ORIGINAL ARTICLE

Value of blood adipose tissue hormones concentration – adiponectin, resistin and leptin in the prediction of major adverse cardiac events (MACE) in 1-year follow-up after primary percutaneous coronary intervention in ST-segment elevation acute myocardial infarction

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Submitted: 2008-05-21 Accepted: 2008-07-02 Published online: 2008-08-30

Key words: **adipokines; major adverse cardiac events; myocardial infarction**

Neuroendocrinol Lett 2008; **29**(4):581–588 **PMID:** 18766137 NEL290408A21

Abstract

OBJECTIVES: The objective of the study was to assess the impact of adipokines on the future major adverse cardiac events (MACE) in patients with acute myocardial infarction.

METHODS: Subjects were 77 men with first, ST-segment elevation acute myocardial infarction undergoing primary percutaneous coronary intervention in whom data were available after one year follow-up. Baseline clinical and angiographic data were collected, blood level of C-reactive protein, uric acid, fasting glucose, lipid profile, adiponectin, resistin and leptin and left ventricular ejection fraction on echocardiography were assessed. MACE was defined as cardiac death, nonfatal myocardial infarction, hospitalization for angina or heart failure.

RESULTS: 12% of patients experienced MACE. As revealed by univariate logistic regression analysis predictors of MACE were diabetes, multivessel disease, ejection fraction, blood C-reactive protein and adiponectin level. In multivariable analysis diabetes (OR=22.19, 95%CI 1.22–402.19; p=0.0360), lower left ventricular ejection fraction (OR=0.78, 95%CI 0.63–0.98; p=0.0298) and lower adiponectin level (OR=0.19, 95%CI 0.04–0.90; p=0.0362) were independent negative predictors of MACE. The optimal value of adiponectin for predicting MACE was 4.23 μg/ml.

CONCLUSION. In male patients with myocardial infarction undergoing primary percutaneous coronary intervention, a baseline blood adiponectin but not resistin or leptin is independently predictive of MACE. The other prognostic factors are diabetes mellitus and left ventricular ejection fraction.

1. BACKGROUND

The ability to predict the adverse outcome in patients with acute coronary syndrome have been studied for the last few years. Several clinical and biochemical parameters have been identified as risk indicators for major cardiovascular events in 6–12 months follow-up after acute myocardial infarction (AMI) [1, 2]. The association of adipose tissue derived peptides – adiponectin, resistin and leptin with glucose and lipid metabolism, insulin resistance, inflammatory process, autoimmune conditions, endothelial function and atherogenesis has recently attracted attention [3, 4]. The value of these adipokines in predicting adverse cardiac events in patients with coronary artery disease and myocardial infarction is still a relevant issue [5–9].

The aim of the study was to assess the impact of the baseline blood adiponectin, resistin and leptin levels on the future major adverse cardiac events (MACE) in patients with first, ST-segment elevation acute myocardial infarction (STEMI).

2. METHODS

2.1. Study population.

From the cohort of patients with the first STEMI, successfully treated with primary percutaneous coronary intervention (PCI), 80 men aged ≤65 years, were initially selected for the study. Acute and chronic inflammation or infection, autoimmune diseases, liver or thyroid diseases and diabetes treated with insulin were considered as exclusion. Additional exclusion criteria were applied due to the requirements of echocardiographic examination performed for the unreported part of this study, concerning the left ventricular systolic and diastolic function. These conditions were: atrial fibrillation, atrio-ventricular or bundle branch block, temporary or permanent stimulation, significant valvular heart disease. In patients with multivessel disease staged PCI of another significant lesion was performed according to the consensual decision of the cardiologist and interventional cardiologist on an individual basis.

Data were available after a one year follow-up in 77 patients via telephone contact, clinical visits and/or hospitalization and were analyzed in two groups: group I – patients with MACE and group II patients without MACE at follow-up.

2.2. Clinical definitions, procedural techniques and pharmacological treatment.

Diagnosis of STEMI was based on the clinical symptoms, electrocardiographic signs, and elevation of myocardial necrotic markers according to the present standards. Angioplasty and stenting procedures were performed using standard techniques, usually through the radial artery approach. Successful PCI was defined as achievement TIMI flow grade 3 and residual stenosis <30%. Multivessel disease was defined as ≥75% stenosis in one or more vessels or their major (≥2.5mm) branches remote from the infarct related artery. 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 at the operator's discretion. The following pharmacological treatment with aspirin, clopidogrel, statins, β-blockers, inhibitors of angiotensin II and diuretics was applied according to the present standards.

