Influence of adiponectin and glycated hemoglobin in prediction of major adverse cardiac events in non-diabetic patients after ST-segment elevation myocardial infarction

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This dissertation was made at the Institute of Cardiovasular Disease, Dubrava University Hospital, Zagreb and Clinic of Cardiology, University Clinical Centre of Kosova, Prishtina.

Mentor: Professor Josip Vincelj, MD, PhD

Co-mentor: Professor Masar Gashi, MD, PhD

Acknowledgement

I would like to gratefully thank Professor Josip Vincelj for supervision. I am also very grateful to Professor Masar Gashi, my co-supervisor being involved in this work. Many thanks go to all the colleagues at Dubrava University Hospital and University Clinical Centre of Kosovo who contributed in different ways to the completion of this work. Finally, I would like to thank my family for their support and motivation during the studies.

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ABBREVIATIONS

ACC - American College of Cardiology

AHA- American Heart Association

ADIPOR1 - Adiponectin receptor 1

ADIPOR 2 - Adiponectin receptor 1

AMP - Adenosine monophosphate

AMI - Acute myocardial infarct

AMPK - Adenosine monophosphate–activated protein kinase

apM1 - Adipose most abundant gene transcript

Arcp30 - Adipocyte complement-related protein of 30 kDa

BMI - Body mass index

BSA - Body surface area

CAD - Coronary artery disease

CABG Coronary artery bypass grafting

COX-2 - Cyclooxygenase 2

E/A - Transmitral early diastolic velocity/ Transmitral late diastolic velocity

ELISA - Enzyme linked immunosorbent assay

eNOS - Endothelial nitric oxide synthase

ESC - European Society of Cardiology

FGF21 - Fibroblast growth factor 21

GBP28 - gelatin-binding-protein, molecular-weigh about 28 kDa

HbA1C - Glycated hemoglobin

HDL - High density lipoprotein

HIF-1α - Hypoxia-inducible factor 1α

ICAM-1- Intercellular Adhesion Molecule 1

iNOS - Inducible nitric oxide synthase

IVS - Interventricular septum

LDL - Low density lipoprotein

LVA - Left ventricular anatomy

LVEdD - Left ventricular end-diastolic diameter

LVEF - Left ventricular ejection fraction

LVEsD - Left ventricular endsystolic diameter

LVH - Left ventricular hypertrophy

LVM - Left ventricular mass

LVMI - Left ventricular mass index

LVR - Left ventricular remodelation

MACE - Major adverse cardiac events

NO - Nitric oxide

oxLDL - Oxidized low density lipoprotein

PPAR - Anti-inflammatory peroxisome-proliferator-activated-receptor

ROS - Reactive oxygen species

RWT - Relative wall thickness

SD - Standard deviation

T-Cad - T-cadherin receptor

TNFα - Tumor necrosis factor alpha

USPSTF - U.S. Preventive Services Task Force

VCAM-1 - Vascular cell adhesion protein 1

1. INTRODUCTION AND OBJECTIVE OF THE STUDY

Coronary artery disease, including myocardial infarction, is the major cause of death in many countries (1-5). The high level of glycemia after acute myocardial infarction in non-diabetic patients is shown to be a predictor of adverse outcomes (6-10). It has been reported that elevated glucose levels increase inflammatory response in patients with acute myocardial infarction (11, 12), and also may be associated with increased free fatty acids which may increase infarct size (13, 14).

The role of novel protein adiponectin in metabolic and inflammatory process after acute myocardial infarction is shown to be very important. However, the different actions of adiponectin are poorly understood, and effects of adiponectin in microvascular damage and angiogenesis have not been thoroughly elucidated to date.

1.1. Adiponectin and coronary artery disease

Adiponectin is protein hormone consisting of 244 amino acids secreted from adipose tissue, in humans is encoded by the ADIPOQ gene located on chromosome 3q27. This novel protein hormone was first detected in mouse from Scherer et al. and called “Adipocyte complement-related protein of 30 kDa” (Arcp30) (15). The human homologue was identified in adipose tissue from Matsuzawa et al., and called “adipose most

abundant gene transcript 1"(apM1) (16). Tomita et al. identified adiponectin as a „gelatin-binding-protein" as a molecule of about 28 kDa (GBP28) (17).

Recent studies suggest that it is also synthesized and secreted by human cardiomyocytes (18). Circulating adiponectin levels in humans account for approximately 0.01% of all plasma proteins. Adiponectin modulates a number of metabolic functions by receptors ADIPOR1 and ADIPOR 2 and T-Cad (19, 20). Denzel et al. showed that T-cadherin is required for the binding of adiponectin to cardiomyocytes (21). However, the precise mechanisms of adiponectin activation are still not fully elucidated.

Adiponectin has been shown to increase AMPK-Akt- phosphorilation pathway and to stimulate anti-inflammatory peroxisome-proliferator-activated-receptor (PPAR)-α- effect (22). PPAR agonists were observed as potential target to reduce cardiovascular risk (23). It has been reported that therapy with Thiazolidindione increase the level of adiponectin (24). Adiponectin increases insulin sensitivity and lipid B-oxidation while decreasing gluconeogenesis, and by these mechanisms reduces hyperglycemia and hyperlipidemia, which was reported to have adverse impact on ischemic cardiomyocytes in experimental models (25, 26). Paradoxically, although adiponectin is a hormone secreted from adipose tissue, adiponectin levels inversely correlate with body weight and obesity. Previous clinical studies also have shown that adiponectin negatively correlates with blood pressure, fasting plasma glucose, insulin resistance, LDL-cholesterol, and triglycerides whereas positively correlates with HDL-cholesterol (27-31). In a 10-year follow-up of healthy elderly patients, higher adiponectin levels were associated with a lower risk of CAD independent of other risk factors such as increased BMI and insulin resistance (32).

Experimental and human studies indicate that adiponectin has antiatherogenic and anti-inflammatory effects (33-38) whereas low plasma adiponectin levels are associated with complexity of coronary lesions and future cardiac events in patients with coronary disease (39-45). Kumada et al. found a low level of adiponectin in patients with coronary artery disease than in placebo-group (40). Adiponectin has also been shown to regulate coronary flow reserve in non-diabetic patients with normal coronary arteries (46).

Effects of adiponectin in endothelial vascular cells are not clear. Binding of adiponectin to endothelial cells was first described by Ouchi et al., and they reported that adiponectin inhibits the expression of adhesion molecules, including intracellular adhesion molecule-1, vascular cellular adhesion molecule-1 and E selectin (47, 48) (Figure 1). Adiponectin has also been shown to increase NO production by activation of the AMPK-Akt-eNOS phosphorilation pathway and to contribute in vasodilatatory cardioprotective effects (49, 50) (Figure 2). However, Tao et al. suggest that adiponectin increases NO by this pathway just under physiological conditions whereas under pathological conditions adiponectin inhibits NO overproduction by inhibiting iNOS expression and thus protects the heart from nitrative stress (51, 52). Paradoxically, reperfusion of ischemic myocardium itself can result in myocyte death. This process is termed reperfusion injury. The critical role of adiponectin in protection against heart injury and failure was proven in mouse models (56). Production of TNF-α after ischemia–reperfusion injury has been shown to have a major role in apoptosis and myocardial damages (53, 54). Shibata et al. reported that adiponectin has anti-apoptic activities through its ability to activate the AMPK protective signaling pathway whereas by COX-2 adiponectin has inhibitory effect on TNF-α production and protects against the development of systolic dysfunction following

myocardial infarction (55, 56). Adiponectin is detected in the injured vessels but not in the intact vascular walls in humans and rodens (57). Adiponectin has also been reported to stimulate the new blood vessel growth by promoting AMP and Akt pathway (49) but a recent study reported that adiponectin is essential for the proangiogenic benefits of cell therapy (58).

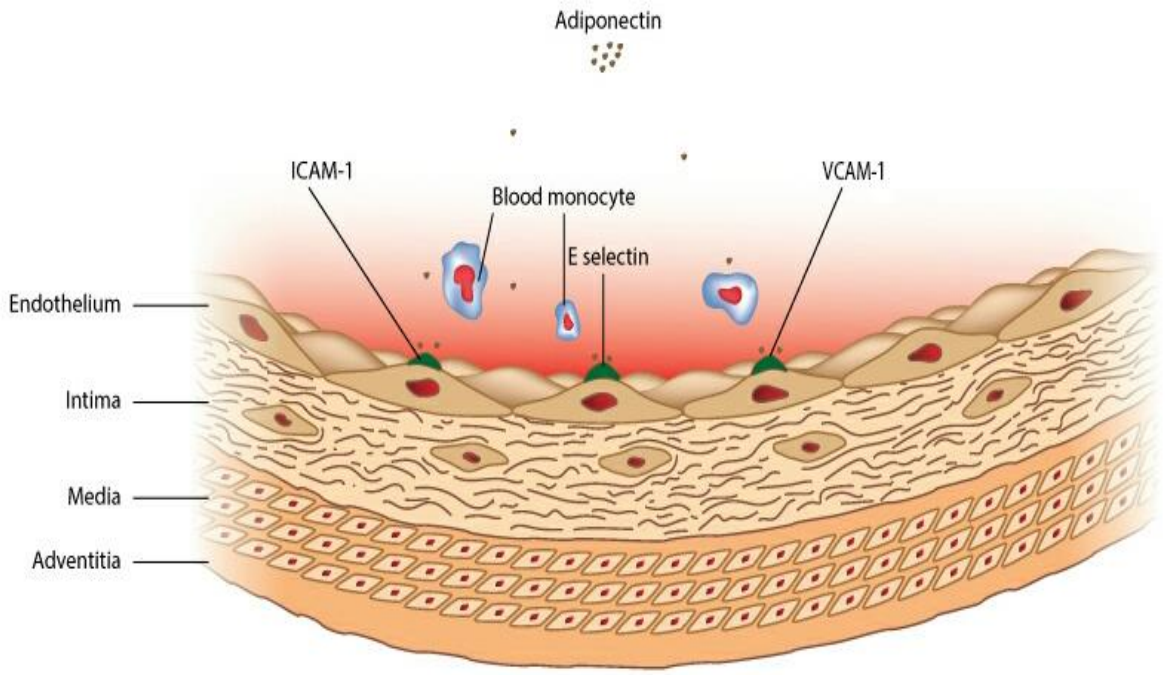

Figure 1. Adiponectin inhibits the expression of adhesion molecules ICAM-1, VCAM-1 and E-Selectin.

