Adiponectinemia, inflammatory process activity, and endothelial dysfunction in patients with type 2 diabetes and acute coronary syndrome with ST elevation in relation to the severity of lesions in the coronary arteries

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Abstract: Introduction. Metabolic disorders developing in diabetes are associated with impaired endothelial function and the presence of subclinical inflammation, in consequence leading to multivessel atherosclerosis. Vasoprotective factors include adiponectin, a cytokine with a diverse antiatherosclerotic activity. **Objectives.** Evaluation of adiponectin concentrations and activity of the inflammatory process and endothelial dysfunction in patients with type 2 diabetes and acute coronary syndrome (ACS) with ST elevation (STEMI) in relation to the severity of lesions in the coronary arteries. **Patients and methods.** This study included 72 patients (24 women, 48 men) with type 2 diabetes, treated with sulphonylurea derivatives, diagnosed with STEMI, who underwent percutaneous coronary angioplasty. The treated group consisted of 41 patients, mean age (± standard deviation) was 64 ±9.6 years, the Gensini score (GS) >32 points (more advanced lesions in the coronary vessels). The control group consisted of 31 patients, a mean age of 63 ±10 years, GS <32 points (less advanced lesions). Within 12 hours after the ACS, troponin T activity (TnT), creatine kinase MB isoenzyme (CK-MB), C-reactive protein (CRP), fibrinogen, two adhesion molecules – soluble vascular adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesive molecule-1 (sICAM-1) were evaluated in the patients. Leucocytosis, glucose and insulin levels, and lipid profiles were obtained after overnight fast conditions. **Results.** Patients in group I demonstrated a significantly higher TnT and CK-MB (1.39 ±1.3 vs. 0.83 ±0.74 ng/ml, p <0.05; 139.6 ±178.5 vs. 57.48 ±52.1 IU/l p <0.05, respectively), higher concentrations of CRP (12.06 ±14.3 vs. 3.59 ±4.1mg/l, p <0.05) fibrinogen (4.59 ±1.93 vs. 3.62 ±1.36 g/l, p <0.05), sVCAM-1 (1393.4 ±865.4 vs. 863.9 ±425.2 ng/ml, p <0.05) and sICAM-1 (735.1 ±316.3 vs. 573.3 ±226.1 ng/ml, p <0.05), higher leucocytosis (11,430 ±3680 vs. 9750 ±3100/µl, p <0.05) and lower adiponectin concentrations (5.8 ±5.2 vs. 8.3 ±2.9 8 µg/ml, p <0.05) as compared to the control group. **Conclusions.** Hypoadiponectinemia, severity of the inflammatory process and endothelial dysfunction could contribute to the progression of atherosclerotic lesions in the coronary arteries in patients with type 2 diabetes.

Key words: acute coronary syndrome, adiponectin, endothelial dysfunction, inflammation, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus is an independent risk factor for cardiovascular disease, especially coronary artery disease. Metabolic abnormalities including hyperglycemia, hyperinsulinemia, insulin resistance, dyslipidemia [1-3], lead to arterial dysfunction, affecting endothelial cells, vascular smooth muscle cells, along with alterations in the blood coagulation and development of systemic inflammatory state.

Clinical manifestations of atherosclerosis are not dependent on the patient age, but on the duration of diabetes [4]. The prevalence of atherosclerosis is 2–4 fold higher in diabetic patients than those without this disease [4]. Atherosclerosis associated with diabetes is more diffuse and characterized by the presence of multiple lesions [4-8]. Atherosclerosis in diabetes is a progressive disease characterized by the accumulation of lipids and fibrous components distally, in the small and medium-sized arteries [4]. The destabilization of the plaque may be

caused by the chronic, systemic and also local inflammatory process [9,10]. Elevated plasma CRP (C-reactive protein), fibrinogen and soluble adhesion molecules such as soluble intercellular adhesive molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1) levels and increased number of granulocytes are indicators of inflammatory state. Endothelial dysfunction leads to impaired vasodilatation, initiation of the coagulation cascade and inflammation [9,10]. Chronic inflammation, rupture of unstable atherosclerotic plaque and thrombus formation results in the acute coronary syndrome (ACS).

