obesity is a low-grade, subclinical inflammatory state, as indicated by leukocytosis, elevated levels of proinflamatory cytokines and acute phase reactants. The significant correlation between inflammatory proteins and measures of obesity further confirms that notion [3,7,11,12,15,19,26,38,46]. Low-grade inflammation was determined as a risk factor involved in the pathogenesis of obesity-related cardiovascular risk factors such as hypertension and type 2 diabetes relatively early in life. C-reactive protein (CRP) is synthesized by the liver, largely under the regulation of the proinflammatory cytokines, primarily interleukin-6 [23]. Several cytokines produced by fat cells may contribute to the hepatic synthesis of CRP. Furthermore, adipose tissue itself expresses CRP and contributes to obesity associated increased CRP levels [32]. It has been shown in numerous studies that elevated CRP blood level is associated with smoking, high blood pressure, dyslipidemia, fasting glucose [3,5,37], indicating that CRP is involved in the interrelation of these factors in promoting atherosclerosis. Chronic elevation of blood CRP levels, even within high normal levels, are strongly associated with coronary artery disease [35]. Adipose tissue is also a source of leptin, adiponectin and resistin – hormone-like peptides called adipokines which have an impact on metabolism, inflammatory process and other bioactivities [27]. Many investigators demonstrate that adipokines are associated with inflammation, endothelial dysfunction and atherogenic process [8,33,46] and correlate with proinflammatory cytokines – leptin and resistin positively and adiponectin negatively [12,21,26,32,38,44]. Recent study of Shiraishi [40] revealed that obesity is significantly associated with AMI, independently of the classic coronary risk factors. It could be suggested that a higher degree of inflammation in obese than in lean patients is one of the possible factors involved in the deleterious effect of obesity, and the role of adipose tissue hormones in this phenomenon is anticipated.

The aim of the study was to assess the impact of obesity on the blood CRP levels and the relations of CRP to traditional risk factors and adipokines in men with acute myocardial infarction (AMI).

MATERIAL AND METHODS

Study population

From the cohort of patients with first AMI, successfully treated with primary percutaneous coronary intervention (TIMI flow grade 3, residual stenosis <30%), 37 obese men aged ≤65 years, who admitted being obese for at least 5 years and 33 lean men were selected for the study. Patients were designated as obese at body mass index (BMI)≥30 kg/m^2 and lean at BMI<25 kg/m^2. Acute and chronic inflammation or infection, autoimmune diseases, liver diseases were considered as exclusion. Additional exclusion criteria were applied due to the unreported in this study requirements for acquisition of echocardiographic parameters: atrial fibrillation, atrio-ventricular or bundle branch block, temporary or permanent stimulation, significant valvular heart disease, technical problems with echocardiographic data acquisition. Only the patients who gave an informed consent entered the study.

Anthropometric measurements, clinical definitions and treatment

Diagnosis of AMI was based on the 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, β-blockers, inhibitors of angiotensin II, nitrates and diuretics was similar in both groups. BMI calculated as the body weight divided by square height (kg/m^2) was used as a marker of obesity. 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. Systolic and diastolic blood pressure was measured before blood sampling.

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

Laboratory measurements and echocardiography

Along with several analyses performed from the samples of blood taken at the admission to the hospital, CRP, glucose on admission and uric acid were assessed. Fasting glucose, lipid profile, and resistin, leptin and adiponectin was determined from the blood drawn on the following day. 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. Plasma glucose concentrations were measured with the oxidize method, uric acid with the colorimetric method and CRP concentrations with an immunotubidymetric assay. Fasting blood samples for measurements of adipokines were taken on the next day after admission and plasma was frozen at –70 °C until analysis with a sandwich enzyme-linked immunosorbent assay (ELISA) in case of leptin and adiponectin or radioimmunoassay in case of resistin. Echocardiographic study was performed on the 2–3rd day after admission. LV ejection fraction (EF) was assessed at 4- and 2-chamber apical views with biplane Simpson's formula to evaluate LV systolic function.