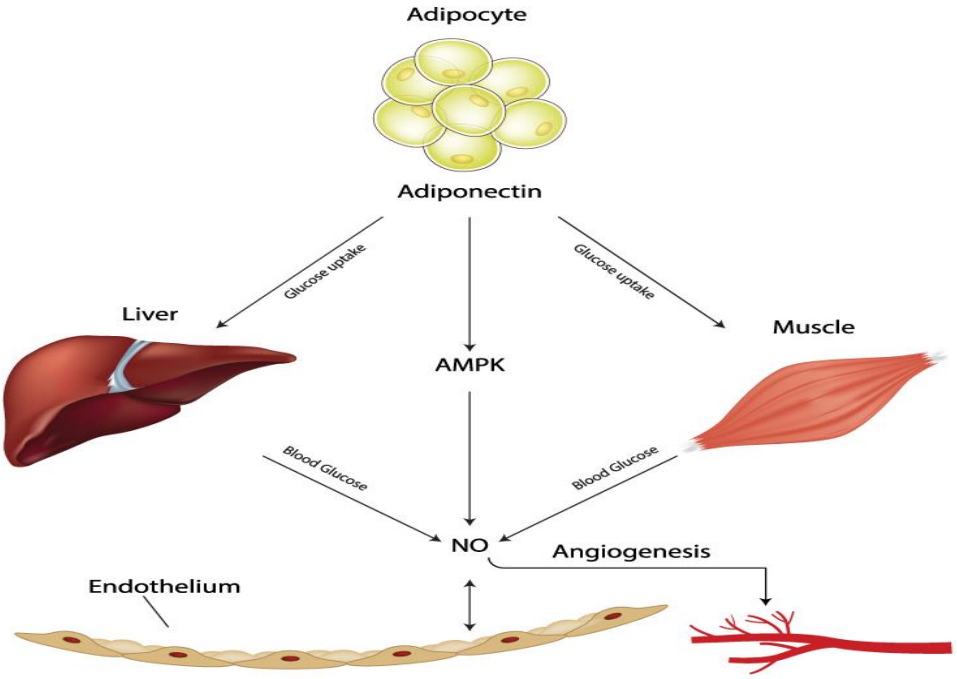

Figure 2. Adiponectin increases NO production directly by activation of the AMPK and indirectly by reducing the glucose level which contributes in vasodilatatory cardioprotective effects and angiogenesis.

1.2. Glycated hemoglobin and myocardial infarction

Hemoglobin consists of globin protein synthesized by ribosomes in the cytosol and hem part synthesized in the mitochondria while in adult humans the most common type is hemoglobin A. Exposure of hemoglobin to high plasma levels of glucose results in glycation of hemoglobin in non-enzymatic pathway and the use of HbA1C as a parameter for monitoring of glucose metabolism was proposed by Koenig et al. (59).

The high level of glycemia in diabetes mellitus type 2 is believed to be a result of defective sensitivity of insulin receptors in human tissue. However, the specific metabolic mechanisms in non-diabetic patients after myocardial infarction are not very clear.

Many studies have shown that abnormal glucose tolerance is common among patients with acute myocardial infarction who have no previous diagnosis of diabetes (60-63). The Euro Heart Survey on diabetes and the heart reported that 36% of observed non-diabetic patients with acute coronary syndrome had impaired glucose tolerance (64).

Fasting glucose and HbA1C are useful in predicting abnormal glucose tolerance in non-diabetic patients who survived AMI (65), whereas elevated HbA1C is also shown to be an independent risk predictor after AMI (66, 67).

The specific mechanisms that contribute to the development and progression of micro- and macrovascular alterations in non-diabetic patients with myocardial infarction are not very clear. After acute myocardial infarction, the decreased partial pressure of cellular oxygen expresses the HIF-1α which activates genes involved in angiogenesis, glycolysis and modulation of vascular tone. A previous study showed that HIF-1α expression is

kinase and phosphatase activity dependent (68) whereas experimentally nitric oxide donors reported to induce HIF-1α expression in cultured human cells independent of a cyclic guanosine monophosphate-mediated pathway (69). Hyperglycemia has been reported to be responsible for pseudohypoxia which is associated with increased production of NO (70) and this could induce HIF-1α expression but studies in experimental models showed that hyperglycemia is associated with reduced expression of the HIF-1α gene, therefore effects of reactive oxygen species produced (ROS) during hyperglycemia should be considered (22). In diabetes mellitus, the microvascular flow is disturbed (71). Studies in autopsied hearts have shown that angiogenesis induced after ischemia is impaired in hearts of diabetic patients compared with infarcted hearts of normoglycemic non-diabetic patients (72). It has been shown that in patients with MI, hyperglycemia reduces collateral flow and may be related to the no-reflow phenomenon (73, 74).

1.3. Atherosclerosis and angiogenesis

The process of atherosclerosis is complex due to inflammatory response in the walls of arteries. Endothelial dysfunction and oxidative modification of LDL appear to be the starting points of the chronic inflammatory process which may lead to the accumulation of macrophages in atrial wall and to the formation of atherosclerotic plaques (75). Adiponectin showed also to reduce the retention of atherogenic lipoprotein particle concentrations in atherosclerotic lesion by activation of specific enzymatic pathways (76, 77). The oxidation of LDL is a complex process during which both the protein and the lipids undergo oxidative changes and form complex products. Under conditions of

oxidative stress, the LDL particles are easily oxidized (78, 79). Increased oxLDL levels in circulation and the vessel wall are associated with endothelial dysfunction by reduction of the expression of eNOS (80, 81), oxLDL induced HIF-1α accumulation and HIF-1–dependent reporter gene activation in human macrophages via a redox-mediated pathway (82).

Adiponectin plays critical roles in metabolic regulation and maintenance for whole body energy homeostasis. Adiponectin exerts anti-atherosclerotic effects through anti-inflammatory effects and antiatherogenic effects (Figure 3). In experimental studies, adiponectin inhibits oxLDL-induced cell proliferation by suppressing cellular superoxide generation. Adiponectin reduces the ability of macrophages to transform into foamy cells (83). It has been recently reported that FGF21-adiponectin axis controlling energy and vascular homeostasis and protects against of cardiometabolic disorders. The FGF21 is shown to protect atherosclerosis via induction of adiponectin in adipose tissue and suppression of cholesterol biosynthesis in the liver (84, 85). FGF21 plays an essential role in preventing against damages caused by myocardial infarction by attenuation of cardiomyocyte apoptosis, oxidative stress, and inflammatory responses (86-88).

Patients with complete coronary artery occlusion manifest ST-segment elevation myocardial infarction. A similar occlusion in the presence of extensive collaterals may present as a myocardial infarction without ST-segment elevation. Adiponectin’s ability to promote angiogenesis has been shown to be beneficial in its ability to prevent ischemia (89). In previous experimentally studies showed that capillary density was significantly decreased in adiponectin deficient mice. However, the receptors mediating the protective effects of adiponectin on the vasculature are not very clear. A recent study reported that

T-cadherin is essential for adiponectin-mediated revascularisation (90). Ohashi et al. reported that adiponectin promotes revascularisation of ischemic muscle through a calreticulin/CD91–PI3K–Akt–COX2signaling pathway (91).

Physiological plasma concentrations of adiponectin promote the migration of endothelial progenitor cells and contribute to the process of new vessel formation. These results suggest therapeutic neovascularisation by adiponectin supplementation may be useful in patients with ischemic heart disease (92).

