ORIGINAL ARTICLE

Serum levels of interleukin-6, interleukin-10 and C-reactive protein in patients with myocardial infarction treated with primary angioplasty during a 6-month follow-up

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KEY WORDS

C-reactive protein, interleukin-6, interleukin-10, myocardial infarction (MI)

ABSTRACT

INTRODUCTION Recent studies indicate that inflammatory and immune factors are involved in the post-infarction cardiac remodeling.

OBJECTIVES We evaluated serum levels of interleukin-6 (IL-6), interleukin-10 (IL-10) and C-reactive protein (CRP) in patients with acute coronary syndrome with ST-segment elevation myocardial infarction (STEMI) in the acute phase of the disease and 6 months later. Moreover we sought to determine the effect of selected clinical parameters on the levels of the inflammatory factors.

PATIENTS AND METHODS The study involved 75 patients with STEMI, aged 36–82 years, treated with primary angioplasty. Blood samples for determination of IL-6, IL-10 and CRP levels were taken on the 3rd and 7th day of hospitalization and after 6 months.

RESULTS In the acute phase of myocardial infarction (MI) the levels of IL-6, IL-10 and CRP, as well as the IL-6/IL-10 and CRP/IL-10 indexes were higher than in the control group. Six months later the CRP level decreased significantly, and the levels of IL-6 and IL-10 and the studied indices normalized. In the acute phase of MI there were positive correlations between the studied factors. The independent predictors of IL-6, IL-10 and CRP levels were body mass index (BMI), troponin I, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and the baseline levels of inflammatory markers.

CONCLUSIONS In the acute phase of MI, inflammatory activation is enhanced with predominant proinflammatory response. In the course of the healing process within 6 months inflammation is suppressed and the balance between pro- and anti-inflammatory activation is restored. The size of MI, BMI, lipid levels and the baseline levels of inflammatory markers influence the levels of inflammatory factors.

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INTRODUCTION During the initial phase of myocardial infarction (MI) in the infarction zone an intensive process of healing, known as remodeling, being a sequence of inflammatory and immunological phenomena leading to the resorption of necrotic tissues and their replacement by a scar is observed.[1] Recent studies show that inflammatory processes also play a role in post-infarction changes in the non-necrotic area, such as an increase in the volume of cardiac chambers and a change in the shape and an increase in muscular mass of the left ventricle (LV), which is known as post-infarction cardiac remodeling.[2] It is assumed that increased and persistent activation of proinflammatory factors, including interleukin-6 (IL-6) and C-reactive protein (CRP), may enhance myocardial injury and contribute to heart failure.[3,4] Moreover, anti-inflammatory factors, particularly interleukin-10 (IL-10), exert protective action by inhibition of excessive activation.[5,6]

TABLE 1 Demographic and clinical characteristics of the analyzed group of patients

Variable	Patients (n = 75)
age [years] ($\bar{x}$ ±SD)	56.94 ±11.38
sex [female/male] n (%)	28 (37)/47 (63)
hypertension n (%)	54 (72)
diabetes n (%)	21 (28)
smoking n (%)	57 (77)
pain-to-reperfusion time [h] ($\bar{x}$ ±SD)	5.8 ±3.94
body mass index [kg/m^2]($\bar{x}$ ±SD)	26.77 ±4.06
localization of infarction [anterior wall/other] n (%)	35 (47)/40 (53)
infarct-related artery [LAD/RCA/Cx] n (%)	36 (48)/33 (45)/6 (7)
single- and multi-vessel disease n (%)	47 (63)/28 (37)
troponin I [ng/ml] ($\bar{x}$ ±SD)	82.53 ±102.83
total cholesterol [mg/dl] ($\bar{x}$ ±SD)	222.13 ±50.37
low-density lipoprotein cholesterol [mg/dl] ($\bar{x}$ ±SD)	146.54 ±45.68
high-density lipoprotein cholesterol [mg/dl] ($\bar{x}$ ±SD)	47.14 ±11.67
triglycerides [mg/dl] ($\bar{x}$ ±SD)	142.39 ±66.63
creatinine [mg/dl] ($\bar{x}$ ±SD)	1.08 ±0.25
glucose [mg/dl] ($\bar{x}$ ±SD)	109.44 ±36.97
acetylsalicylic acid [before hospitalization/during the study] n (%)	11 (14.6)/75 (100)
clopidogrel [before hospitalization/during the study] n (%)	0 (0)/72 (96)
angiotensin-converting enzyme inhibitor [before hospitalization/during the study] n (%)	14 (18)/72 (96)
statin [before hospitalization/during the study] n (%)	2 (2.6)/72 (96)
β-adrenergic receptor blocker [before hospitalization/during the study] n (%)	9 (18)/69 (92)