Statistical analysis:

Descriptive statistics are expressed as mean ± standard deviation (SD). Variables were log-transformed before statistical analysis if necessary. Comparisons between the two groups were performed using the two-tailed, nonpaired Student's t-test or Mann-Whitney test, as appropriate. Categorical variables are presented as number and percentage of patients and comparisons between analyzed groups were analyzed with the χ^2 test. Univariate and multivariate stepwise regression analysis was performed to identify independent factor affecting CRP and estimate the final predictors of CRP variability. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Clinical, anthropometric and biochemical characteristics of the obese and lean groups are showed in Table 1. There was no significant difference in mean age, the occurrence of hypertension, type 2 of diabetes, smoking and hypercholesterolemia between groups. Treatment with aspirin and statins prior to AMI, time since the onset of pain to admission, and proportion of patients with anterior AMI was similar in both groups. The assessed anthropometric measurements (BMI and waist circumference) were significantly higher in obese patients. In obese patients, systolic and diastolic blood pressure, and values of the following parameters were significantly higher than in lean patients: glucose at admission, fasting glucose, leptin and resistin, whereas adiponectin was lower (Table 2). There was significantly more patients with HDL-CH<40mg/dl in obese compared with lean subjects. Obese patients had higher CRP levels than lean subjects (8.10 ± 7.46 vs 4.45 ± 5.20, p<0.01) (figure 1). As revealed by univariate stepwise regression analysis, in the whole study group BMI, waist circumference, fasting glucose, glucose on admission, leptin and resistin appeared to be positive factors and adiponectin and HDL-CH to be negative factors affecting CRP (Table 2). In multivariate linear regression analysis resistin and glucose at admission were the only independent positive factors and adiponectin an independent negative factor associated with CRP levels (R^2= 51.1%).

Table 1. Clinical and biochemical characteristics of the study groups.

	Obese n=37	Lean n=33	p-value
Age	53.76 ± 7.39	53.39 ± 6.21	ns
Time since the onset of symptoms to admission (h)	3.46 ± 1.48	3.58 ± 1.54	ns
Anterior myocardial infarction *	13 (35%)	14 (42%)	ns
Ejection fraction	58.16 ± 9.00	56.12 ± 9.10	ns
Body mass index (kg/m²)	32.19 ± 2.02	24.07 ± 1.08	<0.0001
Waist circumference (cm)	111.78 ± 7.76	89.09 ± 6.84	<0.0001
Smoking *	23 (62%)	25 (76%)	ns
Hypertension *	23 (62%)	15 (45%)	ns
Systolic blood pressure (mmHg)	124.05 ± 9.63	118.79 ± 11.59	<0.05
Diastolic blood pressure (mmHg)	75.68 ± 6.25	72.12 ± 7.18	<0.05
Diabetes mellitus*	10 (27%)	7 (21%)	ns
Glucose at admission (mg/dl)	152.08 ± 65.77	125.00 ± 32.42	<0.05
Fasting glucose (mg/dl)	110.00 ± 14.01	94.70 ± 10.88	<0.0001
Total cholesterol (mg/dl)	224.24 ± 45.55	211.24 ± 40.43	ns
HDL-cholesterol (mg/dl)	45.49 ± 11.54	50.55 ± 12.50	ns
LDL-cholesterol (mg/dl)	147.01 ± 44.22	132.59 ± 43.99	ns
Triglycerides (mg/dl)	158.73 ± 56.57	140.55 ± 52.88	ns
Total cholesterol >200mg/dl*	25 (68%)	19 (58%)	ns
HDL-cholesterol <40mg/dl*	14 (38%)	5 (15%)	<0.05
LDL-cholesterol >100mg/dl*	33 (90%)	27 (82%)	ns
Triglycerides >150mg/dl*	22 (60%)	13 (40%)	ns
Uric acid (mg/dl)	6.05 ± 1.43	5.71 ± 1.57	ns
Leptin (ng/ml)	46.09 ± 19.00	16.46 ± 12.59	<0.0001
Resistin (ng/ml)	28.53 ± 12.36	17.03 ± 11.59	<0.0001
Adiponectin (µg/ml)	6.68 ± 4.07	10.48 ± 7.17	<0.01

* number of patients (%)

Table 2. Univariate and multivariate stepwise regression analysis for CRP.