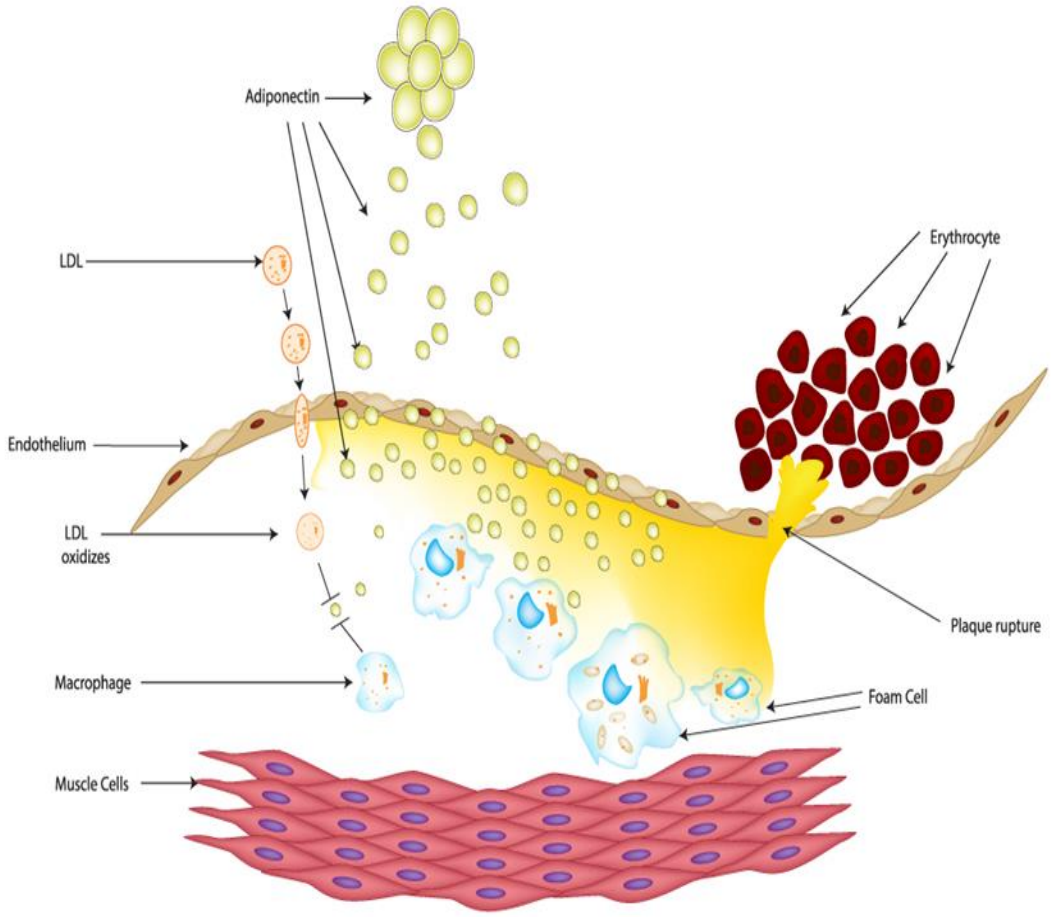

Figure 3. Schematic drawings of atherosclerosis process. Adiponectin inhibits oxLDL and reduces the ability of macrophages to transform into foamy cells. This results in adiponectin consumption in the circulating plasma.

2. HYPOTHESIS

We hypothesized that hypoadiponectinemia might be associated with hyperglycemia and MACE in non-diabetic patients who survived ST-elevation myocardial infarction (STEMI).

3. AIMS AND PURPOSE OF THE RESEARCH

3.1 Aims of the research

- Aims:

The main aim of this study was to measure the levels of HbA1C and adiponectin and to investigate the association of these parameters with major adverse cardiac events in non-diabetic patients who survived STEMI.

3.2. Purpose of the research

Purpose of research is to confirm the impact of hyopadiponectinemia as a independent factor in major adverse cardiac events after STEMI. Increasing of adiponectin levels may be a potential target to improve the new microvessel formation and modulation of vascular tone in patients with coronary artery disease independent of the presence or absence of diabetes.

4. MATERIALS AND METHODOLOGY

The definition of MI proposed by the European Society of Cardiology (ESC), the American College of Cardiology (ACC) and the American Heart Association (AHA) requires a typical clinical syndrome plus a rise of cardiac biomarkers (93, 94). The study enrolled prospectively all patients who experienced STEMI infarction without previous diabetes mellitus.

Inclusion criteria:

- Detection of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit together with the presence at least of the following:
- Symptoms of ischemia
- ECG changes:
    - New ST elevation at the J point in two contiguous leads
    - ≥ 0.2 mV in leads V2-V3 (men)
    - ≥0.15mV in leads V2-V3 (women)
    - ≥0.1mV in other leads

Exclusion criteria:

- Previous myocardial infarction
- Previous diabetes mellitus
- Patients with indications for CABG

- Renal insufficiency
- Inflammatory disease
- Acute infective disease

All patients underwent revascularisation therapy according the current guidelines (94).

Blood samples for analyses of adiponectin and HbA1C were collected. Laboratory parameters measured also included: CRP, glycemia, urea, creatinine, HDL, LDL, and triglycerides. Systolic and diastolic pressure was measured according to Riva-Rocci/ Korotkoff technique (95). The values of 140 /90 or more were treated with anitypertensive therapy.

Two-dimensional echocardiography was performed in all patients.

In one-year follow-up, study subjects were observed for major adverse cardiac events: cardiac death, re-infarction, angina pectoris, revascularisation, stroke and congestive heart failure.

4.1. Subjects

The study enrolled prospectively 73 patients who experienced STEMI infarction. The subjects were divided into two groups: 37 patients with elevated glycated hemoglobin (HbA1C), and 36 patients with normal levels of glycated hemoglobin (HbA1C). Glycated hemoglobin level below 6.0% was considered normal. The International Expert Committee recommended that persons with a HbA1C level between 6.0 and 6.5% are at a particularly high risk and might be considered for diabetes prevention interventions (96).

4.2. Reperfusion therapy

Primary percutaneous coronary intervention PCI was performed in non-diabetics with STEMI within 12h of symptom onset (max 120min from STEMI diagnosis). All patients who received fibrinolytic therapy underwent routine early PCI therapy (2-24h after fibrinolytic therapy). Rescue PCI were performed in the case of failed fibrinolysis (Schimadzu, Japan: UCCK, Prishtina, Kosovo; and General Electric, Dubrava University Hospital, Zagreb, Croatia). Successful reperfusion was defined by TIMI grade 3 blow flow. All patients were diagnosed as a 1- , 2-, or 3-vessel Disease according to Severity-Score: stenosis > 50% were considered significant. All patients with indication to CABG were excluded from the study.

Periprocedural pharmacotherapy was performed according to treatment guidelines. Standard therapies after PCI included aspirin 100mg, clopidogrel 75mg, beta-blockers, lipid lowering agents and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, were used according to the current international guidelines (93, 94).

All patients were admitted to Coronary Care Unit and monitored for at least 24 h. All patients were free from symptoms of angina and on optimal preventive therapy.

4.3. Blood sampling and laboratory methods

Blood samples were taken approximately after 30 minutes. Serum samples for adiponectin were subsequently stored at −70°C until biochemical analyses. Serum adiponectin concentrations were measured with Adiponectin ELISA method in room temperature 20-23°C in accordance with the manufacturer's instruction: ELISA Kits

Phoenix Pharmaceuticals, USA, (Awareness Technologies Inc: UCCK, Prishtina, Kosovo; and Siemens BEP 2000: Dubrava University Hospital, Zagreb, Croatia).

HbA1C levels were measured with immunoturbidimetric method (ILAB 650, USA) (99). Other laboratory tests were measured by standard laboratory procedures. The study was approved by the Institutional Ethics Committee and informed consent was obtained from all subjects.

4.4. Two-dimensional echocardiography

Cardiac structure and function were assessed using two-dimensional transthoracic echocardiography performed by cardiologists who were blind to the adiponectin and glycemic state. All echocardiographic examinations were carried out using 2.5–3.5 MHz transducer (Philipps IE33 and General Electrics). The standardized scan planes were performed (the apical four chamber view, the apical two-chamber view, the parasternal long-axis view and parasternal short-axis view. LVEF was derived from a modified Simpson‘s formula. The value below 55% were considered pathological. Interventricular diastolic septal thickness (IVSd), LV diastolic diameter (LVDd), LV systolic diameter (LVDs) and left atrial diameter were determined. The peak velocity of early (E) and late (A) waves were determined from transmitral flow velocity and the ratio E/A was calculated. After performing echocardiography, we measured left ventricular mass (LVM) determined according to the formula introduced by Devereux et al. (98). LVM was subsequently adjusted for body surface area (BSA) to obtain the LVM index (LVMI) value: LVMI (g/m^2) = LVM/BSA. Left ventricular hypertrophy (LVH) was defined as LVM/BSA

>95 kg/m^2 for women and >115 kg/m^2 for men. Relative wall thickness (RWT) >0.42 was considered normal, determined according to the formula: 2*PWd/LVEDD (98, 99).

Normal LVMI and RWT were defined as normal LV anatomy, normal LVMI with increased RWT as concentric LV remodeling, increased LVMI and increased RWT as concentric LVH and increased LVMI with normal RWT as eccentric LVH.

4.5. Statistical analysis

Descriptive data are presented as means ± standard deviation (SD) for normally distributed variables or as medians, interquartile range, for other variables. Comparisons between groups were performed by Student's t-test. Categorical data were analyzed using the chi-square test when appropriate. Relationships between parameters were assessed by Spearman's and Pearson's correlation analyses. Univariate and multivariate logistic regression analysis was used to determine the predictors of MACE. The significance of associations between categorical variables was analysed by Fisher's exact test. P values of < 0.05 were considered to be significant. Data were analyzed using SPSS statistical software, version 22 .

4.6. Ethical consideration

The study was approved by the institutional Ethics Committee of Dubrava University Hospital-Zagreb and the University Clinical Center of Kosova-Prishtina.

