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Title: Assessment of adipokines, adenine nucleotides and uric acid in the dynamics of coronary intervention

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Assessment of adipokines, adenine nucleotides and uric acid in the dynamics of coronary intervention

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Abstract: Introduction: The association of vaspin and visfatin, with a myocardial infarction is still not fully understood. Reduced levels of adenine nucleotides are hallmarks of chronic heart failure. There is little data concerning the relationship between these markers and their changes over time. Material/Methods: The concentration of adenine nucleotides, vaspin and visfatin were assessed in 41 consecutive patients with acute myocardial infarction one before (day I) and four days after (day IV) percutaneous coronary intervention (PCI) and a control group. Results: Visfatin concentrations were higher before and after PCI vs. control (visfatin I: median 25.55, 20.12 - 30.69 ng/ml; visfatin IV: median 20.79, 16.89 - 25.61 ng/ml vs. control: median 14.94, 10.66 - 25.25 ng/ml; $p < 0.0001$). Vaspin concentrations were lower before and after PCI vs. control (vaspin I: median 0.18, 0.11 - 0.44 ng/ml; vaspin IV: median 0.24, 0.15 - 0.58 ng/ml vs. control: median 1.303, 1.13 - 2.26 ng/ml, $p < 0.00001$). Concentrations of visfatin,

day I, correlated well to vaspin concentrations ($r^2 = 0.201$, $p = 0.011$). ATP levels were significantly lower in patients vs. controls (day I: $p = 0.00012$; day IV: $p = 0.0001$). Conclusions: Changes in the analyzed visfatin and vaspin concentrations can be used as potential MI markers. Visfatin serum concentration may be considered a potential marker to differentiate MI over time.

Keywords: myocardial infarction, visfatin, vaspin, adenine nucleotides, uric acid

1 Introduction

Adipocytokines are a large group of bioactive proteins and they manifest hormone-like attributes with properties similar to some chemokines, cytokines and growth factors. Specific changes in the circulatory levels of adipokines appear to have a proatherogenic, proinflammatory and anti-insulin effects on human cells [1].

Visfatin is an adipokine mainly expressed in visceral fat tissue, and is also produced in the myocardium, bone marrow, skeletal muscle, and liver [2]. Visfatin occurs in a form of a dimer, capable of binding and hydrolyzing ATP. Visfatin undergoes self-phosphorylation which enhances its catalytic function in nicotinate and nicotinamide metabolism [2]. Increased visfatin serum levels were found in some diseases associated with obesity, atherogenesis and insulin-resistance [3]. Visfatin has been considered as a pro-inflammatory factor and is also associated with vascular smooth muscle cell maturation and plaque destabilization [2,4]. The plasma visfatin level was found to be elevated in patients with acute ST-segment elevation myocardial infarction (STEMI) [5].

Vaspin, identified in 2005, is a serine protease inhibitor secreted only by visceral fat tissue [6]. In animal models, it has been shown that vaspin enhances insulin sensitivity in peripheral tissues thus improving glucose tolerance,

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however elevated vaspin serum concentrations were associated with insulin resistance and a lower fitness level [7]. A low vaspin level is suggested to be involved in the pathophysiology of coronary atherosclerosis, microvascular complications in coronary artery disease and carotid stenosis [8-10]. Serum vaspin concentrations were proven to be associated with carotid stenosis in patients with acute ischemic stroke and patients who underwent carotid endarterectomy [11]. Diabetes and body weight loss were shown to decrease vaspin expression, which can be also normalized by insulin or pioglitazone treatment [12,13]. Certain adipokines are considered to be a new link between metabolic diseases, atherosclerosis and cardiovascular disease, with visfatin and vaspin suggested as novel factors involved in atherosclerosis progression [9].

ATP nucleotide (adenosine triphosphate) plays an important role in cell biology, as a multifunctional coenzyme and molecular unit in intracellular energy transfer [14,15]. Reduced levels of total adenine nucleotides ATP, ADP (adenosine diphosphate) and AMP are hallmarks of chronic heart failure [16]. Currently, there are no published reports investigating the relationship between these adenine nucleotides levels and myocardial infarction patients.