UNIVARIATE REGRESSION ANALYSIS				
	RR	**–95%CI**	**+95%CI**	**p-value**
Age	–0.1751	–0.4094	0.0592	0.1404
Body mass index	**0.5358**	**0.1907**	**0.8808**	**0.0028**
Waist circumference	**0.1874**	**0.0765**	**0.2983**	**0.0012**
Systolic blood pressure	0.0188	–0.1306	0.1682	0.8027
Diastolic blood pressure	0.0027	–0.2326	0.2380	0.9817
Glucose at admission	**0.0748**	**0.0509**	**0.0987**	**0.0001**
Fasting glucose	**0.2123**	**0.1148**	**0.3098**	**0.0001**
Total cholesterol	–0.0083	–0.0457	0.0290	0.6574
HDL-Cholesterol	**–0.1509**	**–0.2789**	**–0.0229**	**0.0215**
LDL-Cholesterol	–0.0044	–0.0409	0.0322	0.8128
Triglycerides	0.0251	–0.0037	0.0538	0.0863
Uric acid	0.9898	–0.0693	2.0489	0.0665
Adiponectin	**–0.4174**	**–0.6676**	**–0.1671**	**0.0014**
Leptin	**0.0850**	**0.0142**	**0.1558**	**0.0194**
Resistin	**0.2485**	**0.1418**	**0.3551**	**0.0001**
MULTIVARIATE STEPWISE REGRESSION ANALYSIS				
	RR	**–95%CI**	**+95%CI**	**p-value**
Adiponectin	–0.2478	–0.4456	–0.0501	0.0148
Resistin	0.1596	0.0677	0.2516	0.0009
Glucose at admission	0.0560	0.0331	0.0789	0.0001
R^2 = 51.1%				

