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Influence of treatment strategy on serum adiponectin, resistin and angiogenin concentrations in patients with stable multivessel coronary artery disease after one-year follow-up*

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Abstract

Background: Adiponectin and resistin, as well as the novel angiogenetic factor angiogenin, may be associated with inflammation and atherosclerosis. However, the available data are limited regarding adipocytokines and angiogenesis factors long-term serum concentration changes in patients with coronary artery disease (CAD).

Aim: To evaluate the treatment strategy-dependent changes in serum concentrations of adiponectin, resistin and angiogenin in patients with stable multivessel CAD (MCAD) and their association with cardiovascular events.

Methods: The study group comprised 107 MCAD patients (80 males, mean age 63 ± 8 years); 55 (51%) patients were treated surgically (coronary artery bypass grafting — CABG), while the other 52 (49%) were treated medically. Adiponectin, resistin and angiogenin plasma levels were measured on admission and after one-year follow-up. Major adverse cardiac events (MACE) were defined as cardiac death, non-fatal myocardial infarction, stroke or hospitalisation for angina or heart failure over the 12 month period.

Results: During one-year follow-up, nine (8%) patients died, all from cardiovascular causes, and 34 (32%) patients experienced MACE. The CABG group revealed significant decrease in angiogenin ($p < 0.0001$) and adiponectin ($p = 0.03$) serum levels. In the medically treated group, we noted a significant reduction in the adiponectin serum concentration ($p = 0.003$), with no change in resistin and angiogenin serum levels.

Conclusions: In stable patients with MCAD, the choice of treatment strategy (optimal medical therapy or surgery) influences cytokines profile and modifies serum concentration of angiogenin and adiponectin during 12 months of follow-up. Assessing the dynamic concentration changes of these novel biomarkers may be useful for clinical practice.

Key words: multivessel coronary artery disease, adipocytokines, angiogenesis

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INTRODUCTION

Coronary artery disease (CAD) is the main cause of death in developed countries [1]. Despite recent progress in cardiology, global cardiovascular (CV) mortality is still very high, exceeding 7 million in 2002 [2]. Multivessel CAD (MCAD), defined as subcritical or critical stenosis (cross-section area decreased by ≥ 75%) of at least two of the three main coronary arteries supplying the myocardium, is a common manifestation of advanced coronary atherosclerosis [2] and has been estimated to represent as much as 50% of all cases of CAD.

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Such severity of coronary atherosclerosis leads to common atherothrombotic complications, resulting in exceptionally high mortality rates (ranging from 10% to as much as 60% at five-year follow-up), which depends on the extent of atherosclerotic lesions as well as concomitant risk factor profile [3]. However, such a widely ranging mortality rate suggests inhomogeneity of this clinical group.

Adipose tissue has been recently recognised as an endocrine organ. Adiponectin, an adipocytokine, is a recently discovered protein which modulates and suppresses the inflammatory response in atherosclerotic lesions [4]. Hypoadiponectinaemia has been observed in patients with metabolic syndrome, diabetes mellitus and CAD [5–7]. Published data support a strong association between plasma adiponectin levels and risk stratification in CAD patients [8, 9].

Resistin belongs to a novel family of cysteine-rich proteins called resistin-like molecules or Found in Inflammatory Zone (FIZZ) proteins [10]. Resistin appears to be involved in inflammatory pathways, vascular endothelial cells activation and the stimulation of smooth muscle cell proliferation. Such activity suggests its potential role in atherosclerosis [11, 12]. Recently, resistin and its mRNA have been detected in atherosclerotic lesions [13]. This is consistent with the finding of elevated circulating resistin in patients with CAD. Thus, resistin can be considered as an inflammatory marker of atherosclerosis and atherosclerotic complication in humans [14, 15].

Angiogenin is a soluble protein, one of the angiogenic factors involved in the creation of capillaries. This leads to the formation of new vessels from pre-existing vascular structures [16]. Several studies have suggested that angiogenin and other angiogenic factors could promote atherosclerosis and potentially destabilise coronary plaques by promoting intralesional angiogenesis [17, 18]. Moreover, angiogenin has been shown to be an independent predictor of poor prognosis in CAD [19].