Uric acid (UA) has been widely investigated as the prognostic factor for a number of cardiovascular diseases. Elevated levels of UA are associated with the mortality in the general population, and in patients with congestive heart failure, hypertension, diabetes, coronary artery disease and acute myocardial infarction. Uric acid is considered a variable parameter, which strongly depends on the metabolic condition of the patient. It is reported, that altered and increased UA levels are associated with obesity, raised blood pressure, hyperlipidemia, glucose intolerance, and CVD clustering. In patients with stable coronary artery disease, uric acid predicts the risk of death independently from cardiovascular risk factor, status of renal function or inflammation risk. Nevertheless, the mechanisms between UA level and poor prognosis are not fully understood [17-20].

The aim of the study was to investigate visfatin and vaspin concentrations, the total adenine nucleotides and uric acid states in relation to the dynamics of acute coronary syndrome.

2 Material and Methods

2.1 Subjects and study design

This cross-sectional study was conducted at the Silesian Center for Heart Diseases and at the Department of

Physiology in Zabrze of Silesian University of Medicine. The study population included 41 men (aged mean 55.1 ± 9.7) with myocardial infarction. Myocardial infarction was defined following current ESC guidelines [21]. All patients were qualified for invasive coronary diagnostic treatment (percutaneous coronary interventions) for the first time in their lives. The inclusion criteria were as follows: typical angina pain for < 12 h until admission to the hospital, ST-segment elevation during resting 12-lead ECG, increased myocardial necrotic markers in the serum: troponin-I and CK-MB or non-elevated ST-segment but increased troponin-I and CK-MB levels. Exclusion criteria: pulmonary oedema, cardiogenic shock or contraindications for catheterization, primary cardiomyopathies, myocardial infarction in the last 6 months, unstable angina, significant valvular heart defects, severe chronic heart failure (class NYHA III-IV), inflammatory conditions, acute or chronic infectious disease, malignant disease, and including any kind of a surgical procedure or serious injury 6 months prior to admission to the hospital. Every patient was treated according to the guidelines. Additional pharmacotherapy was induced when individual clinical indications occurred. Blood samples were collected upon admission to the hospital before PCI (I day) and four days after PCI following an overnight fast (IV day).

The control group consisted of 30 healthy men (aged 46.5 ± 7.4). These individuals did not suffer from chronic disease, cardiovascular disease and did not present overt cardiac origin symptoms. Each patient from the control group was evaluated for inclusion in the study. Informed consent was obtained in each case.

2.2 Clinical evaluation

Six patients suffered from type 2 diabetes mellitus, having a mean fasting blood glucose level higher than 6.9 ± 1.9 mmol/l and a glycated hemoglobin $HbA_{1c} > 6\%$. The majority of the patients (92.6%) suffered from hypertension. Body mass index (BMI) was calculated from measured, not declared data, and expressed in kg/m^2 . Each patient's left ventricle contraction (left ventricular ejection fraction) was assessed by echocardiography. A 12 lead ECG was recorded.

2.3 Ethical Considerations

The study was approved by the Ethics Committee of the Medical University of Silesia in Katowice (approval

number KNW-1-001/P/1/0) and was in compliance with the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from every patient before inclusion into the study series.

2.4 Blood analyses

Blood samples were collected from an antecubital vein and then placed into a BD Vacutainer containing 0.117 mL of 15% (k3) EDTA solution. For adipokines analysis, blood samples were immediately centrifuged at 2500 x g for 20 min to obtain serum and stored at - 80°C, thawing only once immediately before analysis. Vaspin concentrations were determined using a commercially available EIA kit (Human Vaspin ELISA kit, Catalogue no. V0712TP AdipoGen Inc., Seoul, Korea). The sensitivity of the set was 12 pg/ml. Visfatin concentration levels were determined enzymatically using a commercial ELISA Kit (C - terminal Visfatin (Human) EIA kit, Catalogue no. EK-003-80, Phoenix Pharmaceuticals, Inc., Belmont, CA, USA). The sensitivity of the set was 2.83 pg/ml.

Blood samples were used to assess the biochemical parameters (Table.1.). The measurement of biochemical parameters was performed with standard procedures at the Silesian Center of Heart Diseases laboratory on a ROCHE INTEGRA 800 (Roche Poland).

Concentrations of ATP and its inter-converts to ADP and AMP and uric acid were evaluated at the Department of Biochemistry of Gdansk Medical University, using high-performance liquid chromatography (HPLC) according to the previously developed method by Smolensky [22].