All patients were informed about the aim and procedures of the study. Written informed consent were obtained from all patients before inclusion in the study.

5. RESULTS

5.1. Baseline clinical characteristics of participants

The mean age of 73 patients (55 males) was 65.9± 11 years. The baseline characteristics of study population are presented in Table 1. There were 50 patients with 1 –vessel disease and 23 patients with multiple-vessel disease without significant difference between group 1 and group 2. The HbA1C value in all study patients was between 4.9-9.9% (Mean: 6.16, SD±0.968). No statistically significant differences were observed between group 1 and group 2 regarding fasting glucose, hypertension, LDL and triglyceride level (p=0.59, p=0.621, p=0.385, p=0.345). Serum values of HDL were significantly lower in patients with elevated HbA1C than in group 2 (p = 0.004). CRP levels were also significantly different between groups (p=0.038). Mean adiponectin level was significantly lower in group 1 than in group 2 (p = 0.004). There was not any significant difference in blood pressure values (p = 0.621, p = 0.214). The frequency of MACE was significantly higher in group 1 than in group 2 (p = 0.048). In group 1, 7 cases had angina pectoris, 6 cases had congestive heart failure, 1 case had cardiac death and 2 cases underwent emergency revascularisation. In group 2, there were 5 cases of angina pectoris, 2 cases of congestive heart failure and 1 case of emergency revascularisation.

Table 1. Baseline clinical characteristics of study population

Parameter	Total(n=73) (n=73)	HbA1C>6% (n=37)	HbA1C<6% (n=36)	*p*
Age, years	65.97±11.8	69.2±10.86	62.5±11.95	.015
Male, n (%)	55 (75.3)	28 (75.7)	27 (75)	.948
BMI (kg/m²)	27.9±3.99	28.8±3.9	27±3.924	.046
Current smoker, n (%)	24 (32.9)	14 (37.8)	10 (27.7)	.368
Systolic BP (mmHg)	137.9±21	136±16.1	139±25.41	.621
Diastolic BP (mmHg)	81.5±12.5	79.7±10.68	83.3±14.06	.214
Glucose (mmol/l)	7.29±2.1	7.77±2.61	6.79±1.44	.059
Adiponectin (ng/ml)	2.28±2.08	1.59±1.56	2.98±2.32	.004
HDL cholesterol (mmol/l)	1.08±0.37	.958±.185	1.20±.462	.004
LDL cholesterol (mmol/l)	3.49±0.98	3.39±1.07	3.59±.883	.385
Trigliceryde (mmol/l)	2.03±1.57	2.21±1.82	1.86±1.25	.345
Creatinine (µmol/l)	98.6±22.8	99.7±23.7	95.4±27.3	.472
Urea (mmol/l)	6.77±2.78	7.26±3.35	6.27±1.98	.130
CRP (mg/l)	18.1±42.4	28.2±56.3	7.74±13.4	.038
Coronary artery disease				
Single-vessel, n (%)	50 (68.5)	21 (56.8)	29 (80.6)	
Multiple-vessel, n (%)	23 (31.5)	16 (43.2.)	7 (19.4)	.062
Killip classification				
Killip =1, n (%)	56 (76.7)	23 (62.2)	33 (91.7)	
Killip>1, n (%)	17 (23.3%)	14 (37.8)	3 (8.33)	.001
Medication use				
β-Blocker, n (%)	24 (32.9)	14 (37.8)	10 (27.8)	.257
ACEI/ARB, n (%)	30 (42)	16 (43.2)	14 (38.8)	.710
MACE yes, n (%)	24 (32.8)	16 (43.2)	8 (22%)	.048

Data are expressed as n (%) and mean ± standard deviation. BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker, MACE: major adverse cardiac events.

5.2. Echocardiographic outcomes of participants

Echocardiographic outcomes of study subjects for the two groups are presented in Table 2. No statistically significant differences were observed between the two groups in LVEF (p = 0.124), LVEdD (p = 0.631), E/A (p = 0.517), LVMI (p = 0.462), and RWT (p = 0.321). Left ventricular remodeling was diagnosed in 36 (49.3%) of patients with higher frequency in patients with HbA1C > 6% (56.8% vs 43.2%), specifically concentric left ventricular remodeling (21,6% vs. 11.1%) and concentric left ventricular hypertrophy (10.8 vs. 5.5%). Eccentric LVH was present in 24,3 vs 25% of patients without any differences between groups (Table 3).

Table 2. Echocardiographic parameters of study groups

	Group 1		Group 2		
Variable	*M*	*SD*	*M*	*SD*	*p*
LVEF %	54.9	8.28	58.1	8.94	.124
LVEdDmm	51.9	61.3	52.6	5.90	.631
LVEs Dmm	36.3	6.66	35.5	6.63	.583
IVS mm	10.9	1.16	10.6	1.73	.324
LPW mm	10.5	1.26	9.94	1.57	.093
E/A	1.00	0.66	1.06	0.71	.517
LVMass (g)	217	48.6	206	63.8	.422
LVM index	108	25.1	103	33.5	.462
RWT	1.50	6.67	.376	.059	.321

Table 3. Left ventricular remodeling frequencies

	HbA1C>6%		HbA1C<6%	
Normal LVA n (%)	**16**	**(43.2)**	**21**	**(58.3)**
LVR n (%)	**21**	**(56.8)**	**15**	**(41.7)**
- Concentric LVR	8	(21.6)	4	(11.1)
- Concentric LVH	4	(10.8)	2	(5.5)
- Eccentic LVH	9	(24.3)	9	(25.0)

LVA: left ventricular anatomy, LVR: left ventricular remodelation, LVH: left Ventricular hypertrophy

5.3. Association of adiponectin levels and HbA1C with left ventricular function

Patients with previous coronary disease and known low-LVEF were excluded from the study. The mean LVEF% of patients after successful revascularisation was borderline and lower in Group 1 than in Group 2 (54.9% vs 58.1%), without any statistically significant difference between the two groups ($p = 0.124$). To test the correlation between adiponectin and LVEF, Pearson's correlation test was performed but no significant correlation found (Figure 4). Although the incidence of LV remodeling in the study patients was high, no statistically significant correlation between adiponectin and LVEdD was found (Figure 5). We found also no statistically significant correlation between HbA1C and LVEdD (Figure 6).

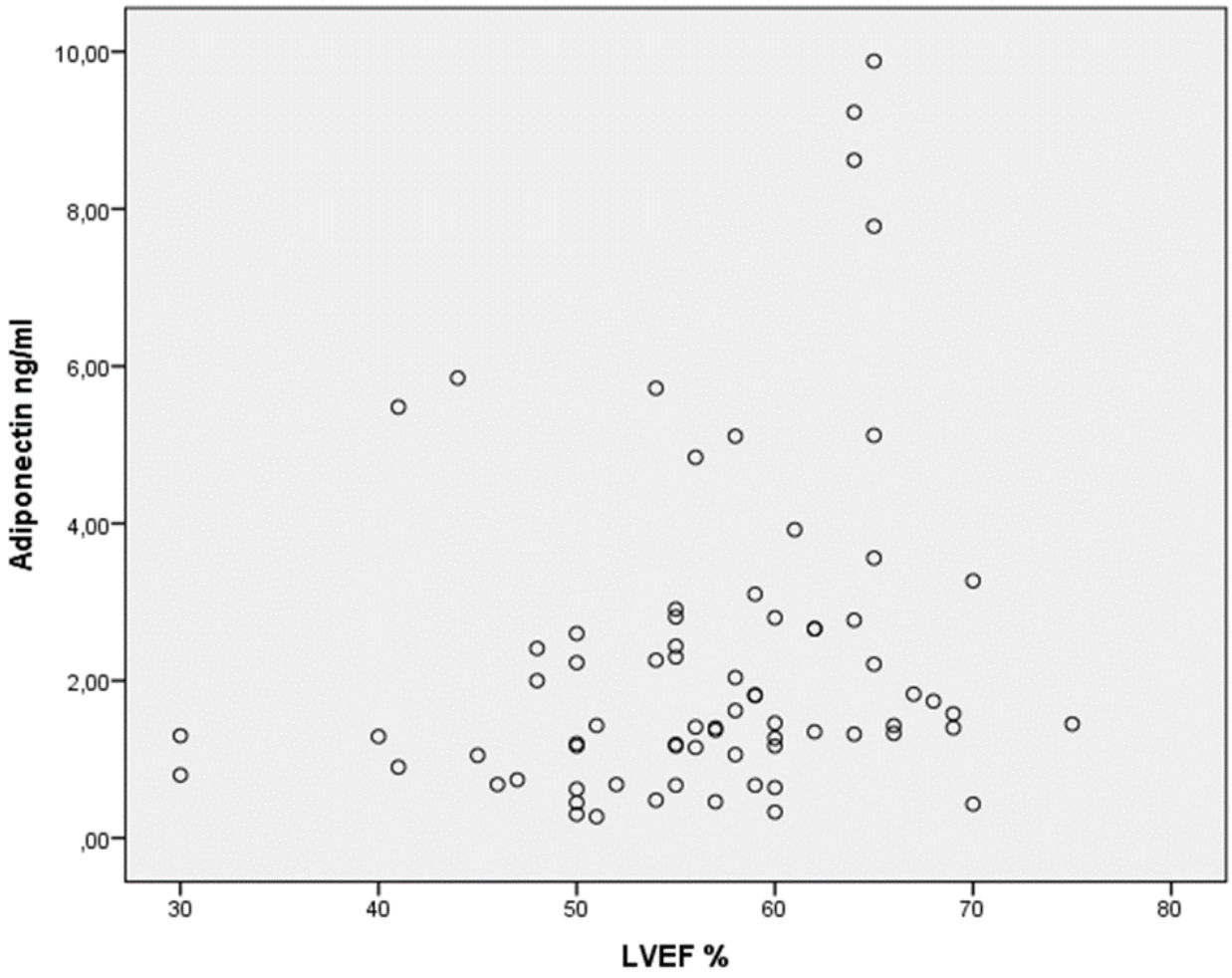

Figure 4. Correlation between adiponectin and LVEF% in all study patients (Pearson's correlation coefficient r = -.209, p = 0.075)