Adiponectin belongs to the agents that may protect the coronary vasculature from atherosclerosis. Adiponectin contains 244 amino acids, is an active protein of 30 kDa [11,12]. It has similar structure to collagen type VIII, X, TNF-α (tumor necrosis factor) and C1q complement. Adiponectin binds to collagen I, III and V, which are abundant in the vascular wall [13]. Serum adiponectin concentrations ranged from 5 to 30 μg/ml [14] and it seems to be dependent on gender- in women is higher than in men [15]. Adiponectin modulates inflammatory reactions, which play an important role in early stages of atherosclerosis. Adiponectin inhibits inflammatory and atherosclerotic processes as it suppresses the adhesion of monocytes to endothelial cells by decressing the TNF-alpha-mediated expression of sVCAM-1, sICAM-1 and E-selectin [16,17], decreasing activity nuclear factor β, suppressing the foam cell formation by macrophages and inhibition of vascular smooth muscle proliferation and migration.

The aim of this study was to assess adiponectin concentrations and activity of inflammatory process and endothelial dysfunction in patients with type 2 diabetes and acute coronary syndrome with ST elevation (STEMI) in relation to the severity of lesions in the coronary arteries.

PATIENTS AND METHODS

Seventy-two patients with type 2 diabetes, treated with sulphonylurea derivates, diagnosed with ACS with ST segment elevation were enrolled in the study. This form of ACS was diagnosed, based on a medical history, physical examination and electrocardiogram. The patients underwent percutaneous coronary angioplasty at the Department of Invasive Cardiology in the Chair of Cadiology and Cardiosurgery of Medical University in Lodz. The patients were divided into two groups based on the Gensini score:

– the study group – 41 patients (18 women and 23 men), the mean age ± standard deviation (SD) – 64 ±9.6 years, with severe atherosclerosis, Gensini score >32 points (more advanced)

– the control group – 31 patients (6 women and 25 men), the mean age ± SD – 63 ±10 years, with less severe atherosclerosis, Gensini score <32 points.

We excluded patients with infectious disease in the last 6 months, advanced liver disease, renal failure, anemia regardless of its cause, endocrinologic and other severe diseases, malignant disease and psychiatric diseases.

Written informed consent was obtained from each patient. The protocol of this study was approved by the ethics committee of our institution.

Medical records, physical examinations and blood samples, regardless of the fasting state at that time or not, were taken on admission for ACS. Antropometric variables such as height, hip, waist were measured. The waist to hip ratio (WHR) and body mass index (BMI) in kg/m^2 were estimated.

Blood samples were obtained for cardiac ischemic biomarker: troponin TnT and creatine kinase MB isoenzyme (CK-MB) were measured with the immunoassay method. High sensitivity CRP was measured by latex-enhanced immunonephelometric assay (OLYMPUS), fibrinogen – using the ACL 10,000 analyzer. White blood cell count was measured by automated haematology analyzer %-DIFF-STSTEM XF--4500. Levels of soluble adhesion molecules: sVCAM-1 (normal range: 675–1693 ng/ml) and sICAM (normal range: ≤400 ng/ml) were measured using enzyme linked immunosorbent assay kits supplied by R&D Systems (USA). Total cholesterol, triglyceride, high-density lipoprotein – cholesterol (HDL) were measured by standard laboratory procedures (Biosystems, Spain). Low-density lipoprotein – cholesterol (LDL) was estimated using the Friedewald formula (at triglycerides <400 mg/dl) [14]. Hemoglobin A_{1c} measurement was carried out by high-performance liquid chromatography; normal range: 3.5–6.1%. Plasma glucose levels were determined by a glucose oxidase method and insulin by using an immunoenzymatic assay (ELISA) using the DakoCytomation kits (Denmark), normal range for insulinemia 11–86 pmol/l in serum. The homeostasis model assessment of insulin resistance (HOMA-IR) was determined based on the formula: insulinemia/22.5xe–ln glikemia. Adiponecitin was determined in serum by ELISA (R&D Systems), normal range: 0.87–21.4 μg/ml.

All patients underwent selective coronary angiography, and the extent of coronary stenosis was assessed using a scoring system. Echocardiography with assessment of left ventricular ejection fraction was obtained on the fifth day from the onset of chest pain (ejection fraction – EF).