2.5 Statistical analysis

The results of continuous variables are expressed as mean \pm SD for all data except for the concentrations of vaspin and visfatin, where the median \pm min/max was calculated. The normality of the distribution was assessed using Levene's test. Comparisons between adenine nucleotide groups were made using the *post hoc* HSD (Tukey's T-test). Comparisons between concentrations of visfatin vaspin in patient and control groups were made using the Mann-Whitney U test. Correlations between parameters were calculated using the Spearman's rank correlation test. Statistical significance was set at the p level < 0.05. All statistical analysis was performed using Statistica 10.0 (StatSoft, Poland).

3 Results

Biochemical, demographical and cardiological characteristics of all the patients included in the study are presented in Table 1. Intergroup statistical analysis revealed that the visfatin levels in patients with MI were significantly higher before (day I) and four days after (day IV) PCI compared with healthy individuals (Visfatin-I median 25.55, 20.12 - 30.694 ng/ml; $p = 0.00001$; Visfatin-IV median 20.79, 16.89 - 25.61 ng/ml vs. control median 14.94, 10.66 - 25.25 ng/ml; $p < 0.00001$, Fig. 1). Vaspin concentrations in patients with MI were significantly lower I and IV days after PCI compared to healthy individuals (Vaspin-I median 0.18, 0.11 - 0.44 ng/ml; Vaspin-IV median 0.24, 0.15 - 0.58 ng/ml vs. control median 1.30, 1.13 - 2.26 ng/ml, $p < 0.00001$) (Fig. 2). Visfatin levels measured on day I were significantly correlated to vaspin concentrations ($r^2 = 0.201$, $p = 0.01$). Visfatin concentration 4 days after PCI was related to the following parameters: ADP ($r^2 = 0.51$, $p = 0.000006$); NADP ($r^2 = 0.57$, $p = 0.000001$); ATP/ADP ($r^2 = 0.56$, $p = 0.000001$); UA ($r^2 = 0.15$, $p = 0.02$) (Table 2).

The whole blood concentration of ATP was significantly lower in examined patients when compared to the controls (ATP-I 495.2 ± 62.4 $\mu\text{mol/l}$, $p = 0.00012$; ATP-IV 513.7 ± 70.6 $\mu\text{mol/l}$, $p = 0.0001$ vs. control 604.2 ± 61.2 $\mu\text{mol/l}$; Fig.3.). The concentration of adenosine diphosphate (ADP) in every analyzed group did not differ from control, Fig.3. The concentration of AMP was significantly higher on day I and day IV after PCI compared to the control group (AMP-I 7.54 ± 2.7 ; AMP-IV 7.25 ± 2.1 vs. control 4.6 ± 1.6 $\mu\text{mol/l}$, $p = 0.0001$) (Fig. 4). The ratio of ATP/ADP in whole blood samples was significantly lower in ATP/ADP-I group when compared to the control (ATP/ADP-I 7.79 ± 1.12 vs. control 8.75 ± 0.77 $\mu\text{mol/l}$; $p = 0.005$; Fig. 4). The level of NADP and NAD were significantly lower on day I and IV after PCI in comparison to the control group (NADP-I 15.63 ± 1.89 ; NADP-IV 15.74 ± 2.32 vs. control 18.92 ± 1.93 $\mu\text{mol/l}$, $p = 0.00014$; $p = 0.0002$; NAD-I 21.37 ± 5.27 ; NAD-IV 21.17 ± 4.68 vs. control 27.74 ± 3.69 $\mu\text{mol/l}$; $p = 0.00017$; $p = 0.0002$; Fig.5). The level of uric acid in the blood of patients from the UA-I group was significantly lower compared with the control group (UA-I 88.07 ± 29.5 vs. control 115.54 ± 24.9 $\mu\text{mol/l}$, $p = 0.005$; Fig.6). We further analyzed correlative relationships between adenine nucleotides and adipokine concentrations and found significant correlations ($p < 0.05$) among selected adenine nucleotides and adipokines (Table 2).

Table 1. Demographic, biochemical and cardiological parameters for patients included into the program.