Body mass index calculated as the body weight divided by square height (kg/m^2) was used as a marker of obesity. 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.

MACE was defined as cardiac death, confirmed nonfatal acute myocardial infarction, hospitalization for angina or heart failure. Death was classified as cardiac if the cause was related to myocardial infarction, ischemia, arrhythmia or if the death was sudden and unexpected in nature.

2.3. Laboratory measurements and echocardiography

From the samples of blood taken at the admission to the hospital C-reactive protein (CRP) and uric acid were assessed. Fasting glucose, lipid profile, adiponectin, resistin and leptin were 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 oxidase method, uric acid with the colorimetric method and CRP concentrations with an immunoturbidimetric assay. Fasting blood samples for measurements of adipokines were taken on the day after admission and plasma was frozen at -70° until analysis with the quantitative sandwich enzyme immunoassay technique (enzyme-linked immunosorbent assay) obtained from R&D Systems Minneapolis, USA.

An echocardiographic study was performed on the 2–3rd day after admission. Left ventricular ejection fraction (EF) was assessed at 4- and 2-chamber apical views with biplane Simpson's formula.

2.4. Statistical analysis

Descriptive statistics are expressed as mean ± SD and as median (with interquartile ranges). Comparisons between the study groups were performed using the nonparametric U-Whitney-Mann test. Categorical variables are 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 ap-

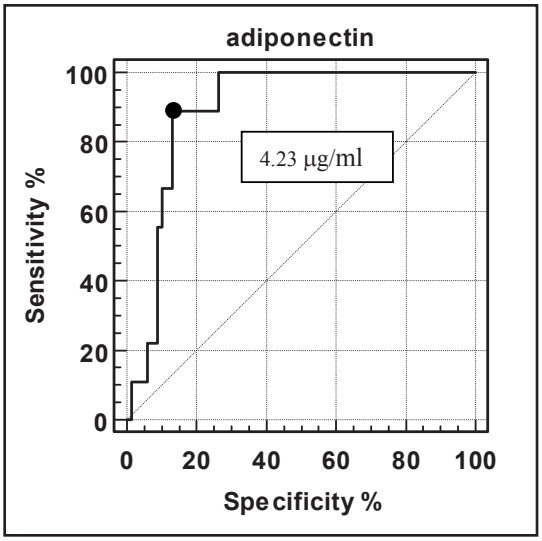

Figure 1. ROC curve for adiponectin in patients with and without MACE during the follow-up period.

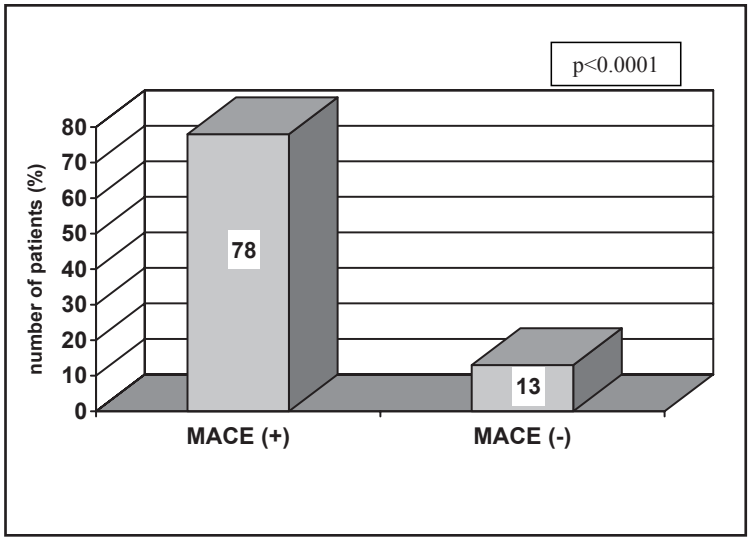

Figure 2. Adiponectin below the cut-off value of 4.23µg/ml in patients with MACE and without MACE.