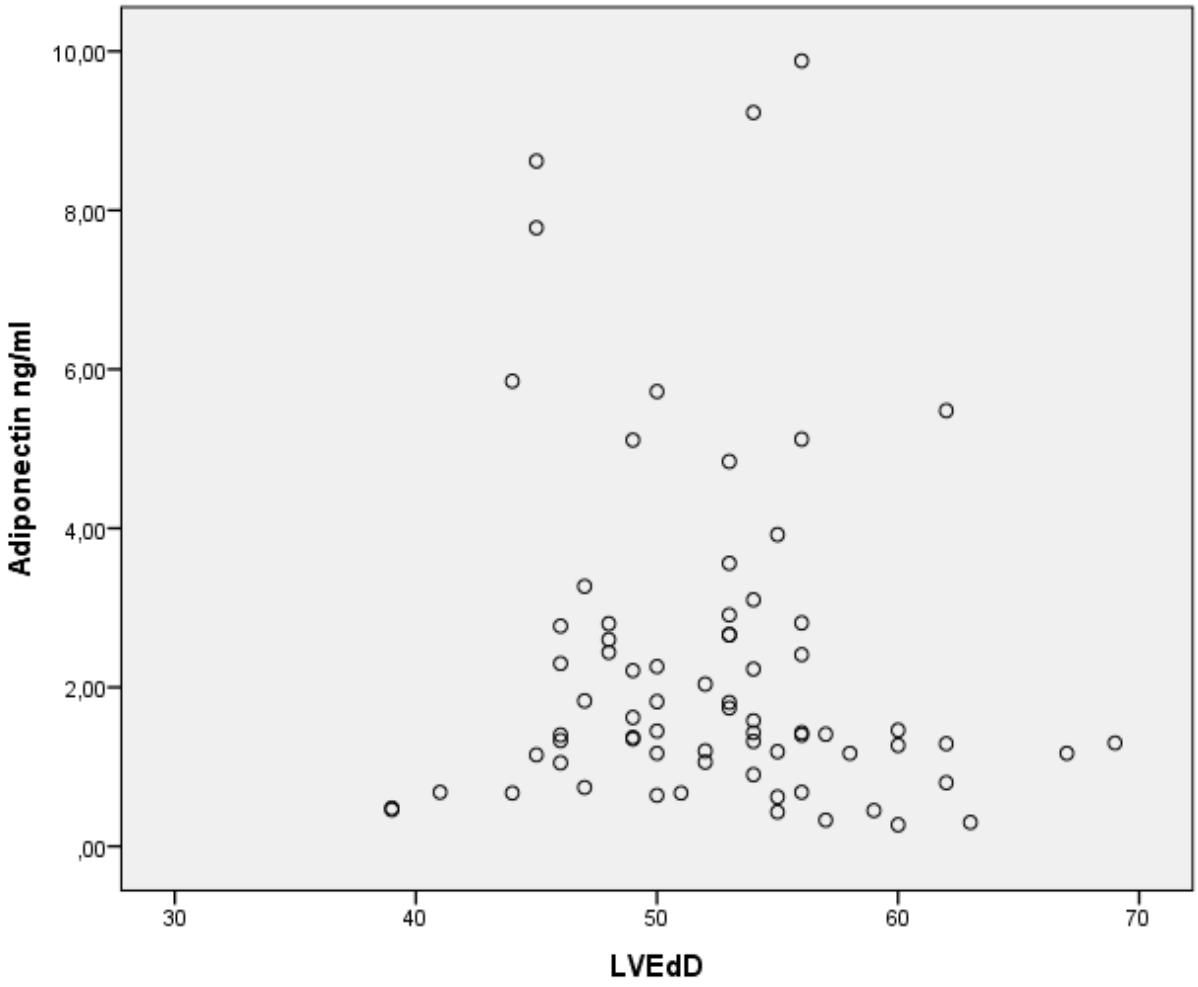

Figure 5. Correlation between adiponectin and LVEdD in all study patients (Pearson's Correlation coefficient r = -.096, p = 0.422

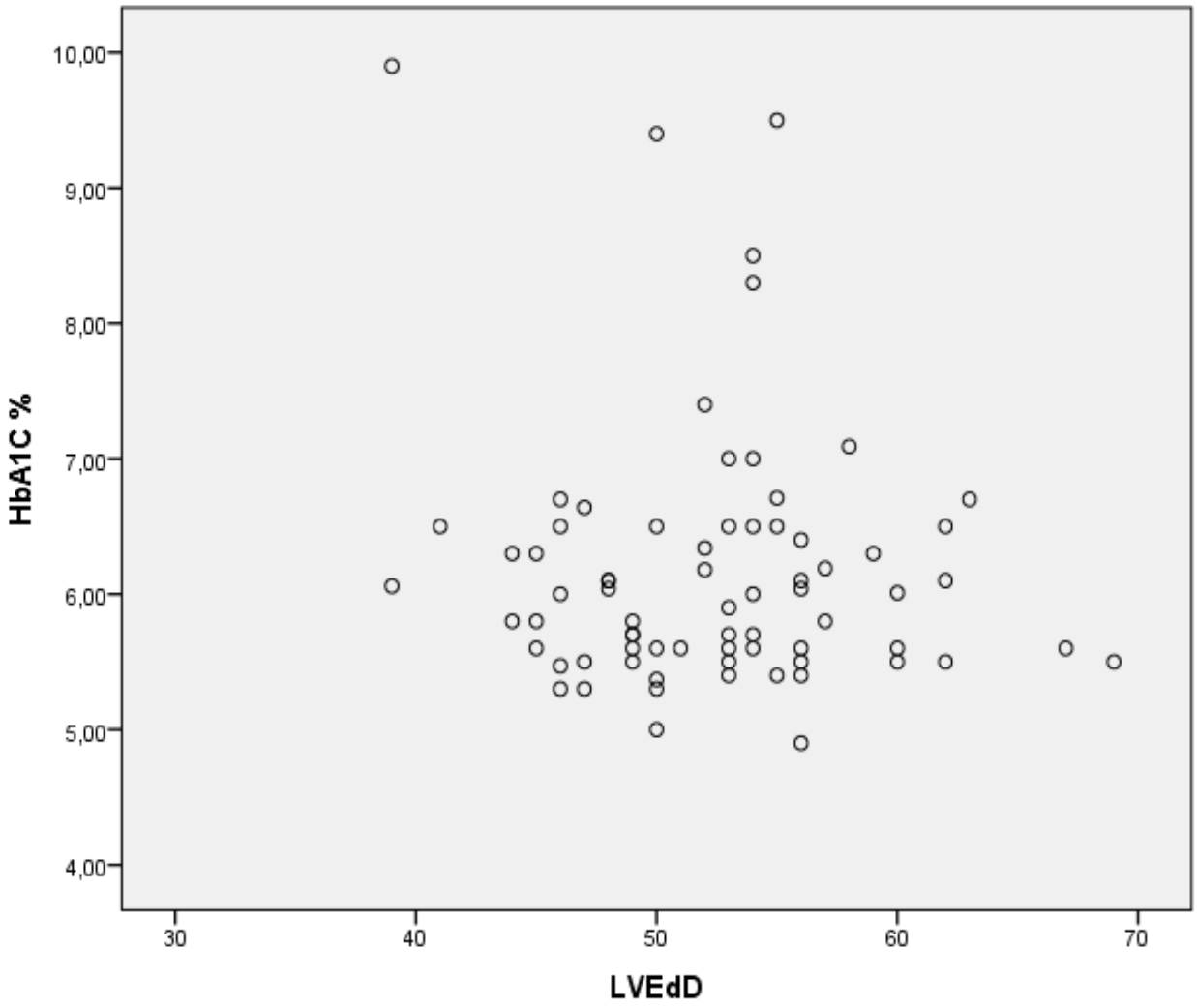

Figure 6. Correlation between HbA1C and LVEdD in all study patients (Pearson's correlation coefficient r = -.106, p = 0.375)

5.4. Association of adiponectin, HbA1C and BMI with MACE

In the study population, the frequency of MACE was significantly higher in Group 1 than in Group 2 ($p = 0.048$) (Table 1). Spearman's correlation analysis revealed that adiponectin correlated inversely with HbA1C in all study subjects ($p < 0.001$) (Figure 7). Most study subjects were not within the normal or healthy weight range with a significant difference of BMI between two groups ($p = 0.046$) (Table 1). We observed a significant negative correlation between adiponectin and body mass index ($p < 0.01$) (Figure 8).