Demographic parameters			
Age	55.19 ± 9.73		
Smokers, N	8 (19.51%)		
BMI [kg/m ²]	28.08 ± 3.43		
Hypertension, N	38 (92.6%)		
Diabetes 2 mellitus, N	6 (14.63%)		
Dislipidemia, N	25 (62.5%)		
Cardiological parameters			
LVEF [%]	48 ± 7		
Angiography	Number of patients		
1-vessel	16		
2-vessel	5		
3-vessel	20		
CAD score	Number of patients		
2	2		
3	10		
4	29		
Biochemical parameters			
	Day I	Day IV	p
T-cholesterol [mmol/L]	5.26 ± 1.0	4.76 ± 1.17	0.00001
HDL [mmol/L]	1.22 ± 0.2	1.24 ± 0.05	0.975
LDL [mmol/L]	3.34 ± 0.8	2.95 ± 1.02	0.339
TG [mmol/L]	1.62 ± 1.6	1.64 ± 1.4	0.969
Glucose in blood [mmol/L]	6.7 ± 1.8	5.35 ± 0.6	0.001
*HbA _{1c} %	6	-	-
Leukocytosis [10 ⁹ /L]	11.04 ± 2.9	8.8 ± 0.9	0.0001
Erythrocytes [mln/mm ³]	4.8 ± 0.4	4.6 ± 0.5	0.235
Hemoglobin [mmol/L]	9.3 ± 1.0	8.8 ± 0.9	0.08
Hematocrit [L/L]	0.43 ± 0.04	0.41 ± 0.03	0.219
CRP [mg/dL]	42.94 ± 34.59	-	-
CK – MBI [ng/mL]	58.54 ± 11.8	92.1 ± 11.3	0.267
Troponin [ng/mL]	0.51 ± 0.8	1.9 ± 1.4	0.004
Creatinine [μmol/L]	80 ± 18	78.6 ± 15.0	0.797
AspAT [IU/l]	56.18 ± 61.3	90.5 ± 11.1	0.736
ALAT [IU/l]	38.8 ± 84	54 ± 8.0	0.036

Clinical data is presented as means ± SD, N- number of patients; * - measured only for diabetic group, p < 0.05.

BMI - body mass index, HDL-C – condensation of HDL cholesterol; LDL-C – condensation of LDL cholesterol, TG - triglycerides, HbA_{1c} - the level of glycated hemoglobin, WBC - leukocytosis, LVEF - left ventricular ejection fraction; IU - International Units (International Unit), CK-MBI - creatine kinase, T-cholesterol - total cholesterol hsCRP - C-reactive protein test, SBP - systolic blood pressure, DBP - diastolic blood pressure, CAD – coronary artery disease.

4 Discussion

The purpose of this study was to test the hypothesis that the levels of selected adipokines and nucleotides could show different dynamics over time and these levels can be altered before and after PCI. We demonstrated that the levels of visfatin were increased in patients with the MI, both before and 4 days after PCI. Visfatin serum levels on the day I and IV after PCI were around 1.6 and 1.3 (respectively) times higher in patients with MI compared to healthy individuals. Dhal et al. described the relationship

between visfatin and unstable lesions at the plaque rupture site in patients with acute myocardial infarction [2]. The increased visfatin plasma levels were also assessed in ACS [5,23]. The visfatin levels, in MI patients, peaked 24 h after MI and decreased during the first week in comparison to the control group [23]. Our results are consistent with this data and suggests that changes in this adipokine level may result from the repair processes present in myocardium. Increased concentrations of visfatin were shown to be significantly associated with a high risk of infarct-related artery occlusion, where the plasma visfatin levels

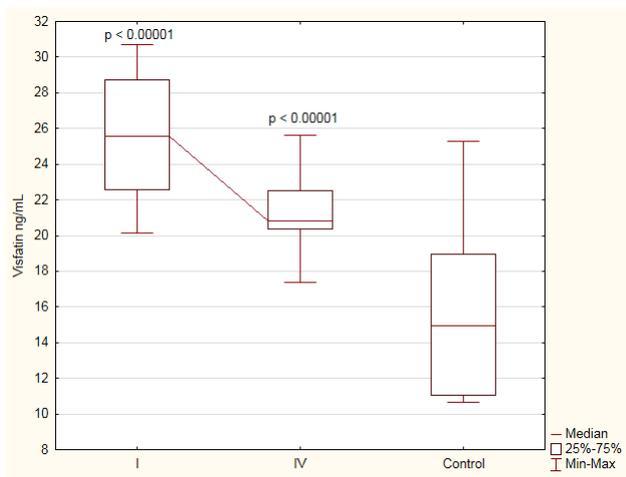


Figure 1. Visfatin plasma levels [ng/mL] in patients with MI at admission (day I) and four days after PCI following an overnight fast (day IV) in comparison to control.