The aim of this study was to evaluate treatment strategy-dependent changes in serum concentrations of adiponectin, resistin and angiogenin in patients with stable MCAD, and their association with CV events.

METHODS

Study group

The study involved a consecutive group of 107 patients with CAD undergoing angiography in our department during 2007 who met the following criteria: (1) CAD with ≥ 75% diameter stenosis in three main coronary branches as confirmed on coronary angiography, (stenosis of the left main coronary artery > 50% was an exclusion criterion due to the need for urgent revascularisation); (2) stable coronary heart disease (CCS I–III); (3) absence of significant acquired valve disease that would result in predicted survival < one year; and (4) qualification for surgical or medical treatment strategy (selection for percutaneous angioplasty at baseline was an exclusion criterion).

Following discharge from the department, all patients remained under the care of the Outpatient Clinic and were prospectively followed with regard to the development of clinical events over the 12 months following index coronary angiography. Four patients withdrew their consent to participate in a follow-up visit at 12 months (all the clinically important data were collected via telephone and there were no significant events during the investigated period). Thus, 103 patients were included in the final biochemical analysis. All were treated pharmacologically according to the guidelines of the European Society of Cardiology. The choice of treatment strategy i.e. coronary artery bypass grafting (CABG) or medical strategy, was made during consultations between cardiologists and cardiac surgeons. The main factors determining treatment strategy were the angiographic severity of the disease and patient's preference. All patients selected for CABG received left internal mammary artery grafting of the left descending branch (LIMA to LAD) and at least two saphenous vein grafts to other coronary vessels. All patients included in the study signed an informed consent form; the study was also approved by the regional Bioethics Committee at the Medical University in Lodz.

Baseline and follow-up biochemical tests

Laboratory tests included: complete blood count, complete lipid profile, fasting blood glucose (and in non-diabetic patients an oral glucose tolerance test with blood glucose measurement after two hours), creatine kinase-MB, urea, creatinine, glomerular filtration rate measured with the Cockroft--Goult formula, hepatic transferases, C-reactive protein and NT-proBNP levels.

Cytokine plasma concentrations were measured in blood samples drawn at baseline and at 12-month follow-up visit. Aliquoted plasma samples stored at –70°C were thawed, and the concentrations of angiogenin, adiponectin, resistin, TNF-α and interleukin-8 were measured using commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA).

Electrocardiography, echocardiography, exercise stress test and coronary angiography

Transthoracic echocardiography, resting electrocardiography and an exercise test were performed at baseline in all patients. Based on coronary angiographic results, the severity of atherosclerotic changes was assessed semiquantitatively using the Gensini score. Lesions formed (involving lesion severity and location) in the left main and proximal segments of left descending artery, circumflex and right coronary artery were grouped to calculate the proximal Gensini score, and distal lesions located in the remaining coronary segments yielded the distal Gensini score.

Clinical end-points

Patients were followed for at least 12 months with regard to the occurrence of major adverse cardiac events (MACE) defined as: death, stroke, myocardial infarction (MI) and hospitalisation due to the progression of ischaemic and/or heart failure (HF) symptoms. The MI occurring during follow-up was defined according to the recent universal definition [20]. Death was classified as cardiac if the predominant and immediate cause was related to ischaemia, arrhythmia or refractory HF or if the death was sudden and unexpected. Information regarding death was obtained by review of the death certificate and reports from family members.

Statistical analysis

The Shapiro-Wilk test was used to determine the normality of the analysed variables distribution. Continuous variables showing normal distribution are presented as means ± standard deviations, whereas those with distribution different from normal and ordinal variables are expressed as medians with interquantile range (25^{th}–75^{th} percentile). Analysis of variance and the Wilcoxon non-parametric test were applied to compare the differences in analysed parameters between the patient groups. The results were considered statistically significant if a p value was < 0.05.