Abbreviations: Cx – circumflex artery, LAD – left anterior descending artery, n – number of patients, RCA – right coronary artery, SD – standard deviation, $\bar{x}$ – mean value

The aim of the study was to assess serum levels of proinflammatory factors IL-6, CRP, and anti-inflammatory interleukin-10 in the acute phase of MI and 6 months after acute coronary event, and to evaluate the effect of chosen clinical parameters on the level of analyzed inflammatory factors.

PATIENTS AND METHODS

The study involved 75 patients aged 36–82 (mean age 56.94 ±11.38) years, including 28 women and 47 men hospitalized in the Department of Cardiology at the Medical Academy in Wrocław from November 2005 to March 2006 because of the first ST-segment elevation myocardial infarction (STEMI), treated with percutaneous transluminal coronary angioplasty with bare metal stent implantation.

The inclusion criteria were as follows: typical chest pain, the time from pain onset to admission <12 hours, J point ST-segment elevation in at least 2 contiguous leads ≥0.2 mV in V1-V3 or ≥0.1 mV in remaining leads in resting 12-lead electrocardiogram, increased serum troponin I levels, infarct-related artery occlusion (TIMI 0) and normal flow restoration in the infarct-related artery (TIMI 3).

The exclusion criteria were: acute or chronic inflammatory state, autoimmune diseases, cancer, previous MI, previous coronary revascularization or need for revascularization during the study, primary cardiomyopathies, major valvular heart disease, previous stroke, peripheral arterial occlusive disease, renal insufficiency, surgery or severe trauma within the last 6 months.

24 sex- and age-matched asymptomatic patients (mean age 59.35 ±7.97 years), including 10 women (61.30 ±7.13 years) and 14 men (57.40 ±8.65 years), with normal results of basic laboratory tests served as the control group. In these subjects hypertension and overt coronary artery disease were not observed. Their resting electrocardiograms were normal and the results of exercise test were negative.

The study protocol was accepted by the Bioethical Committee of the Medical Academy in Wrocław. Informed consent for participation in the study was obtained from each patient.

Blood was sampled on the 3rd and 7th day of hospitalization and 6 months after the infarction to measure IL-6, IL-10 and CRP levels.

The levels of IL-6 and IL-10 were determined using the immunoenzymatic assay (ELISA) with kits by the Bender MedSystems Company (Wien, Austria). The kits had the following catalogue numbers: IL-6-BMS 213/2CE, IL-10-BMS 215/2. Sensitivity of assayed IL-6 and IL-10 levels was 0.92 pg/ml and 1.5 pg/ml, respectively. Intra- and interassay variability was 3.4 and 5.2% for IL-6 and 3.2% and 5.6% for IL-10.

The level of CRP was determined with the high-sensitivity nephelometry using the CardioPhasehsCRP kit manufactured by the Dade Behring Marburg GmbH Company (Marburg, Germany). Sensitivity of the CRP level was 0.175 mg/l with inter- and intraassay variation coefficient of 3.1–4.4% and 2.5–5.7%, respectively.

Statistical analysis

The obtained results were analyzed with the STATISTICA 5.1. Matching of variable distribution with normal distribution was assessed using the Kolmogorov-Smirnov and Lilliefors tests. Differences in the variables analyzed based on the dependent variable were assessed using the Mann-Whitney U test. Correlation analysis was performed with calculation of the Spearman's rank correlation coefficient. A stepwise multiple regression analysis of chosen parameters was performed. Results were statistically significant if a p was <0.05. Values of $p > 0.1$ – statistically not significant – were marked with the NS abbreviation (not significant).