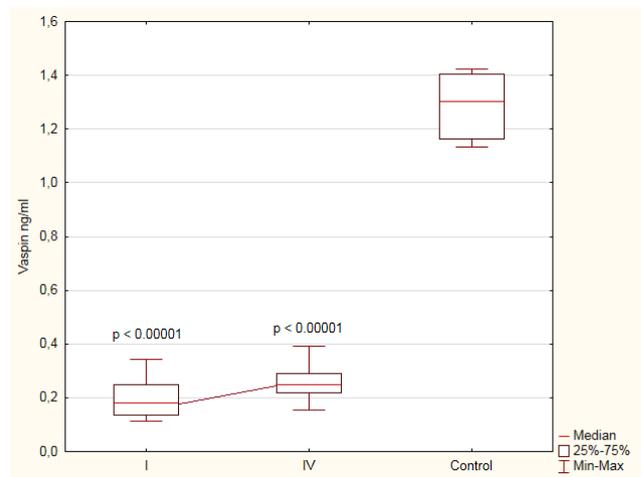


Figure 2. Vaspin plasma levels [ng/mL] in patients with MI at admission (day I) and four days after PCI following an overnight fast (day IV) in comparison to control.

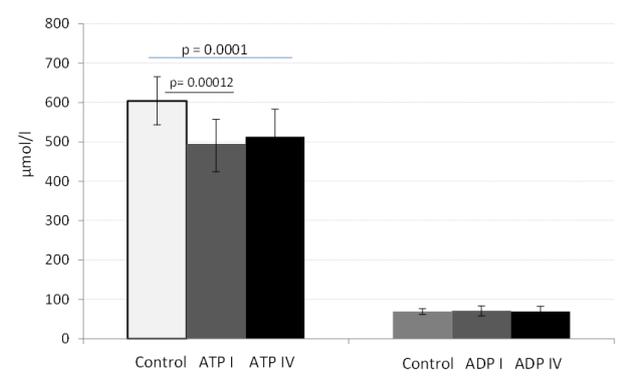


Figure 3. ATP, ADP blood concentrations [µmol/L] in patients with MI at admission (day I) and four days after PCI following an overnight fast (day IV) in comparison to control.

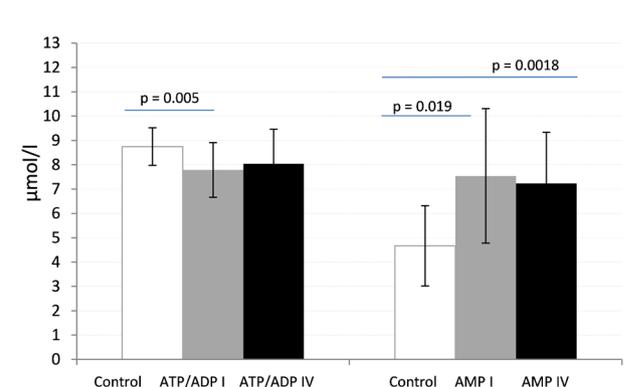


Figure 4. ATP/ADP ratio and AMP blood concentrations [µmol/L] in patients with MI at admission (day I) and four days after PCI following an overnight fast (day IV) in comparison to control.

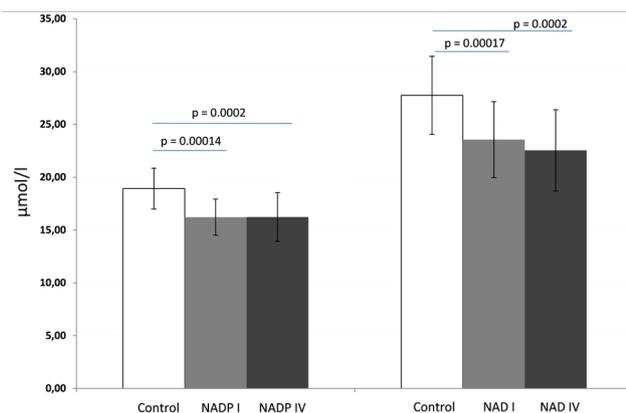


Figure 5. NADP, NAD blood concentrations [µmol/L] in patients with MI at admission (day I) and four days after PCI following an overnight fast (day IV) in comparison to control.