Statistical analysis

Clinical and biological variables were compared by different methods depanding on the nature of variables. Data are shown as mean ± SD. Continuosus quantitative data were

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Table 1. Demographic and clinical characteristics of the study populations

	Study group GS >32 (n = 42)	Control group GS <32 (n = 31)	Significance
Age (yr)	64.6 ±9.6	63.6 ±10.7	NS
Gender (female/ male)	23/18	25/6	p <0.05
BMI (kg/m^2)	30 ±4.3	29.7 ±5.2	NS
Waist (cm)	100 ±11.0	103 ±8.4	NS
WHR	0.94 ±0.06	0.96 ±0.058	NS
Smokers (yes/no)	23/8	23/18	p <0.05
Hypertension (yes/no)	36/5	21/10	p <0.05
Duration of diabetes (yr)	5.7 ±2.2	3 ±2.2	p <0.05

Data are mean ± standard deviation or number. Abbreviations: BMI – body mass index, GS – Gensini score index, NS – statistical nonsignificant, WHR – waist to hip ratio

compared by matched Student t-test. Because results showed nongaussian distribution, data were presented as medians; comparison was performed with the Mann-Whitney U test. Categorical quantitative data were compared by χ^2 test with Yates correction or the Fischer test (depending on the numbers of subgroups). Correlation coefficients were calculated according to Spearman analysis.

All analyses were performed using STATISTICA 5.5 PL 2000 (StatSoft, Tulsa, USA).

RESULTS

The clinical characteristics of the patients are presented in detail in table 1. There were no significant differences in gender, age, BMI, WHR and waist between the two groups.

Compared with the control group, among the study group, there were more women with hypertension and smoking. The duration of type 2 diabetes was significantly longer in this group than in controls (5.7 ±2.2 vs. 3 ±2.2, years; p <0.05).

In STEMI patients with more advanced lesions, serum troponin T and MB isoenzyme levels (Tab. 2) and serum inflammatory markers (Tab. 3) were higher than in others.

There were no differences in serum total cholesterol, LDL – cholesterol, HDL – cholesterol and triglycerides levels and also in HOMA-IR and left ventricular ejection fraction that were measured on the fifth day from onset of chest pain in both groups. The mean value of blood hemoglobin A_{1c} was 7.3 ±1.4% and was higher than in controls (6.5 ±1.3%; p <0.005). There was no relationship between duration of type 2 diabetes and advanced coronary artery disease (Tab. 2).

Adiponectin was lower in the study group compared with controls (5.8 ±5.2 vs. 8.3 ±2.9 μg/ml; p <0.05) (Fig.). There was a negative correlation (r = –0.54; p <0.05) between adiponectin levels and single or multiple complex lesions among diabetes patients with STEMI and GS >32, but it was not observed in patients with STEMI and GS <32.

There was a negative correlation between adiponectin and sVCAM concentrations (r = –0.68; p <0.05) among the patients with CAD with multiple complex lesions. There was a negative correlation (r = –0.62; p <0.05) between concentrations at adiponectin and CRP in the control group. There were no significant relationships between adiponectin and other inflammatory markers in both groups.

DISCUSSION

Type 2 diabetes increases the risk of ACS. Classical risk factors for atherosclerosis, including arterial hypertension, dyslipidemia, smoking, as well as overweight and obesity, occur in combination in diabetics. In the absence of diabetes, women have less atherosclerosis than men do, but this female advantage is lost in the presence of diabetes [19]. The presence of metabolic abnormalities characteristic of diabetes may contribute to the premature and accelerated development of atherosclerosis in the coronary arteries.

Epidemiologic studies of Framingham and Multiple Risk Factor Intervention Trial (MRFIT) [20] showed that diabetic subjects have a 2–4-fold increased risk factor for coronary artery disease compared with nondiabetic subjects. Therefore, investigators seek new prognostic factors in the development of atherosclerosis in this patient group. Inflammatory markers and adiponectin belong to these factors.

In the present study, the patients with multiple complex lesions in coronary arteries (GS >32) were studied. The causes of severe atherosclerosis among these patients may be established risk factors (hypertension, smoking) but also longer duration of diabetes.