RESULTS

83 patients with STEMI were initially included in the study. Patients who died during the follow-up were excluded from the study (4 cases) in order to obtain all the planned results. During the 6-month follow-up recurrent angina with subsequent revascularization was observed in 5 participants. Since a change in immune-inflammatory activation as a result of revascularization could not been ruled out, these subjects were excluded from the study.

TABLE 2 Serum levels of IL-6, IL-10, CRP and ratios of IL-6/IL-10 and CRP/IL-10 in the analyzed and the control group

Parameter	Patients (n = 75) ($\bar{x}$ ±SD) time of evaluation			Control group (C) (n = 20) ($\bar{x}$ ±SD)	Level of statistical significance (p)		
	3d	7d	6m		3d/C	7d/C	6m/C
IL-6 (pg/ml)	12.62 ±22.58	4.12 ±4.03	3.5 ±4.68	1.67 ±0.24	p <0.001	p = 0.006	NS
IL-10 (pg/ml)	6.19 ±6.96	4.64 ±2.83	4.13 ±2.41	3.08 ±0.71	p = 0.009	p = 0.008	NS
CRP (mg/l)	29.22 ±36.64	19.76 ±22.88	2.99 ±4.89	0.91 ±0.79	p <0.001	p = 0.002	p = 0.02
IL-6/IL-10	2.97 ±4.10	1.70 ±3.75	0.95 ±1.89	0.56 ±0.12	p <0.001	NS	NS
CRP/IL-10	4.74 ±12.23	4.20 ±9.75	0.75 ±0.88	0.31 ±0.24	p <0.001	p <0.001	NS

Abbreviations: CRP – C-reactive protein, IL-6 – interleukin-6, IL-10 – interleukin-10, 3d – third day, 7d – seventh day, 6m – sixth month, other: see TABLE 1

Finally, 75 patients took part in the study. Their demographic and clinical characteristics are presented in TABLE 1 including the most commonly used cardiac medications prior to hospital stay and during the study.

No significant differences between patients with MI and the control group with respect to age, sex, lipids, creatinine and glucose levels and body mass index (BMI) values were observed.

Levels of inflammatory factors The levels of IL-6, IL-10 and CRP were significantly higher compared to the control group on the 3rd and 7th day of hospitalization in patients with STEMI, with the peak value on the 3rd day of MI. After 6 months IL-6 and IL-10 levels were normalized, and the level of CRP remained increased (TABLE 2). The highest ratio of IL-6 to IL-10 (IL-6/IL-10) and CRP to IL-10 (CRP/IL-10) was observed on the 3rd day of MI, compared to the control group.

In further analyses the IL-6/IL-10 ratio was not different compared to the control group, but the CRP/IL-10 ratio was significantly higher on the 7th day compared to the control group and became normal after 6 months (TABLE 2).

Relations between the analyzed inflammatory factors Significant positive correlations between IL-6 and CRP (r = 0.60, p <0.001) and IL-10 levels (r = 0.39, p <0.001) were observed on the 3rd day of hospitalization. Moreover, there was a significant positive correlation between IL-10 and CRP levels (r = 0.31, p = 0.006). On the 7th day and 6 months after the infarction, a significant positive association between IL-6 and CRP levels (r = 0.28, p = 0.01; r = 0.35; p = 0.001, respectively) was observed.

Factors modifying the level of the analyzed factors of inflammation – single variable analysis

Localization of infarction A significantly higher IL-6 level on the 3rd day (13.63 ±15.95 vs. 11.73 ±27.28 pg/ml; p = 0.04) and a significantly higher CRP level on the 3rd (39.17 ±40.64 vs. 20.51 ±30.68 mg/l; p = 0.001) and the 7th day of MI (27.24 ±25.13 vs. 13.21 ±18.67 mg/l; p <0.001) were observed in patients with anterior infarction compared to patients with other localization of infarction.

Infarction size There was a significant positive correlation between CRP and troponin I levels on the 3rd and 7th day of MI (r = 0.31, r = 0.37 at p ≤0.007, respectively).

Pain-to-reperfusion time There was a significant positive correlation between the IL-10 level and pain-to-reperfusion time on the 3rd day of MI (r = 0.29, p = 0.01).