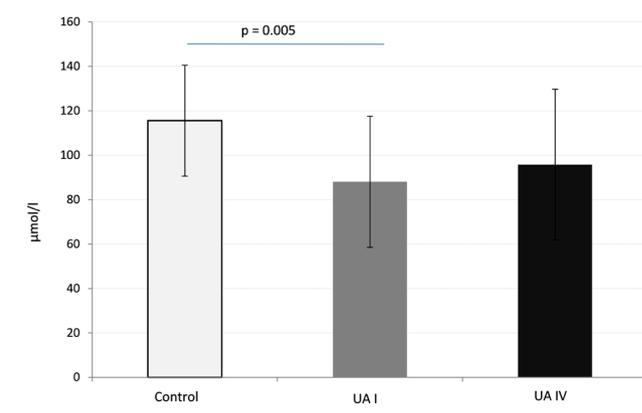


Figure 6. Uric acid (UA) blood concentrations [µmol/L] in patients with MI at admission (day I) and four days after PCI following an overnight fast (day IV) in comparison to control.

Table 2. Correlations between the nucleotides occurring one (I) and four (IV) days after PCI.

Day I	r(X,Y)	r ²	p
ADP vs. AMP	0.703	0.495	0.00001
AMP vs. ATP/ADP	-0.827	0.685	0.0000001
AMP vs. NADP	-0.452	0.204	0.01
NADP vs. NAD	0.729	0.532	0.000003
NADP vs. ATP/ADP	0.4091	0.1673	0.022
NAD vs. ATP	-0.409	0.167	0.022
NAD vs. ATP/ADP	0.392	0.154	0.028
Visfatin vs. Vaspin	-0.449	0.201	0.011
Vaspin vs. CRP	-0.627	0.394	0.016
Day IV	r(X,Y)	r ²	P
NADP vs. UA	0.478	0.228	0.006
NADP vs. ATP	0.864	0.747	0.0000001
NADP vs. ADP	0.762	0.58	0.00001
NADP vs. NAD	0.856	0.733	0.0000001
NADP vs. ATP/ADP	0.822	0.677	0.0000001
NADP vs. VISFATIN	0.7577	0.574	0.000001
NAD vs. UA	0.444	0.197	0.012
NAD vs. ATP	0.791	0.626	0.0000001
NAD vs. ADP	0.622	0.387	0.00018
NAD vs. ATP/ADP	0.722	0.522	0.000004
NAD vs. VISFATIN	0.735	0.541	0.000002
UA vs. ATP/ADP	0.49	0.240	0.005
ATP/ADP vs. VISFATIN	0.752	0.566	0.000001
UA vs. VISFATIN	0.398	0.158	0.02
VISFATIN vs. ADP	0.716	0.512	0.000006

correlated with the peak CK-MB and troponin I levels [5], a finding not supported in our study. Furthermore, in our study, before and four days after PCI, the plasma levels of visfatin were negatively correlated with corresponding vaspin levels. This may suggest the involvement of vaspin in the pathophysiology of coronary artery disease. Vaspin has been assumed to be an important risk factor for heart disease, associated with cardiovascular disease and atherosclerosis-related metabolic variables [10]. Visfatin is known to be independently associated with inflammation, atherosclerosis and acute coronary syndromes. The elevation of visfatin serum levels were observed in patients with stable angina, where visfatin plays a role in the pro-inflammatory process of the atherosclerosis development [4]. Based on our findings and available literature, it can be assumed that the increased visfatin level could result from myocardial cells injury, *via* ischemic way, and plaque

destabilization. The decrease in visfatin concentration 4 days after PCI could be explained by the occurrence of repair processes, but further investigations are needed to explore whether the visfatin level would continuously decrease to the levels found within in a healthy subject.