propriate. The independent predictors of MACE were identified using the multivariate logistic regression analysis including variables that were significantly associated with MACE in univariate analysis. The variables included in the univariate logistic regression analysis were: age, history of angina, smoking, obesity, diabetes mellitus, hypertension, dyslipidemia, time since the onset of symptoms to admission, anterior myocardial infarction, multivessel disease, left ventricular EF and blood levels of CRP, uric acid, creatinine, adiponectin, resistin and leptin. Results were expressed as odds ratio (OR) and 95% confidence intervals (CI). A receiver-operating characteristics (ROC) curve analysis was used to determine the cut-off values for adiponectin which found to be an independent predictor of MACE in multivariate logistic regression analysis. A *P* value less than .05 was considered to be statistically significant. Statistical analysis was performed using Statistica software (version 5.0, Statsoft, Tulsa, OK, USA) and MedCalc statistical software (version 7.2.1.0 for Windows; Mariakerke, Belgium).

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

3. RESULTS

During the 12 months follow-up period, 9 patients (12%) experienced MACE: cardiac death in 2 patients, myocardial infarction in 2 patients, unstable angina in 4 patients, and heart failure in 1 patient.

Baseline clinical characteristics and biochemical parameters of the study groups are presented in Table 1. Age, history of angina, smoking, hypertension, dyslipidemia, obesity, time since the onset of chest pain to admission, and anterior localization of AMI were not significantly different between the study groups. Diabetes and multivessel disease were present significantly more often and left ventricular EF was significantly lower in patients with MACE. There was no significant difference in the invasive and pharmacological treatment between the analyzed groups. Fasting glucose, triglycerides and CRP concentrations were significantly higher whereas HDL-cholesterol and adiponectin were significantly lower in patients with MACE.

As revealed by univariate logistic regression analysis, predictors of MACE were: diabetes mellitus, multivessel disease, left ventricular EF, CRP and blood adiponectin level. Diabetes 20-fold (OR=20.3, 95%CI 3.67–112.10; p=0.0006) and multivessel disease almost 5-fold (OR=4.8, 95%CI 1.09–21.10; p=0.0379) increased the risk of MACE. Increase in CRP by each 1mg/dl increased the risk of MACE by 15% (OR=1.15, 95%CI 1.04–1.27; p=0.0047). Increase in EF by each 1% and adiponectin by each 1µg/ml decreased the risk of MACE by 10% (OR=0.90, 95%CI 0.83–0.97; p=0.0127) and almost 60% (OR=0.41, 95%CI 0.21–0.80; p=0.0088), respectively. The final model of multivariable regression analysis demonstrates that lower adiponectin level is an independent negative predictor of MACE, along with diabetes and lower left ventricular EF (Table 2).

Figure 1 shows the area under the ROC curves for adiponectin for prediction MACE (0.89, 95%CI 0.801–0.951). The optimal values of adiponectin was defined as the concentration with the largest sum of sensitivity plus specificity for each of the curve. The optimal cut-off for adiponectin was 4.23µg/ml; the sensitivity and specificity were 89% and 88%, respectively. Patients with blood adiponectin level ≤4.23 µg/ml were more likely to develop MACE (7 patients) than those with adiponectin >4.23 µg/ml (9 patients) (78% vs 13%, p<0.0001) (Figure 2).

Table 1. Baseline characteristics of the study groups.