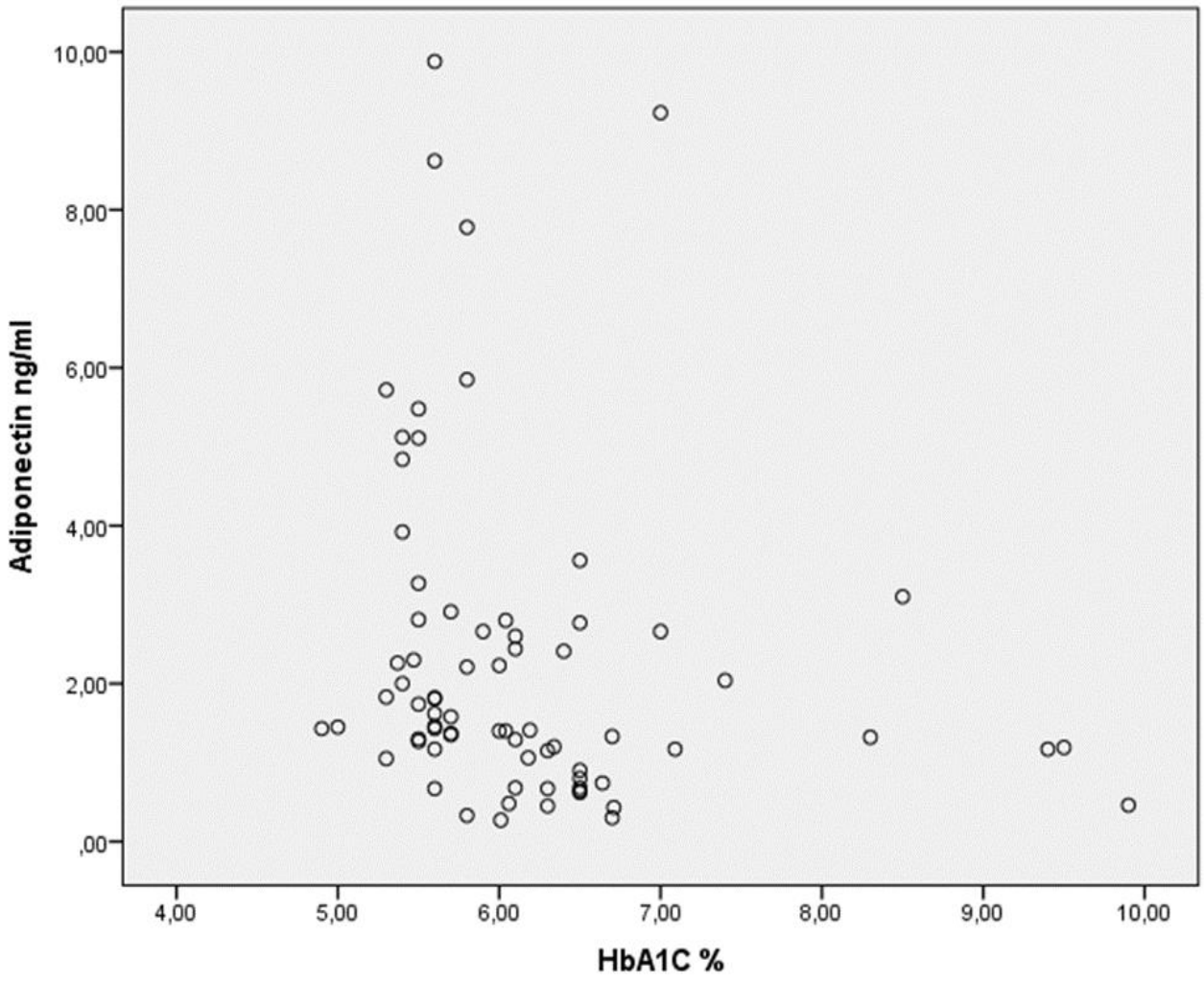

Figure 7. Correlation of adiponectin with HbA1C levels in all study subjects (Spearman's correlation coefficient rs = - 0,381352, $p < 0.001$).

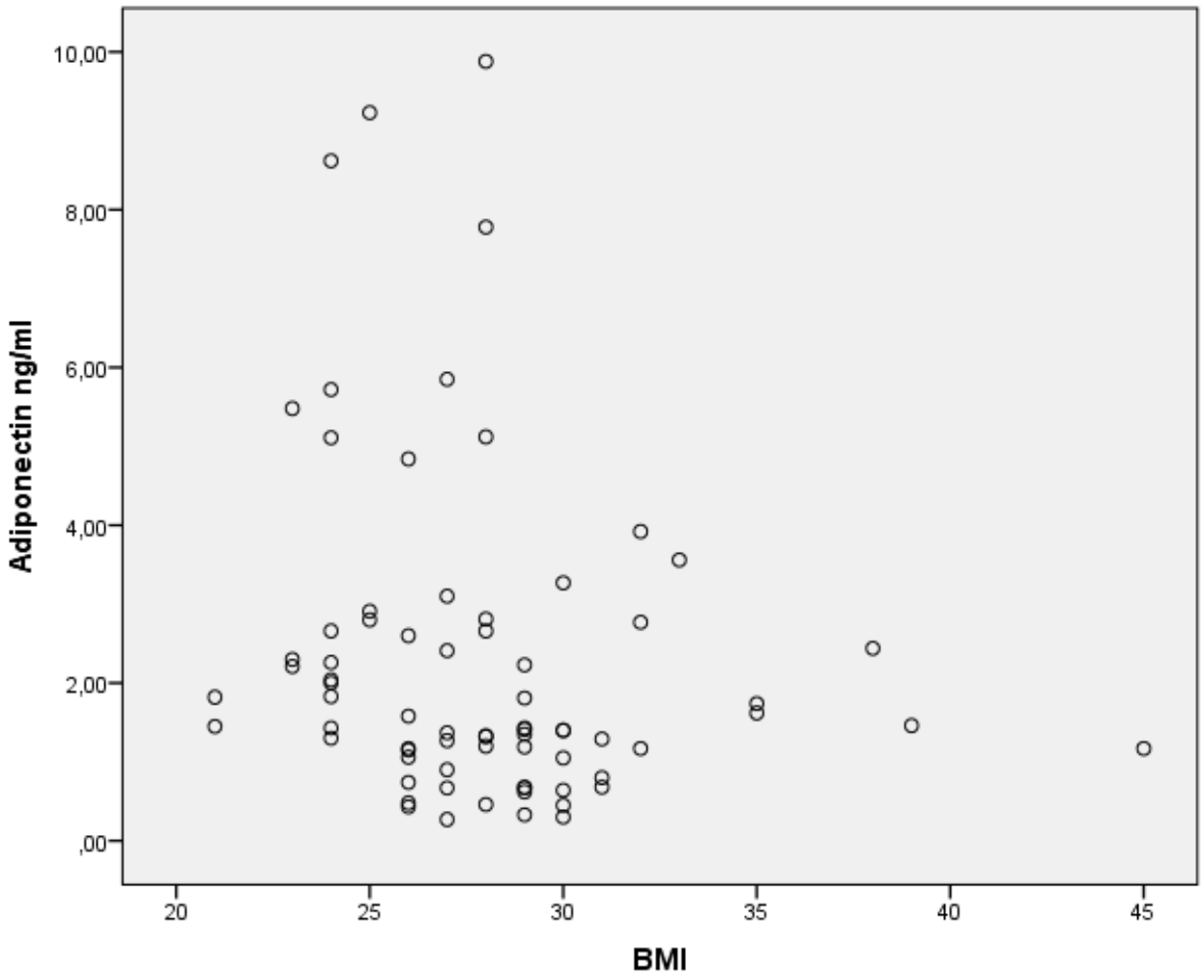

Figure 8. Correlation of adiponectin levels with BMI in all study subjects (Spearman's correlation coefficient r= - 0.277186, $p < 0.01$).

As shown in Table 1, the frequency of MACE was significantly higher in Group 1 than in Group 2. HbA1C levels in most study patients who survived myocardial infarction were 5.5-7 %. Exactly in this group of patients, the frequency of MACE during follow-up was higher. To evaluate the factors associated with the occurrence of MACE, we performed univariate logistic regression analysis using the following parameters: age, gender, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, adiponectin, HbA1C, LDL- cholesterol, HDL- cholesterol, triglycerides, fasting glucose, creatinine and CRP levels. Adiponectin, HbA1C and BMI were significantly associated with MACE (p=0.018, p=0.018, p=0.034) (Table 4). Multivariate regression analysis shows that serum adiponectin predicts MACE after STEMI (p= 0.011) (Table 5).

Table 4 Predictors of MACE in univariate regression analysis

Parameter	OR	95% Cl	*p* -value
Age	1.005	0.125-1.124	0.810
Gender (male)	0.375	0.000-12.44	0.080
BMI (kg/m²)	1.161	1.011-1.333	0.034
Waist circumference (cm)	1.051	1.0-1.106	0.52
Systolic BP (mmHg)	0.966	0.973-1.020	0.733
Diastolic BP (mmHg)	0.990	0.951-1.030	0.615
Adiponectin (ng/ml)	0.531	0.314-0.896	0.018
HbA1C %	2.062	1.132-3.757	0.018
LDL(mmol/l)	1.125	0.683-1.853	0.643
HDL(mmol/l)	0.903	0.235-3.465	0.882
CRP(mg/l)	1.022	0.999-1.046	0.058
Trigliceride (mmol/l)	0.760	0.772-1.425	0.760
Fasting glucose (mmol/l)	1.351	1.051-1.736	0.019
Urea (mmol/l)	1.062	0.894-1.262	0.491
Creatinine(µmol/l)	1.000	0.981-1.020	0.998

OR: odds ratio; Cl: confidence interval; HbA1C: glycated haemoglobin; BMI: body mass index; BP: blood pressure; HDL:high- density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction.