Advancement of atherosclerotic changes in coronary arteries In the multi-vessel coronary artery disease group compared to the one-vessel coronary artery disease group, there were significant positive correlations between IL-6 (20.09 ±33.11 vs. 8.17 ±11.08 pg/ml; p = 0.01), IL-10 (9.52 ±10.02 vs. 4.04 ±2.20 pg/ml; p = 0.01) and CRP levels (41.81 ±39.05 vs. 21.71 ±33.33 mg/l; p = 0.005) on the 3rd day of MI.

Diabetes A significantly higher IL-6 level on the 3rd day (18.65 ±36.69 vs. 10.27 ±13.57 pg/ml; p = 0.05) and CRP level on the 3rd (43.92 ±41.73 vs. 23.50 ±33.14 mg/l; p = 0.01) and the 7th day of MI (29.89 ±23.29 vs. 15.82 ±21.67 mg/l; p = 0.003) were found in patients with diabetes compared to non-diabetes patients.

Lipid level There was a significant positive correlation between IL-6 and low density lipoprotein cholesterol (LDL-C) levels (r = 0.26, p = 0.02) on the 3rd day of MI, and after 6 months a significant positive correlation with the triglyceride level (r = 0.25, p = 0.02). A significant positive correlation between the IL-10 level and the high-density lipoprotein cholesterol (HDL-C) level (r = 0.41, p <0.001) on the 3rd day of MI was observed. CRP and LDL-C levels after 6 months of observation showed a positive association (r = 0.34. p = 0.002).

Body mass index Significant positive correlations between the CRP level and BMI on the 3rd day of MI (r = 0.29, p = 0.01), and between the IL-6 level and BMI on the 3rd and 7th day of MI and after 6 months were observed (r = 0.41,

TABLE 3 Results of multiple regression analysis of factors having influence on the IL-6, IL-10 and CRP level in the analyzed population of patients with myocardial infarction

	BMI	LDL-C	HDL-C	Troponin I	IL-6 [3d]	IL-10 [3d]	CRP [3d]
IL-6 [3d]	β = 0.61 p <0.001						
IL-10 [3d]			β = 0.31 p <0.001		β = 0.60 p <0.001		
CRP [3d]				β = 0.23 p = 0.007	β = 0.35 p <0.001		
IL-6 [7d]	β = 0.21 p = 0.05				β = 0.35 p = 0.003		
IL-10 [7d]						β = 0.29 p = 0.01	
CRP [7d]				β = 0.18 p = 0.008			β = 0.77 p <0.001
IL-6 [6m]	β = 0.30 p = 0.01						
IL-10 [6m]							
CRP [6m]		β = 0.22 p = 0.03				β = 0.42 p <0.001	

Abbreviations: BMI – body mass index, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, β – regression coefficient, other: see TABLES 1 and 2

p <0.001; r = 0.31, p = 0.006; r = 0.27, p = 0.01, respectively).

Other variables No significant correlations between the level of analyzed indices of inflammatory reaction and patients' age were found. There were no significant differences in the levels of the analyzed inflammatory factors in relation to sex, hypertension and smoking.

Given that neither the level of lipids nor BMI values changed significantly after 6 months of follow-up compared to the baseline analysis, a change in the values of these factors during follow-up was insignificant in assessing levels of the inflammatory factors measured 6 months after MI.

Since the majority of the patients either during hospitalization or follow-up were taking anti-inflammatory agents (statins, in particular), and in the period prior to MI they used these medications only in low doses, the effect of drug administration on the level of inflammatory indices was not assessed.

Factors modifying the level of inflammatory factors – multivariable analysis In the stepwise multiple regression analysis factors which might influence indices of the inflammatory reaction were as follows: age, sex, BMI, pain-to-reperfusion time, diabetes, hypertension, localization of infarction, the degree of stenosis in the coronary arteries, troponin I, lipids and initial levels of inflammatory markers.

It has been shown that BMI, IL-10, HDL-C, and IL-6 were independent predictors of the IL-6 level, as well as troponin I and IL-6 levels predict the CRP level on the 3rd day of MI in the analyzed population (TABLE 3).