	Statistics	MACE (+) n=9	MACE (-) n=68	p
Clinical characteristics				
Age	Mean ± SD Median (25^{th}; 75^{th})	57.00 ± 6.69 57.0 (51.0; 63.0)	53.99 ± 6.77 53.5 (50.0; 59.5)	ns
History of angina	N (%)	5 (55)	26 (38)	ns
Smoking	N (%)	8 (89)	43 (63)	ns
Hypertension	N (%)	7 (78)	34 (50)	ns
Systolic blood pressure (mmHg)	Mean ± SD Median (25^{th}; 75^{th})	120.56 ± 11.30 125.0 (115.0; 130.0)	120.88 ± 11.26 120.0 (115.0; 130.0)	ns
Diastolic blood pressure (mmHg)	Mean ± SD Median (25^{th}; 75^{th})	71.11 ± 5.46 70.0 (70.0; 75.0)	74.49 ± 7.59 75.0 (70.0; 80.0)	ns
Diabetes mellitus	N (%)	7 (78)	10 (15)	<0.0001
Dyslipidemia	N (%)	8 (89)	54 (79)	ns
Body mass index (kg/m^2)	Mean ± SD Median (25^{th}; 75^{th})	28.25 ± 5.16 24.74 (24.30; 33.21)	27.96 ± 4.51 27.60 (24.31; 31.80)	ns
Obesity	N (%)	4 (44)	34 (50)	ns
Waist circumference (cm)	Mean ± SD Median (25^{th}; 75^{th})	105.00 ± 14.15 97.0 (93.0; 111.0)	99.12 ± 14.09 99.0 (88.0; 111.0)	ns
History of myocardial infarction				
Time since the onset of symptoms to admission (h)	Mean ± SD Median (25^{th}; 75^{th})	4.33 ± 2.45 4.0 (3.0; 5.0)	4.46 ± 2.88 4.0 (2.5; 5.5)	ns
Anterior myocardial infarction	N (%)	4 (44)	27 (40)	ns
Multivessel disease	N (%)	6 (67)	20 (29)	<0.05
Stent implantation	N (%)	9 (100)	68 (100)	ns
Abciximab	N (%)	6 (67)	37 (54)	
Left ventricular ejection fraction (%)	Mean ± SD Median (25^{th}; 75^{th})	48.67 ± 9.82 44.0 (42.0; 56.0)	57.47 ± 8.76 58.0 (52.0; 64.0)	<0.05
Biochemical parameters				
Fasting glucose (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	116.11 ± 14.09 122.0 (104.0; 125.0)	99.71 ± 13.12 98.0 (89.0; 106.5)	<0.01
Total cholesterol (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	216.11 ± 68.67 223.0 (187.0; 240.0)	221.47 ± 38.80 218.0 (196.0; 244.0)	ns
LDL-cholesterol (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	139.24 ± 81.68 144.0 (95.6; 171.8)	143.08 ± 36.71 137.6 (114.8; 167.4)	ns
Triglycerides (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	185.44 ± 22.81 186.0 (172.0; 196.0)	141.31 ± 57.90 133.0 (94.0; 183.5)	<0.05
HDL-cholesterol (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	40.00 ± 13.91 42.0 (30.0; 45.0)	50.13 ± 11.94 48.5 (41.5; 56.5)	<0.05
C-reactive protein (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	11.78 ± 7.38 8.0 (6.0; 16.0)	4.96 ± 5.10 3.0 (2.0; 6.0)	<0.001
Uric acid (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	6.56 ± 2.40 6.0 (5.0; 8.0)	5.81 ± 1.22 6.0 (5.0; 7.0)	ns
Creatinine (mg/dl)	Mean ± SD Median (25^{th}; 75^{th})	0.96 ± 0.22 0.95 (0.8; 1.2)	0.95 ± 0.16 0.94 (0.81; 1.05)	ns
Adiponectin (μg/ml)	Mean ± SD Median (25^{th}; 75^{th})	3.97 ± 0.88 3.8 (3.7; 4.1)	9.93 ± 6.39 8.4 (5.8; 11.5)	<0.001
Resistin (ng/ml)	Mean ± SD Median (25^{th}; 75^{th})	27.94 ± 16.47 23.5 (20.5; 27.0)	21.37 ± 11.20 18.7 (12.5; 28.5)	ns
Leptin (ng/ml)	Mean ± SD Median (25^{th}; 75^{th})	45.28 ± 22.86 61.2 (27.7; 63.2)	29.36 ± 21.89 22.2 (11.1; 47.3)	ns
Cardiac medication after myocardial infarction				
Aspirin	N (%)	9 (100)	68 (100)	ns
Clopidogrel*	N (%)	9 (100)	68 (100)	ns
Statins	N (%)	9 (100)	68 (100)	ns
Beta-blockers	N (%)	8 (89)	66 (97)	ns
ACEI**	N (%)	7 (78)	39 (57)	ns
Diuretics	N (%)	5 (55)	20 (29)	ns
Oral hypoglycemic drugs	N (%)	7/7 (100)	10/10 (100)	ns

* at the period of 4 weeks following angioplasty ** ACEI - Angiotensin Converting Enzyme Inhibitor