Table 5. Multivariate regression analysis for MACE

MACE	OR	95% Cl	*p* -value
Adiponectin (ng/ml)	2.964	1.27-6.86	.011
HbA1C %	.687	.326-1.44	.324
HDL(mmol/l)	.105	.011-.961	.046
LDL(mmol/l)	.680	.289-1.599	.376
BMI (kg/m^2)	.886	.732-1.072	.214
Systolic BP (mmHg)	1.011	.969-1.056	.605
LVEF %	.946	.842-1.062	.345
Killip class> 1	.088	.008-970	.047
Multiple vessel>1	.103	.015-.719	.022

OR: odds ratio; Cl: confidence interval; . BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction.

6. DISCUSSION

Collateral blood flow is very important after acute coronary ischemia. In many patients with acute coronary ischemia after revascularisation, perfusion in the infarct-related artery is normal despite a wall motion abnormality. Previous evidence suggests that adiponectin modulates cardiac remodeling in patients with coronary artery disease (100). The aim of this study was to observe the correlation of adiponectin with major adverse cardiac events especially in non-diabetic patients. To the best of our knowledge this is the first study investigating the adiponectin and glycated hemoglobin in prediction of MACE after STEMI in non-diabetic patients. In our study were 31,5% of patients with multiple-vessel disease without any significant difference between groups, however patients with indication for CABG were excluded from this study. This study found a low level of adiponectin in all patients independently of anatomical localization and number of diseased arteries. This suggests that adiponectin may respond to the acute phase of coronary artery disease. One possible explanation is that the process of new microvessel formation after acute myocardial infarction may lead to decrease in plasma adiponectin levels. A recent study showed that adiponectin promotes migration activities of endothelial progenitor cells (92). Therefore, it is possible that adiponectin induced revascularisation resulting in its consumption in the circulating plasma. Low plasma adiponectin level may also relate to microvascular myocardial ischaemia or to impaired myocardial energy utilization.

We showed significant associations of adiponectin and HbA1C. Previous studies highlighted that the cardiovascular risk associated with glycemic dysregulation starts well before the diagnosis of diabetes (101-103). The HbA1C values in most of our study patients who experienced MACE were between 5.7 – 6.4%. This result was in line with the guideline of the American Diabetes Association, which suggests HbA1C 5.7% – 6.4% as the high-risk range (104). The degree of hyperglycemia may change quickly, depending on the extent of the disease process. Hyperglycemia in the acute stage of acute myocardial infarction is associated with an increased risk of in-hospital mortality independent of the presence or absence of diabetes (105). Whether hyperglycemia occurs secondary to a larger infarction and therefore a larger area of no reflow or whether it contributes to the no-reflow phenomenon, is not known. We speculate that consumption of adiponectin during the process of new vessel formation after acute coronary syndrome may lead to hyperglycemia (Figures 2 and 3). Thus, the degree of hyperglycemia reflects the severity of hypoadiponectinemia and that might induce contra-protective mechanisms responsible for major adverse cardiac events. The recent report of the American Diabetes Association recommends screening adults aged ≥45 years or those younger with at least 1 risk factor (106); however the USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese (107).

Our study subjects were not within the normal or healthy weight range with a significant difference between two groups. Previous study reported that weight reduction therapy increased the plasma adiponectin concentration (108). Adiponectin levels have been shown to inversely correlate with body weight and obesity (30, 31). The present study

confirmed those results in non-diabetic patients. Our findings that adiponectin correlated inversely with HbA1C and BMI, while all of these parameters were associated with MACE, support the idea that adiponectin alone or together with HbA1C level and not just HbA1C alone predicts the cardiovascular risk. It has been reported recently that adiponectin induced via fibroblast growth factor 21 controlling energy and vascular homeostasis protects against cardiometabolic disorders (84, 85). The present study, showing that serum adiponectin level was indirectly associated with plasma HDL cholesterol concentrations, suggests that HDL plays an intermediate role in the relationship between serum adiponectin and coronary disease. Adiponectin showed to increase level of HDL by inhibition of Liver-Lipase expression. Adiponectin, and also HDL, was shown in previous studies to increase nitric oxide production by activation of the AMPK-Akt-eNOS phosphorilation pathway and contributes in vasodilatatory cardioprotective effects (49, 50, 109-111). It has been also reported that statins (HMG-CoA reductase-Inhibitors) in association with adiponectin induce the expression of eNOS (4). In this study, the mean LDL–cholesterol and triglyceridemia levels were also significantly different between the two groups. Adiponectin showed to stimulate the peripheric and liver LDL receptors and in this way adiponectin may stimulate the cholesterol-clearance. Thus, the association between adiponectin and HDL also may reflect indirectly the concept that defect in angiogenesis and modulation of vascular tone in non-diabetic patients after acute myocardial infarction plays a central role in the pathophysiology of major adverse cardiac events.

Adiponectin is closely related to metabolism and may have both, antiatherogenic and anti-inflammatory properties. It has been reported that adiponectin is associated with

subclinical atherosclerosis (112). In Patients with significant coronary stenosis coronary flow reserve is associated with vulnerable plaques as well as with higher levels of CRP. Anti-inflammatory activities of adiponectin seem to be crucial in creating a homeostatic/antiatherogenic response which is disturbed after acute myocardial infarction. In this study we found that the CRP level in patients with HbA1C > 6% was significantly higher than that in patients with HbA1C < 6%. However, in our study, no relationship between the CRP levels and prediction of MACE was found. This suggests that CRP may respond to the acute phase of coronary artery disease. Thus, we assume that patients after acute coronary syndrome may have lost the protective effect of adiponectin, which may be reduced due to inhibition of oxLDL and reduction the ability of macrophages to transform into foamy cells (Figure 3). This results in adiponectin consumption in the circulating plasma and high level of CRP.

We speculate that low level of serum adiponectin promotes the generation of reactive oxygen species and inflammation of small vessels, which then directly influences the development of high blood pressure. Thus, it is possible that patients with low level of adiponectin and arterial hypertension could have more rapid progression of major adverse cardiac events after acute coronary syndrome. However in most of our study patients where present normal high blood pressure, diastolic and systolic blood pressure values do not differ significantly among the groups. Our limited sample size and use of antihypertensive drugs could be an explanation for these results. Previous evidence suggest that left ventricular remodeling related with diabetes mellitus, hypertension and coronary artery disease (113).

A previous clinical study showed that plasma adiponectin level is an independent predictor of left ventricular systolic dysfunction in patients referred for coronary angiography (114). In our study population, after successful revascularisation, we found normal or 'borderline' ventricular ejection fraction (EF) at echocardiography during examination, without any significant difference between the groups. The left ventricular abnormalities were found in about 49.3% and were more present in patients with HbA1C >6%. Specifically, concentric remodeling was the most prevalent abnormal LV geometric pattern in this group of patients. In our study 23.3% of patient experienced heart failure Killip>1 with significant difference between groups. We speculate that low level of adiponectin is responsible for systemic microvascular dysregulation associated with abnormalities in filling and this could also be the consequence for abnormalities in diastole. The arteriolar remodeling due to hypoxemia and hypoxic vasoconstriction after acute myocardial infarction, could cause left myocardial remodeling. Furthermore, triglyceride and free-fatty-acid deposition in the myocardium especially by obese subjects could lead to the development of a cardiomyopathy. The increased vascular stiffness and peripheral vascular resistance leading to hemodynamic overload. Thus elevation of left ventricular filling pressures caused by diastolic dysfunction together with an impairment in systolic reserve after acute myocardial infarction might be responsible for heart failure and adverse outcomes. Our speculation is in line with an previous study which suggest that epicardial adipose tissue is related to left ventricular mass and other features of the metabolic syndrome, such as concentrations of LDL cholesterol, fasting insulin and adiponectin, and arterial blood pressure (115), and this plays an important role in the development of an unfavorable cardiac outcome after acute myocardial infarction.

Although in the present study left ventricular mass index (LVMI) did not differ significantly between groups, it is conceivable that exclusion form this study of diabetic patients and patients with previous complicated cardiovascular disease may have contributed to these results. In the Framingham Heart Study participants, the heart failure rates were higher in patients with concentric remodeling and those patients were at a higher risk for heart failure with preserved ejection fraction (117). The association between diabetes mellitus and diastolic dysfunction with cardiovascular morbidity has been well documented in previous studies (116-118). The mechanisms responsible for the diastolic dysfunction are probably multifactorial. A recent study identified decreased levels of adiponectin in diabetic and non-diabetic patients with diastolic dysfunction (119). Thus, the idea that hyperglycemia plays a central role in the pathophysiology of microvascular cardiac damages is not sufficient to explain the left ventricular remodeling after myocardial infarction in adiponectin deficient subjects. In the present study, the correlation of LVEdD with adiponectin and HbA1C in all study patients was not statistically significant. These findings may be explained by the fact that patients with diabetes mellitus and with previous coronary disease who already suffered cardiac complications were excluded from the study. However, in our study, during follow up the frequency of MACE was significantly higher in patients with HbA1C >6%, and we assume that hypoadiponectinemia was responsible for progression of left ventricular dysfunction with poor clinical outcome. Univariate and multivariate regression analysis shows that serum adiponectin predicts MACE after STEMI. Our findings in nondiabetics may reflect indirectly the concept that adiponectin regulate selectively angiogenesis and modulation of vascular tone and plays a central role in the pathophysiology of major adverse cardiac

events after acute myocardial infarction independent of diabetes mellitus presence. Thus our results suggest that the measure of adiponectin either alone or in combination with HbA1C may improve identification of patients with microvascular damages and glucometabolic dysregulation after ACS.