We report that patients had reduced vaspin levels before (by 7 times) and after (by 5.5 times) PCI, when compared to healthy individuals. This result may indicate the effectiveness of the interventional treatment and the decrease of micro-inflammation. Further, we observed that day I vaspin values were negatively correlated with CRP levels. Literature has shown that, for patients with MI, there is an association between lower circulating vaspin levels and the severity of CAD [9]. Vaspin has anti-atherosclerotic properties and its increasing concentration is a compensation mechanism for the developing atherosclerotic process [8]. Decreased vaspin mRNA expression in peripheral blood mononuclear cells was observed in patients with unstable angina pectoris in comparison with patients with stable CAD [24]. CAD is considered a systemic micro-inflammatory disease, and as it was shown that pro-inflammatory factors can reduce vaspin expression [25] and vaspin concentration, which is associated with a high level of C-reactive protein. The decreased vaspin level can be explained by the severity of acute coronary syndromes (ACS) in CAD. Further studies are required to confirm whether the significantly lower concentrations of circulating vaspin in patients with myocardial ischemia might be a predictor of this pathophysiological condition.

The region of myocardial infarction contains a difference of perfusion levels. In regions of relatively severe ischemia, glycolysis and oxidative phosphorylation may be inhibited while in regions with less severe ischemia, oxidative phosphorylation may contribute to a relatively greater fraction of ATP synthesis [26]. During normoxia, the myofilaments are supplied with a high amount of ATP, synthesized from glycolysis and oxidative phosphorylation. In normal physiological conditions, high ATP, low ADP and inorganic phosphate (P_i) levels maximize the free energy available from ATP hydrolysis [26]. During ischemia, the activity of aerobic and anaerobic pathways are determined both by the amount of residual coronary flow and available carbon substrates [26]. Reduced levels of total adenine nucleotides (TAN), understood as the sum of ATP, ADP and AMP, are characteristics of chronic heart failure. The reconditioning of TAN pools leads to an increased energy state of the diseased heart [16]. Cave et al. showed that in low-flow ischemia simulating a region of acute myocardial infarction, oxidative phosphorylation accounted for 90% of the ATP synthesis [26]. Analysis of the adenine nucleotide

patterns in the blood serum showed a lower concentration of ATP, NAD, and NADP day I and day IV after PCI. Significantly lower concentrations of ATP/ADP ratio and UA were observed the first day before coronarography, and the ATP serum concentration was significantly higher compared to healthy counterparts. Therefore, ATP levels may be useful in the assessment of acute myocardial infarction during the early phase, as this is the only time it significantly differs from the control levels.

In our study all patients were normouricemic, where hyperuricemia was defined as serum uric acid level > 6.5 mg/dl. Serum UA is the final product of purine metabolism. UA is produced by enzymatic activity of xanthine oxidoreductase (XO). During this process, oxygen free radicals are also generated. In humans, XO has the highest activity in the capillary and small artery endothelium [18]. The role of UA as a risk factor of cardiovascular diseases is raised but not fully supported. Depending on the physiological status of the patients, the cohort analysis showed that UA concentration was significantly associated with dyslipidemia, impaired glucose tolerance and metabolic syndrome, which leads to increased risk of cardiovascular disease [27]. To date, many studies suggest hyperuricemia to be a risk factor for hypertension, with its major consequences including stroke, heart failure and cardiovascular mortality [28]. Nevertheless, UA is also one of the strongest plasma antioxidants. It has been shown that, dependent upon the concentration, uric acid promotes inflammation, increases oxidative stress and endothelial dysfunction. Physiological concentrations of uric acid work as endogenous antioxidant factors [21]. In this study, we have found that one day before PCI, the UA level was reduced faster in patients compared to healthy individuals, which may suggest it has an antioxidative role. Although, increased concentration of uric acid in the group four days after myocardial incident and PCI may be interpreted as a harmful prognostic, correlated with higher mortality of patients [18-20,29]. These conditions may suggest that successful revascularization, with optimal effect, contribute more to the coronary flow while biochemical markers of low ATP levels, are the effect of acute or long-term ischemia.

In conclusion, higher visfatin and lower vaspin levels in plasma of the male patients significantly differed in time of onset of ischemia and reperfusion, thus these adipokines may be considered as potential markers to differentiate morbidity in myocardial infarction. Adenine nucleotides in blood serum can be used for differentiation in term of onset of time. Low concentrations of ATP and UA may be considered as biochemical markers for patients with acute ischemia.

5 Conclusions

In summary, we focused on patients with acute coronary syndrome one day before and four days after PCI. Changes in analyzed visfatin and vaspin levels suggest that these could be used as potential markers to identify plaque destabilization and myocardium necrosis. The monitoring of serum visfatin level may be a prognostic factor of myocardium regeneration, however, further, detailed investigations are required.

Conflict of interest: Authors declare nothing to disclose.

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