RESULTS

Baseline characteristics

One-year follow-up data was available for all patients. Of the 107 patients, 80 (75%) were male and the mean age in the group was 62.5 years. All the patients complained of chest pain — the mean CCS class in the study group was 2.5 (range 2–3) and the mean history of angina duration was 71 ± 64 months. The mean Gensini score in the whole study group was 91 (66–132), with the proximal Gensini score being 45 (20–90) and the distal one being 39 (20–70). The baseline demographic, clinical, laboratory and angiographic characteristics of the study population stratified by the treatment strategy are shown in Tables 1 and 2. Fifty five (51%) patients underwent CABG, while 52 (49%) were treated medically. Patients selected for medical therapy had a significantly longer history of angina duration, more severe HF symptoms, higher serum

Table 1. Selected demographic and clinical data of patients with multivessel coronary artery disease stratified by treatment strategy (CABG *vs* medical)

	CABG group (n = 55)	Medical group (n = 52)	P
Male gender	43 (77%)	36 (72%)	NS
Age [years]	61.5 ± 8.5	64.6 ± 8.1	NS
Duration of angina [months]	28 (18–84)	72 (24–120)	0.004
History of myocardial infarction	40 (73%)	33 (63%)	NS
NYHA class	2 (1–2)	2 (1–3)	0.03
CCS class	2.5 (2–3)	2.5 (2–2.5)	NS
Kidney failure	0 (0%)	3 (6%)	NS
Hypertension	53 (96%)	51 (98%)	NS
Diabetes mellitus	27 (49%)	24 (46%)	NS
Impaired glucose tolerance	18 (33%)	16 (31%)	NS
Obesity	17 (31%)	20 (38%)	NS
Body mass index	28.3 ± 3.9	29.1 ± 3.9	NS
Smoking	20 (36%)	14 (27%)	NS
Positive family history	14 (25%)	14 (27%)	NS
Atrial fibrillation	1 (2%)	4 (8%)	NS
Atherosclerosis of peripheral arteries	6 (12%)	12 (23%)	NS
Stroke	3 (5%)	2 (4%)	NS
METS during exercise test	5.7 (4.6–7)	5.5 (4–7)	NS
Ejection fraction [%]	47 (37–54)	44 (34–57)	NS
ST depression > 1 mm in resting ECG	17 (31%)	13 (25%)	NS
Q wave in resting ECG	31 (56%)	31 (60%)	NS
Left bundle branch block	1 (2%)	2 (4%)	NS

CABG — coronary artery bypass grafting; NYHA — New York Heart Association; CCS — Canadian Cardiovascular Society; METS — metabolic equivalents; ECG — electrocardiography

Table 2. Selected baseline laboratory test results in multivessel coronary artery disease patients according to treatment strategy (CABG *vs* medical)

	CABG group (n = 55)	Medical group (n = 52)	P
Adiponectin [μg/mL]	7.5 (5.5–12.9)	8.67 (6.8–13.5)	NS
Resistin [ng/mL]	17.4 (12.7–25.4)	17.5 (12.3–25.8)	NS
Interleukin-8 [pg/mL]	23 (12–30)	18.4 (11.3–26.9)	NS
TNF-α [pg/mL]	4.1 (2.2–4.4)	4.1 (2.4–5.3)	NS
Angiogenin [ng/mL]	409 (326–498)	418.5 (302–540)	NS
Haemoglobin [g/dL]	14.5 ± 1.3	14.5 ± 1.4	NS
WBC [×10³/μL]	7.6 (6.4–9.6)	7.35 (6.2–8.4)	NS
PLT [×10³/μL]	249 ± 67	254 ± 63	NS
Total cholesterol [mg/dL]	166 (138–208)	177 (159–219)	NS
HDL cholesterol [mg/dL]	45 (39–52)	45 (37.7–52.4)	NS
LDL cholesterol [mg/dL]	92 (68–118)	109 (90–134)	0.03
Triglycerides [mg/dL]	130 (94–179)	133 (101–194)	NS
hsCRP [mg/L]	2.2 (1.3–5.2)	3.4 (1.9–5.8)	NS
Urea [mg/dL]	32 (28–42)	37 (32–42)	NS
Creatinine [mg/dL]	0.91 ± 0.12	0.94 ± 0.15	NS
Uric acid [mg/dL]	6 ± 1.2	6.12 ± 1.2	NS
GFR [mL/min/1.73 m²]	94 (81–118)	87 (70–110)	NS
NT-proBNP [pg/mL]	294 (162–840)	490 (145–855)	NS
Haemoglobin A1C [%]	6 (5.5–6.8)	6.1 (5.7–7.3)	NS
Fibrinogen [mg/dL]	385 (335–440)	390 (356–446)	NS
Gensini score	90 (66–132)	91 (67–116)	NS
Proximal Gensini score	48 (30–98)	35 (10–80)	0.04
Distal Gensini score	38 (20–64)	50 (20–70)	NS
CTO RCA	21	24	NS
CTO LAD	11	14	NS
CTO Cx	11	9	NS