The effects of PPAR agonists in adiponectin level and insulin sensitivity are previously documented. However the pharmacological activation of PPAR through Thiazolidindione is associated with anti-proliferative, anti-inflammatory and direct vasodilatory effects in the vasculature (23, 24). Based on the properties of adiponectin resulting in vascular effects, the use of adiponectin in the therapeutic scenario should be more investigated. Furthermore studies investigating the vascular effects of various multimeric forms of adiponectin will help in developing novel therapeutic strategies in patients with cardiovascular disease.

The sample in this study was too small and we have not performed serial measurements of adiponectin and HbA1C. Further research with a larger number of patients is warranted to confirm our findings.

7. CONCLUSSION

We found significant associations of adiponectin and HbA1C with MACE in nondiabetic patients who survived acute ST-elevation myocardial infarction. The frequency of left ventricular remodeling was high, especially in patients with HbA1C >6%.

Despite the limited number of participans, our findings support the hypothesis that low level of adiponectin is a predictor of adverse outcomes after acute myocardial infarction.

This suggest that adiponectin may play a main role in maintaining of endothelial function and vascular tone.

Better knowledge of microangiogenesis and inflammation, may establish new preventive strategies. The precise mechanisms responsible for the association between plasma adiponectin and progression of cardiovascular disease remain to be determined. This study shows indirectly that adiponectin may play an important role in the detection of microvascular damages prior to the manifestation of symptoms and irreversible complications. The improved microvascularisation results in improved systolic and diastolic function during ischemia and after reperfusion. Thus, the adiponectin serum level could be implemented in routine laboratory for primary and secondary prevention. The measurement of adiponectin by ELISA -Test is easy and practically to use. Research studies to date have proven that exogen administration of recombinant adiponectin is difficult. Therefore increasing of adiponectin levels by pharmacological interventions or

lifestyle-based interventions may be a potential target to prevent cardiovascular events in patients with coronary artery disease.

8. ABSTRACT IN CROATIAN

Uvod: Poremećaji mikrovaskularne funkcije i glukometaboličke regulacije povezani su s lošom prognozom nakon akutnog infarkta miokarda. Uočeno je da adiponektin modulira vaskularnu homeostazu i štiti od srčanih metaboličkih poremećaja. Hipoadiponektinemija je povezana s remodeliranjem lijeve klijetke i lošim kliničkim ishodom. Cilj ovog istraživanja bio je proučiti povezanost razine adiponektina i HbA1C s velikim neželjenim kardijalnim događajima (MACE) u bolesnika bez šećerne bolesti nakon infarkta miokarda s elevacijom ST-spojnice (STEMI).

Metode: U istraživanje su bila uključena 73 pacijenta bez šećerne bolesti nakon infarkta miokarda s elevacijom ST-spojnice. Svim bolesnicima mjerene su razine adiponektina i HbA1C. Ispitanici su bili podijeljeni u dvije skupine: 37 bolesnika s povišenom razinom HbA1C i 36 bolesnika s normalnim vrijednostima HbA1C. Srčana struktura i funkcija bile su procijenjene korištenjem dvodimenzionalne transtorakalne ekokardiografije. Tijekom godine dana praćenja bolesnika nakon akutnog infarkta miokarda ustanovljeni su veliki neželjeni kardijalni događaji.

Rezultati: Uočena je obrnuta povezanost razine adiponektina s HbA1C kod svih ispitanika ($p < 0,001$). Prosječne vrijednosti adiponektina bile su značajno niže u skupini 1 u odnosu na skupinu 2 ($p = 0,004$). Vrijednosti HDL-a u serumu također su bile značajno niže kod ispitanika s povišenim HbA1C ($p = 0,004$) u odnosu na skupinu 2. Uočena je negativna povezanost između razine adiponektina i indeksa tjelesne mase ($p < 0,01$).

Remodeliranje lijeve klijetke dijagnosticirano je kod 36 (49,3%) bolesnika s višim frekvencijama u skupini 1 nego u skupini 2; konkretno, koncentrično remodeliranje lijeve klijetke (21,6% vs. 11,1%) i koncentrična hipertrofija lijeve klijetke (10,8 vs. 5,6%). Povezanost razine adiponektina i LVEdD (p = 0,422) te HbA1C i LVEdD (p = 0,375) nije bila statistički značajna. Tijekom godinu dana praćenja, učestalost velikih neželjenih kardijalnih događaja bila je značajno veća u bolesnika s povišenom razinom HbA1C (p= 0,048).

Zaključak: Ovo je istraživanje pokazalo da je razina adiponektina u obrnutoj korelaciji s HbA1C i indeksom tjelesne mase, te povezana s velikim neželjenim kardijalnim događajima nakon infarkta miokarda s elevacijom ST-spojnice. Učestalost remodeliranja lijeve klijetke, osobito koncentričnog remodeliranja, bila je viša kod bolesnika s razinom HbA1C >6%. Međutim, povezanost razine adiponektina i HbA1C s LVEdD nije bila statističi značajna. Bolesnici s razinom HbA1C između 5,7 i 6,5% bili su izrazito rizična skupina te je za takve pacijente potrebno uzeti u obzir preventivne mjere.

9. ABSTRACT IN ENGLISH

Introduction: Microvascular dysfunction and glucometabolic dysregulation are associated with poor prognosis after acute myocardial infarction. It has been reported that adiponectin modulates vascular homeostasis and protects against cardiometabolic disorders. Hypoadiponectinemia is associated with left ventricular remodeling and poor clinical outcome. This study aimed to investigate the association of adiponectin and HbA1C with major adverse cardiac events in non-diabetic patients who survived ST-elevation myocardial infarction.

Methods: The study enrolled prospectively 73 non-diabetic patients who experienced STEMI infarction. We measured the level of adiponectin and HbA1C in all patients. The subjects were divided into two groups: 37 patients with elevated HbA1C and 36 patients with normal levels of HbA1C. Cardiac structure and function were assessed using two-dimensional transthoracic echocardiography.

In a one-year follow-up, the study subjects were observed for major adverse cardiac events (MACE).

Results: Adiponectin correlated inversely with HbA1C in all study subjects ($p < 0.001$). Mean adiponectin levels were significantly lower in Group 1 than in Group 2 ($p = 0.004$). Serum values of HDL were also significantly lower in patients with elevated HbA1C than in Group 2 ($p = 0.004$). In our study patients we found a negative correlation between adiponectin and body mass index ($p < 0.01$). Left ventricular remodeling was diagnosed

in 36 (49.3%) patients with higher frequency in Group 1 than in Group 2, specifically concentric left ventricular remodeling (21.6% vs. 11.1%) and concentric left ventricular hypertrophy (10.8 vs. 5.6%). The correlation between adiponectin and LVEdD ($p = 0.422$) and between HbA1C and LVEdD ($p = 0.375$) was not statistically significant. During follow up, the frequency of MACE in patients with elevated HbA1C was significantly higher ($p = 0.048$).

Conclusion: Adiponectin correlated inversely with HbA1C and BMI and was associated with major adverse cardiac events after STEMI. The frequency of left ventricular remodeling especially concentric remodeling was higher in patients with HbA1C >6%. However, the correlation of adiponectin and HbA1C with LVEdD was not statistically significant. The patients with a HbA1C level between 5.7 and 6.5% were at a particularly high risk and might be considered for prevention interventions.

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11. CURRICULUM VITAE

Blerim Berisha, MD, was born on May 27, 1978 in Pejë, Republic of Kosovo. He finished primary and secondary school in Klinë, and completed medical studies at the Medical School, University of Prishtina, Republic of Kosovo. From 2004 to 2007, he worked as a medical doctor at 'Mother Teresa' Health Center in Klinë, and from 2007 to 2011, he did specialization of internal medicine at Internal Clinic of University Clinic Centre of Kosovo. In 2012, he did a two-month training at Cardiology Klinikum Fulda, Germany, and a two-month training in invasive cardiology at Herzzentrum in Chemnitz, Germany.

During subspecialization at Cardiology Clinic, University Clinic Centre of Kosovo, he worked in Coronary Care Unit and Cardiology Department 1, focusing on coronary artery disease, cardiometabolic syndrome, and cardiac electrostimulation. In 2013, he worked for 4 months at Cardiology Clinic of Sana Klinik, Hof, Germany. In 2014, he finished subspecalization in cardiology, during which period he was actively involved in clinical research. He is an author and coauthor of 11 published research papers and 9 abstracts, and an author of book chapter on bicuspid aortic valve. He has presented his clinical research at many scientific conferences.