On the 7th day of MI the independent predictors of IL-6 level were BMI and the initial IL-6 level, for IL-10 – the initial level of this interleukin, and for CRP – the troponin I level and the initial level of this protein (TABLE 3). While evaluating 6 months after the infarction, independent predictors were BMI for IL-6, as well as IL-10 and LDL-C for CRP (TABLE 3). Statistically significant common interactions of factors on the IL-6 level measured after 6 months of observation were not obtained. Levels of the analyzed systemic inflammatory markers were higher at elevated BMI, troponin I, LDL-C, and HDL-C as well as initial levels of the analyzed inflammatory markers.

DISCUSSION

The obtained results of the cytokines level in the same group of the studied patients with MI were preliminary presented by the authors in the publication, in which the relation of the IL-6, IL-10 and CRP level to left ventricular function was assessed.[7] We decided to perform the more detailed analyses regarding the levels of inflammatory reaction factors given the fact that studies which evaluate the mutual relations between the level of pro- and anti-inflammatory factors and identification of independent predictors, that influence their concentration in patients with MI treated with current methods, are unavailable so far.

The present study suggests that in the acute phase of MI the serum levels of proinflammatory factors, IL-6 and CRP, and an anti-inflammatory IL-10 are increased, but the increased IL-6 and IL-10 level ratio indicates prevailing activation of proinflammatory factors. The observed significant decrease in the level of proinflammatory factors and IL-6/IL-10 ratio during the 6-month follow-up indicates inhibition of inflammatory state and restoration of the disturbed balance

between activation of pro- and anti-inflammatory processes.

Other studies demonstrated that in patients with MI the IL-6 level was significantly higher in the acute phase of MI compared to the control group.[8,9] In some studies on changes in the IL-6 level in the long-term follow-up, but no longer than 1 month, persistently increased serum levels of this interleukin were reported.[10,11] Ziakas et al.[12] showed the normalization of IL-6 level values after 6 months of observation, which is similar to the present study.

Available data show that IL-10 serum levels in patients with recent MI have been evaluated only in the acute phase, and in the majority of studies, as in the current one, increased levels of this interleukin in the first days of MI have been observed.[13] However, in some studies increased IL-10 levels in serum have not been found[14], which could be due to early (first hours of MI) measurement, when most probably a significant secretion of this factor into blood is not observed.

In a number of studies, as in the current one, it has been shown that the CRP level was increased in the acute phase of MI, with a significantly higher value in the first days (1st–3rd) compared to the next days of hospitalization.[9,15] In some studies, in which the CRP level following MI was assessed during longer follow-up, its decrease after 12 weeks was found (according to Gabriel et al.)[9] and the association with the HDL-C level ($r = 0.41$, $p < 0.001$) was observed after 6 months (according to Jahn et al.)[16] compared to the value in the first days of hospitalization, but the level after a few months was still higher compared to the controls. Similar observations were made in the current work. Lack of normalization of the CRP level after a few months following MI probably results from post-infarction cardiac remodeling with the LV dilatation observed in some patients. Moreover, increased CRP values in patients with post-infarction LV enlargement are observed.[17]

The relation between levels of all analyzed factors of inflammatory reaction in the first days of MI supports the argument that acute ischemia causes activation of the inflammatory process with the subsequent increased synthesis of pro- and anti-inflammatory factors. In other studies, in patients with MI there has been a positive correlation between IL-6 and CRP levels.[9,13] This relation is understandable, given the fact that IL-6 is a main stimulator of the production of acute phase proteins such as CRP. However, the relation between IL-10, IL-6 and CRP levels in patients with MI is less documented. Bossowska et al. and Kotajima et al. did not find an association between the levels of these factors.[13,14] However, in the above studies the correlation considered the IL-10 level measured on admission, whereas in the present study – on the 3rd day of hospitalization. It cannot be ruled out that assessment of the dynamic balance between activation of pro- and anti-inflammatory processes takes time and this may have had an influence on the obtained results.