CABG — coronary artery bypass grafting; GFR — glomerular filtration rate; WBC — white blood cell; PLT — platelets; CRP — C-reactive protein; CTO — chronic total occlusion; RCA — right coronary artery; LAD — left anterior descending artery; Cx — circumflex artery

Table 3. Medication at baseline

	CABG group (n = 55)	Medical group (n = 52)	P
ASA	54 (98%)	51 (98%)	NS
Clopidogrel	3 (5%)	5 (10%)	NS
ACE inhibitors	54 (98%)	52 (100%)	NS
Beta-blockers	55 (100%)	49 (94%)	NS
Statins	54 (98%)	50 (96%)	NS
Nitrates	44 (80%)	39 (75%)	NS
Digoxin	3 (5%)	7 (13%)	NS
Diuretics	12 (22%)	20 (38%)	NS

CABG — coronary artery bypass grafting; ASA — acetylsalicylic acid; ACE — angiotensin converting enzyme

LDL cholesterol and lower values of proximal Gensini score. Pharmacological treatment during the 12 month study period is summarised in Table 3.

Clinical end-points

Among the 107 patients followed for 12 months, there were nine deaths (8%, all from CV reasons), including six (11.5%)

in medically treated patients (two due to MI, two to stroke, and there were two sudden cardiac deaths at home) and three (5.5%) in the CABG group (two periprocedural deaths, one due to stroke). Patients treated pharmacologically were more frequently hospitalised due to the progression of angina symptoms (20 *vs* 5; p = 0.003). Six (11.5%) patients developed MI in the medical group and one (1.3%) in the CABG group (NS). In seven (13.5%) patients from the pharmacologically treated group, a palliative percutaneous procedure (PTCA) was performed on one diseased vessel with drug eluting stent implantation (without complete revascularisation). Composite end-point (MACE) was significantly more frequent in the medical group compared to the surgical group (24 *vs* 10; p = 0.002).

CABG and medical group comparison after 12 months and at baseline

At 12 month follow-up, patients treated surgically experienced significantly more pronounced improvement of ischaemic (p < 0.0001) and HF (p = 0.0007) symptoms compared to the medical group. Significant differences were visible in exercise test results (better in the CABG group, p = 0.006), left ventricular systolic function (better in the CABG group, p = = 0.02) and serum angiogenin concentrations (higher in the medical group, p = 0.009). No differences were found in serum adiponectin and resistin levels after 12 months in both groups (Table 4).

In the medical group, at 12 month follow-up we observed significant improvement of ischaemic symptoms in the CCS class (p < 0.0001), and reduced adiponectin serum concentration (p = 0.003). We did not observe any significant differences in resistin and angiogenin serum levels at baseline and after 12 months in this group of patients. The CABG group revealed significant improvement of ischaemic symptoms in the CCS class (p < 0.0001), HF symptoms in the NYHA class (p = 0.003), improvement of exercise test results (p = = 0.0001), a significant decrease in angiogenin (p < 0.0001) and adiponectin (p = 0.03) serum levels. However, we did not observe any significant differences in the global systolic function after 12 months. Nevertheless, we observed significant improvement of the contractile function of the apical and lateral segments (p = 0.01) of the left ventricle (Table 5).