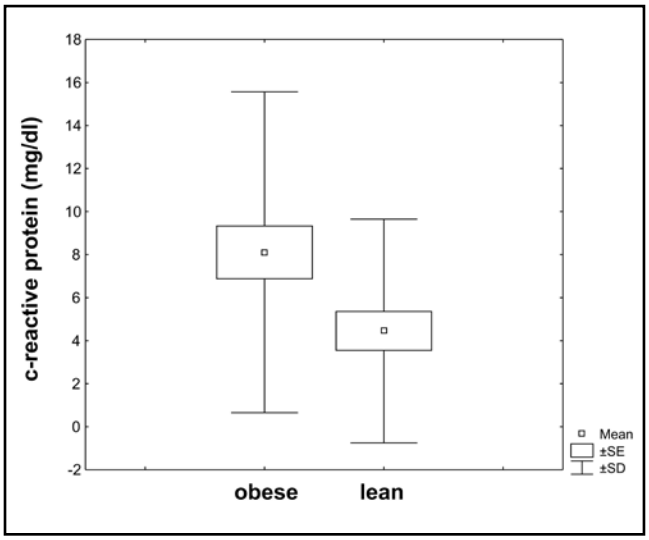

Figure 1. The mean value of blood CRP in obese and lean patients

DISCUSSION

The association of CRP with the measurements of obesity has been widely documented. In the present study we have confirmed this observation and according to Festa *et al.* [14] BMI was not an independent predictor of CRP level in our mail population. We have shown a relation between CRP and coronary risk factors – HDL-CH and fasting glucose, previously observed in subjects in stable conditions [3,5,11]. The association of CRP with TG revealed by other authors [7,12,37,46] was not confirmed in our group of patients and in the study of Matsushita *et al.* [26]. In agreement with the majority of authors we have shown no relation between CRP and T-CH [11,12,19,37,46] and LDL-CH [11,12,19,46]. Diverse opinions concern the association of CRP with systolic and diastolic function [11,12,19,26,37,38,46] and in our group of patients no such relation was observed. Another interesting observation, previously noted by Marfella *et al.* [25] was an independent relation of CRP to glucose at admission – a recently diagnosed factor negatively affecting outcome in patients with AMI [10]. Hyperglycemia during early hours of AMI is a phenomenon commonly seen in patients even when they have been never previously diagnosed with diabetes [31]. Relation of acute hyperglycemia to CRP and other markers of inflammatory immune process has been suggested as a likely mechanism resulting in the poor outcome in patients with AMI and "stress hyperglycemia" [25]. The principal finding of our study was the demonstration of the relations between CRP and adipokines, which bioactivities and proinflamatory actions have been extensively studied for the last decades. We have shown almost 3 times higher leptin levels in obese than in lean patients and a correlation between CRP and leptin has been revealed, although leptin was not an independent predictor of CRP. These results seem to indicate that leptin is in a larger extend a marker of obesity than of inflammation. In previous studies CRP was independently associated with leptin in healthy subjects [19,38], but not in patients with AMI and coronary atherosclerosis [47]. It is interesting that leptin in the physiological range may play a protective role against cardiovascular risk whereas elevated plasma leptin concentration may act as a trigger and/or marker for cardiovascular risk, possibly due to the leptin resistance [34]. Moreover it has been suggested that leptin may be involved in the acute response to stress and that in patients with AMI leptin is an acute-phase reactant, facilitating metabolic adaptation to increased demands during stress [29]. Leptin enhances sympathetic nervous tone which increases vascular tone and blood pressure but this action is counter-balanced by its direct (the NO-dependent pathway) and indirect peripheral vasorelaxation action [17,20,30]. Leptin may also participate in the improvement of the rheological behavior of erythrocytes and the microcirculation by increasing NO

production [43]. On the contrary CRP inhibits NO synthase [45], so that the endothelial dysfunction related to the increased CRP levels might be partially counteracted by the leptin-induced NO production. Resistin expression in adipose tissue is mostly due to the increased macrophage population infiltrating fat [13], but adipocyte-derived resistin is not negligible as it is secreted from pre-adipocytes and adipocytes independently of the presence of mononuclear blood cells [28]. It has been shown that this molecule may induce endothelial dysfunction, up regulate adhesion molecules, promote smooth muscle cell proliferation [8,9] and is related to local and generalized inflammation [1,21,22,33,44,48]. Our study shows a strong, independent relationship between blood levels of resistin and CRP, revealed previously in cohorts of healthy subjects, patients with diabetes and coronary artery disease [1,48]. This observation confirms previously expressed idea that inflammation is a hyperresistinemic state [22]. Although adipocytes are the most important source of adiponectin – an adipokine considered as a protective cardiovascular factor [6], reduced adiponectin blood levels are observed in obese subjects [2]. It has been suggested that tumor necrosis factor-α, which is increased in the white adipose tissue of obese subjects, might downregulate adiponectin production [18]. On the basis of the inverse association between adiponectin and C-reactive protein in our and previous studies [4,12,26,32,36,39], adiponectin appears to act as an anti-inflammatory molecule. Our study was designed for males to avoid the impact of 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 [5,28]. In a univariate analysis, in agreement with some other authors [12,46] we have shown no impact of age on CRP levels but a positive relation has been revealed in other studies [26,37].

Study limitations

The impact of the medication, especially with aspirin and statins at the pre-AMI treatment and the impact of aspirin administered as a standard treatment before admission to the hospital may obscure the results. CRP is primarily synthesized and secreted in liver 6 hours after an acute inflammatory stimulus [23]. In all patients included in our study the period since the onset of symptoms did not exceed 6 hours, thus CRP remained a marker of chronic inflammation rather than an acute phase reactant without being affected by the effects of myocardial necrosis in course of AMI [42].

CONCLUSIONS

In the early stage of AMI inflammation is more pronounced in obese than in lean patients. The pleiotropic association between CRP and anthropometric measurements, adipokines and cardiovascular risk factors might prove it to be an important link between inflammatory reaction and atherogenesis.

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