Moreover, lower adiponectin level was found in the study group- low serum adiponectin level in diabetes is prognostic

Table 2. Biochemical characteristics of the study group

Parametry	Study group GS >32 (n = 42)	Control group GS <32 (n = 31)	statistically significant
Troponin T (ng/ml)	1.39 ±1.27	0.83 ±0.74	p <0.05
CK-MB (IU/l)	139.6 ±178.5	57.48 ±52.1	p <0.05
Serum total cholesterol level (mg/dl)	192 ±40.2	210 ±54.7	NS
Serum LDL cholesterol level (mg/dl)	127 ±51	108 ±36	NS
Serum triglyceride level (mg/dl)	174 ±134	194 ±111	NS
Serum HDL cholesterol level (mg/dl)	49 ±11.8	51 ±14.5	NS
Hemoglobin A_{1c} (%)	7.3 ±1.4	6.5 ±1.3	p <0.05
HOMA-IR	4.6 ±2.1	4.9 ±2	NS
EF (%)	50 ±12.5	54 ±7.6	NS

Data are mean ±standard deviation or number (percent). Abbreviations: CK-MB – creatine kinase MB isoenzyme, EF – ejection fraction, hemoglobin A_{1c} – glycated hemoglobin, HDL – high-density lipoprotein, HOMA-IR – insulin resistance index, LDL – low-density lipoprotein, others – see Table 1

Table 3. Markers of inflammation and endothelial injury

Parametry	Study group GS >32 (n = 42)	Control group GS <32 (n = 31)	statistically significant
Serum CRP level (mg/dl)	12.06 ±14.31	3.59 ±4.1	p <0.05
Serum fibrinogen level (g/l)	4.59 ±1.93	3.62 ±1.36	p <0.05
Leukocytes (/μl)	11 430 ±3680	9750 ±3100	p <0.05
sVCAM-1 (ng/ml)	1393.4 ±865.4	863.9 ±425.2	p <0.05
sICAM-1 (ng/ml)	735.1 ±316.3	573.3 ±226.1	p <0.05

Data are mean ±standard deviation. Abbreviations: CRP – C-reactive protein, sICAM-1 – soluble intracellular adhesion molecule-1, sVCAM-1 – soluble vascular adhesion molecule-1, others – see Table 1

factor for prevalence acute coronary syndrome (ACS). There was negative relationship between adiponectin and sVCAM levels in patients with multiple complex lesions. It was confirmed by Ouchi et al. [16,17], who showed that adiponectin could reduce atherosclerosis by inhibiting endothelial expression of adhesion molecules, sVCAM-1, sICAM-1, E-selectin.

Serum adiponectin levels in patients with diabetes depend on a number of factors, like female gender and overweight. Schaeffler at al. [21] reported elevated adiponectin levels in overweight women with diabetes compared with in men. Moreover, there was no such relationship in nondiabetic patients in our study. Miyazaki et al. [22] demonstrated that among patients with coronary artery disease, serum adiponectin levels were lower in current smokers than in never smokers. Some investigators suggested that the adiponectin concentration is dependent on duration of diabetes. Looker at al. [23] showed among 724 Indian Pima that elevated serum adiponectin levels were associated with duration of diabetes.

Inflammation plays a major role at all stages of atherosclerosis and can cause ACS. Elevated CRP, fibrinogen, adhesion molecules sVCAM, sICAM levels and increased number of white cell count were found in patients with ACS and severe atherosclerosis compared with diabetes patients with less advanced atherosclerosis. Elevated CRP levels in ACS patients are associated with local inflammation in plaque, predisposing the plaque to rupture. It was confirmed by Versaci et al [24], who showed, that elevated levels of CRP was observed in patients undergoing percutaneous transluminal coronary angioplasty after stent implantation (local in the arterial wall). A few-fold increase in CRP levels was observed by Pudil et al. [25] in patients during the first hours after the onset of acute myocardial infarction and reached a peak value on the second day [26]. Quantitative CRP and troponin T help make prognosis [25]. In the published data in 2000 [27], there was a relationship between CRP levels and complexity of culprit coronary lesions. In multivariate analysis including age, gender, smoking, hypertension, diabetes, hyperlipidemia and family