Table 2. Univariate and the final model logistic regression analysis

Univariate logistic regression analysis for MACE				
	OR	-95%CI	+95%CI	p
Age	1.0751	0.9593	1.2047	0.2129
History of angina	2.0192	0.4965	8.2116	0.3262
Smoking	4.6512	0.5491	39.3956	0.1585
Obesity	0.8000	0.1977	3.2380	0.7544
Diabetes mellitus	***20.3000***	***3.6760***	***112.1032***	***0.0006***
Hypertension	3.5000	0.6777	18.0760	0.1348
Dyslipidemia	2.0741	0.2391	17.9918	0.5081
Time from onset symptoms to admission	0.9841	0.7628	1.2696	0.9018
Anterior myocardial infarction	1.2148	0.2991	4.9346	0.7855
Multivessel disease	***4.8000***	***1.0917***	***21.1040***	***0.0379***
Ejection fraction	***0.9035***	***0.8343***	***0.9785***	***0.0127***
C-reactive protein	***1.1564***	***1.0454***	***1.2790***	***0.0047***
Uric acid	1.4130	0.8890	2.2461	0.1437
Creatinine	1.6697	0.0240	116.3229	0.8128
Adiponectin	***0.4140***	***0.2141***	***0.8007***	***0.0088***
Resistin	1.0386	0.9882	1.0915	0.1356
Leptin	1.0312	0.9993	1.0642	0.0554
Multivariate logistic regression analysis for MACE (final model)				
	OR	-95%CI	+95%CI	p
Diabetes mellitus	22.1877	1.2243	402.0903	0.0360
Adiponectin	0.1970	0.0431	0.9006	0.0362
Ejection fraction	0.7849	0.6308	0.9766	0.0298

4. DISCUSSION

The most interesting finding of our study is that low baseline blood adiponectin concentration is an independent predictor of MACE in a one year follow up after STEMI. The predictive value of adiponectin was also shown in other, recently published studies. Kojima *et al*. [8] has revealed that the plasma adiponectin level on admission in men and the decline in plasma adiponectin level at hospital in women were independent predictors of MACE in AMI patients. In the study of Shioji *et al* [9] adiponectin assessed in the blood taken before the angioplasty was predictive for MACE in patients with stable angina or myocardial infarction.

Indeed, adiponectin is assumed as a protective adipokine. There is evidence that a higher blood adiponectin level is associated with lower risk of cardiovascular events in patients with chest pain [5] and a lower risk of major adverse cardiac and cerebrovascular events after PCI [9].

Surprisingly, although a low blood adiponectin level is associated with an atherogenic lipid profile, increased oxidative state in the arterial wall, and low-grade inflammation [10–11], the British Regional Heart Study (BRHS) and a metaanalysis of previous studies did not show a significant association between adiponectin and coronary heart disease risk [12]. However, experimental studies performed by Shibata *et al* [13–15] and Tao *et al* [16] revealed that adiponectin diminishes ischemia-reperfusion injury. The authors present several possible explanations of this action: the accumulation of adiponectin in the heart following ischemic damage through its leakage from the vascular compartment, the inhibitory effect of adiponectin on apoptosis and stimulation of angiogenesis through AMP-activated protein kinase and the improved cell survival through COX-2 dependent signaling that suppresses tumor necrotic factor-alfa (TNF-alpha) production and oxidative stress inhibition. Adiponectin may also limit the neointimal thickening due to the angioplasty related injury by attenuation cell proliferation and migration and growth factor induced DNA synthesis [17].

Resistin is considered as a factor related to early atherogenesis through its association with cardiovascular risk factors and inflammation, however the independent role of resistin in coronary artery disease is still controversial [18–20]. It has been shown that this adipokine may induce endothelial dysfunction, up regulate adhesion molecules, promote smooth muscle cell proliferation and is related to local and generalized inflammation [19, 21–23]. Resistin-induced impairment of the dilatation in the coronary circulation was expected to be at the bradykinin receptor or a closely associated signal transduction machinery proximal to NO synthase or cyclooxygenase [21]. Resistin was also shown to impair cardiac recovery following ischaemia through the stimulation of the cardiac TNF-alpha secretion, and modulation of TNF-alpha related signalling mecha-

nism [24]. In spite of these numerous deleterious actions of resistin we have not revealed this adipokine to be independently related to MACE. Our observation is in agreement with the study of Lubos *et al* [6] who have shown that blood resistin level, although moderately associated with future cardiovascular death in patients with documented coronary artery disease was not related to MACE in patients with myocardial infarction.