In the current study the following factors appeared to be independent predictors of the level of analyzed markers of inflammatory reaction: MI size, lipid level, BMI and initial levels of analyzed inflammatory parameters. The present study showed that the intensity of immunologic-inflammatory processes was greater in patients with large anterior infarction and the higher troponin I level, and manifest itself with higher IL-6 and CRP levels. Results of other studies are ambiguous. In some studies a relation between IL-6 and CRP levels and the level of markers of myocardial necrosis and localization of the infarction was shown[16], contrary to other studies.[9,11,14] The majority of researchers claim that increased CRP and IL-6 levels in patients with MI does not simply reflect its extension; however, it may be a measure of immune-inflammatory damage to the myocardium. Similarly to the present study, other authors did not find a relation between the extension of the infarction and the IL-10 level.[18]

The studies performed previously have demonstrated a direct proportional association between the IL-10 level on the 3rd day of MI and the pain-to-reperfusion time. Such relation has not been observed for IL-6 and CRP. As shown in experimental studies, reperfusion results in increased serum IL-10 levels[19] and for this reason a longer time of myocardial ischemia with prolonged pain-to-reperfusion time may contribute to enhanced secretion of this interleukin. The source of increased serum levels of inflammatory factors in patients with ischemic heart disease could be both ischemic myocardium and atherosclerotic segments of the coronary arteries. For this reason, attempts to identify a relation between levels of particular inflammatory factors and the magnitude of atherosclerotic lesions in the coronary arteries assessed as a number of significantly stenosed coronary arteries during coronary angiography were made. It was established that in patients with multi-vessel disease the serum level of IL-6, IL-10 and CRP during hospitalization was significantly higher compared to patients with one-vessel disease. Similar results were obtained by other authors.[20,21]

Examinations performed in the course of the present study showed that IL-6 and CRP levels during hospitalization were significantly higher in patients with diabetes compared to the group without diabetes, which was demonstrated in other studies.[22] It is well known that diabetes is characterized by increased inflammatory state. In turn, enhanced activation of pro-inflammatory factors augments oxidative stress and inflammatory processes, which leads to impaired insulin endocytosis in endothelial cells and, in consequence, to insulin resistance.

In the present study a significant, direct proportional relation between IL-6 and CRP levels

and the BMI value was shown. Similar results were obtained by other authors.[14,22] This relation is understandable, as the adipose tissue is an important source of cytokines. In the light of available data, 30–40% of circulating IL-6 in healthy humans are synthesized by the adipocytes, while IL-6 increases CRP synthesis.[23]

The data on relations between the level of analyzed factors of inflammatory reaction and the blood lipid level in patients with MI could not be found. The presented positive correlations between IL-6 and CRP and LDL-C levels can be explained by the pro-inflammatory effect of LDL-C, depending on the activation of macrophage accumulation within atherosclerotic lesions and the stimulation of cytokine production. The relation between IL-6 and triglyceride levels may result from the fact that this interleukin decreases lipoprotein lipase activity, which leads to decreased uptake and, in consequence, to the increased blood triglyceride level.

In addition, the relation between IL-10 and HDL-C levels may result from the observation that cholesterol HDL – bound molecules such as IL-10 have anti-inflammatory features, for example an inhibition of LDL cholesterol oxidation and decreased adhesive molecule expression.

The limitation of the study was a relatively small number of the analyzed patients. The serum level of analyzed inflammatory markers was assessed with the biochemical immunoenzymatic method. Its drawback is the fact that while determining systemic blood levels of these markers, it is unlikely to identify their origin. Besides MI these factors are secreted by the atherosclerotic vessel wall and adipose tissue, which was considered in additional analyses. In the current study the selection of an ideal control group with a normal mean BMI value was difficult. The value was insignificantly increased. However, large population studies show a high frequency of overweight and obesity in the Polish population, which is typical of the whole of Europe[24], and has been reported also in the current study.

In summary, the present study showed that in the acute phase of MI increased activation of pro- and anti-inflammatory factors with dominant proinflammatory processes is observed. In the course of healing within 6 months after the infarction the inflammatory reaction disappears with restoration of the disturbed balance between activation of pro- and anti-inflammatory processes. The size of MI, the lipid level, the BMI value and the initial levels of inflammatory markers affect the level of the factors of inflammatory reaction.

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