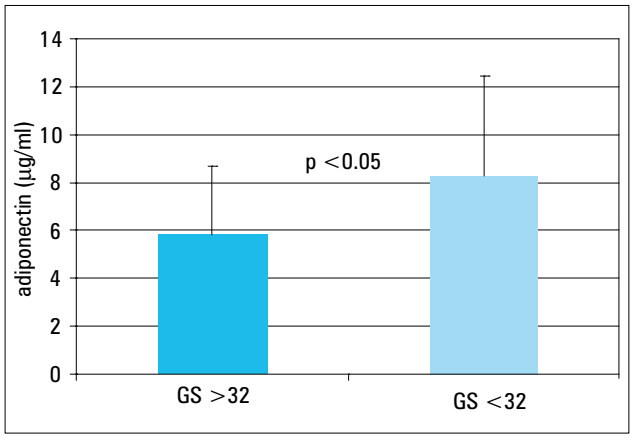

Fig. Serum adiponectin concentration (µg/ml). GS – Gensini score index

history, only CRP levels correlated with anatomic complexity of coronary atherosclerotic lesions [27].

The associations between fibrinogen and ACS were observed in the Northwick Park Heart Study [28]. In this study, among white men there was a relationship between increased fibrinogen levels and cardiovascular events during a 4 to 5-year follow-up. In the Scottish Heart Study [29], performed in 10,000 patients, it was shown that fibrinogen increases proportionally to the severity of coronary disease, with the highest levels of fibrinogen among patients who died from coronary events. This correlation was not so strong among women, because there were less cardiovascular events and lower levels of fibrinogen in this population [29]. In the study of Abrignani et al. [30], elevated fibrinogen levels were found in patients with Q wave myocardial infarction compared with patients with other types of ACS, and these patients showed a further increase in fibrinogen on day 5 in comparison with baseline levels regardless of the administration of fibrinolytic treatment or not. Filipiak et Opolski [31] showed a positive correlation between fibrinogen levels and the severity of coronary atherosclerotic lesions.

In several clinical and epidemiological studies, serum levels of soluble adhesion molecules, considered as markers of inflammatory activity that may predict the occurrence of ACS were measured. Wallen et al. [32] showed that patients with acute coronary syndrome had elevated serum levels of soluble adhesion molecules and the value of soluble adhesion molecules could be as prognostic markers in patients with stable ischemic heart disease. Mulvihill et al. [33] demonstrated that elevated levels of sVCAM-1 in patients with stable ischemic heart disease is a prognostic factor for recurrent ACS within six months.

In conclusion, the present study demonstrates that among acute coronary syndrome patients with type 2 diabetes treated with oral hypoglycemic agents, the presence of more advanced coronary lesions can be associated with hypoadiponectinemia, elevated inflammatory activity, along with coexistent classical atherosclerotic risk factors (arterial hypertension, smoking) and diabetes-related factors (duration of diabetes, poor metabolic control). This cross-over study does not, however, allow establishing the cause-and-effect relationship between decreased serum adiponectin levels and the severity of atherosclerotic lesions. It cannot be excluded that there is such a link, as hypoadiponectinemia is commonly accompanied by insulin resistance and metabolic syndrome, well known as atherogenic states.

In summary, our findings indicate that in patients with type 2 diabetes and ACS treated with sulphonylurea, there are lower adiponectin levels and enhanced subclinical inflammatory state and endothelial dysfunction coronary lesions, that may be accounted for by advanced atherosclerotic lesions in the coronary arteries.

Conclusions from the present study are as follows:

1) among acute coronary syndrome patients with type 2 diabetes, treated with sulphonylurea, lower adiponectin concentrations are associated with more advanced coronary lesions
2) lower levels of adiponectin in patients with type 2 diabetes correlate with more advanced atherosclerotic lesions in the coronary arteries among patients with STEMI and GS >32; such a correlation is not observed in patients with STEMI and GS <32
3) among acute coronary syndrome patients with type 2 diabetes, treated with sulphonylurea, the degree of atherosclerotic lesions in the coronary arteries are associated with active inflammatory state
4) elevated inflammatory markers (sVCAM-1 and CRP) correlate with low serum adiponectin levels among acute coronary syndrome patients with type 2 diabetes and ACS.

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