Chronic hyperleptinemia induces intra-cellular signaling that results in oxidative stress that may activate atherogenic process and early restenosis after coronary stenting [25, 26]. Leptin was identified as a predictor of future cardiovascular events in patients with angiographically confirmed coronary atherosclerosis [7] but the predictive value of leptin was not, so far, assessed in acute myocardial infarction patients and was not revealed in our study. Leptin acts via its receptor (LRb) in the brain to regulate energy balance and neuroendocrine function. The failure of elevated leptin levels to suppress feeding and mediate weight loss defines a state of leptin resistance observed in obesity [27]. Experimental studies showed that acute leptin exposure stimulates endothelial nitric oxide (NO) production, whereas prolonged leptin stimulation is associated with endothelial dysfunction and impaired endothelial NO production [28].

Elevated levels of CRP as a marker of inflammation, were identified as another risk factors for adverse late outcome after AMI. We have shown that CRP assessed at admission was significantly associated with MACE, but multivariate analysis did not confirm CRP to be an independent negative predictor in our group of patients. Although in the study of Hoffman admission CRP was a predictor of subsequent survival, serial measurements of CRP after AMI performed by other authors revealed that long-term prognostic value of CRP concerns the peak concentration [29] or measurements made 24–48 hours after symptom onset [30]. It has also been suggested that CRP is less predictive of long-term outcomes when measured after AMI than after unstable angina pectoris or stable angina pectoris [31].

Several studies showed that diabetes mellitus is associated with a long-term, low-grade inflammatory state and activation of platelet aggregation [32]. As such it is clear that although PCI improves the outcome in diabetic patients with myocardial infarction more dramatically than for nondiabetic patients [33] it may still bring about a risk of clinical reinfarction [34]. Indeed, in our study in agreement Shihara *et al* [35], 1-year prognosis STEMI was found to be worsened by diabetes.

Surprisingly, obesity, although defined as a low-grade inflammatory state has been revealed as a positive prognostic factor after PCI in patients with AMI [36]. This has been attributed to younger age, better renal function and less frequent anterior infarction. In our study obesity was not independently related to MACE. Age, Killip class, renal failure and/or initial serum creatinine concentration, multivessel disease previously identified as risk indicators for future death and myocardial infarction in GRACE and some other studies [1, 35, 37] were not revealed as negative prognostic factors in our group of patients. It is possibly due to the exclusion criteria applied in the present study, which eliminated elderly patients (over 65 years of age), patients with prior myocardial infarction and therefore limited the proportion of severely ill individuals. There was no patient in the IV Killip class or with renal failure defined as serum creatinine ≥2.5 mg/dl in our study group. Still, in agreement with Halkin *et al* [2] we have identified left ventricular EF as independent negative predictors of MACE.

4.1. Study limitations

The main limitation of our study is a small sample size and lack of a priori calculations with respect to sample size or statistical power. It was conducted exclusively in males so that the conclusions can not be generalized for the whole population. Moreover, the population was a low-risk cohort, mostly due to the exclusion criteria. Unfortunately serial measurements of myocardial necrotic markers or adipokines were not performed. Troponin T was assessed only at admission and, if negative another measurement was performed after 6 hours to confirm the diagnosis of myocardial infarction. The blood sampling for adipokines differed in individual patients by between 24 and 72 hours in our patients. The study of Kojima [38] showed that adiponectin significantly declines during the initial 24 hours of AMI but is relatively stable through the following 48 hours. Further, larger studies with multiple measurements of adipokines would provide more reliable results.

4.2. Clinical implications

The present study is anther vote for the need for better understanding of the genetic background and molecular mechanisms of adipose tissue hormones action. It seems appropriate to target adiponectin for cardioprotection. As there is no specific treatment of hipoadiponectinemia, lifestyle intervention with the weight loss and exercise training are at present, the only accepted therapeutic strategies that increase circulating adiponectin and may enhance the expression of its receptors in muscles [39, 40]. The impact of the diet modification [41] and pharmacological agents on the blood adiponectin levels is being studied [42].

5. CONCLUSION

In male patients with ST-segment elevation acute myocardial infarction undergoing primary percutaneous coronary intervention, a single baseline determination of blood adiponectin but not resistin or leptin is independently predictive of the future cardiac events. The other prognostic factors are diabetes mellitus and left ventricular ejection fraction.

Acknowledgements:
This study was supported by a Medical University of Łódź research grants No 502-11-584 and No. 503-10-052.

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