Table 4. Comparison of selected test results after 12-month follow-up in the CABG group and the medical group

	N	CABG group	N	Medical group	P
NYHA class	52	1 (0–2)	46	2 (1.5–2.5)	0.0007
CCS class	52	0 (0–0)	46	2 (1–2)	< 0.0001
METS (exercise test)	49	7 (5.5–9.2)	35	6 (4–7)	0.006
Positive exercise test	49	10 (20%)	35	19 (53%)	0.003
Ejection fraction [%]	49	52 (43–56)	45	45 (37–54)	0.02
Adiponectin [μg/mL]	49	7.05 (4.1–10.8)	45	6.8 (4.5–12.8)	NS
Resistin [ng/mL]	49	20 (14.7–29.8)	45	19.5 (15.7–25.1)	NS
Angiogenin [ng/mL]	49	236 (189–323)	45	349 (209–546)	0.009

CABG — coronary artery bypass grafting; NYHA — New York Heart Association; CCS — Canadian Cardiovascular Society; METS — metabolic equivalents

Table 5. Functional and biochemical findings at baseline and after 12-month follow-up in the medical and the CABG groups

	Medical group		P	CABG group		P
	At baseline (n = 52)	After 12 month follow-up (n = 46)		At baseline (n = 55)	After 12 month follow-up (n = 52)	
NYHA class	2 (1–3)	2 (1.5–2.5)	NS	2 (1–2)	1 (0–2)	0.003
CCS class	2.5 (2–2.5)	2 (1–2)	< 0.0001	2.5 (2–3)	0 (0–0)	< 0.0001
Ejection fraction [%]	44 (34–57)	45 (37–54)	NS	47 (37–54)	52 (43–56)	NS
METS (exercise test)	5.5 (4–7)	6 (4–7)	NS	5.7 (4.6–7)	7 (5.5–9.2)	0.0001
Adiponectin [μg/mL]	8.67 (6.8–13.5)	6.8 (4.5–12.8)	0.003	7.5 (5.5–12.9)	7.05 (4.1–10.8)	0.03
Resistin [ng/mL]	17.5 (12.3–25.8)	19.5 (15.7–25.1)	NS	17.4 (12.7–25.4)	20 (14.7–29.8)	NS
Angiogenin [ng/mL]	418.5 (302–540)	349 (209–546)	NS	409 (326–498)	236 (189–323)	< 0.0001

CABG — coronary artery bypass grafting; NYHA — New York Heart Association; CCS — Canadian Cardiovascular Society; METS — metabolic equivalents

DISCUSSION

Identifying biomarkers potentially useful for clinical decision-making in patients with CAD is of great importance. Our study showed that treatment strategy (optimal medical therapy or surgery) influences serum concentrations of selected biomarkers during 12-month follow-up in patients with MCAD. Patients treated surgically had significantly lower values of angiogenin serum concentration than the medically-treated group after 12 months. In addition, we observed in both groups significant reduction of adiponectin serum level and no change of resistin concentration. Moreover, due to a lower rate of CV events in the surgical group, we found that a decreased circulating level of angiogenin was indirectly associated with a better prognosis.

The presence of coronary collateralisation improves the prognosis of patients with advanced CAD. Collaterals improve ventricular function and overall perfusion in the ischaemic myocardium [21]. The development of coronary collaterals appears to be initiated by ischaemia resulting in the opening of pre-existing anastomotic channels through an increase in shear forces and pressure or by formation of new capillary sprouts (angiogenesis). On the other hand, there is strong evidence that the development of human atherosclerotic plaques is associated with the formation of new microvessels within the plaque [22–24]. Therefore, the role of angiogenesis remains highly controversial, and no consensus exists as to whether angiogenesis is the key causative factor in the pathogenesis of atherosclerotic plaque formation or plays a role in the treatment of CAD.

Our data demonstrates that the baseline serum level of angiogenin in patients with MCAD is much higher than reference values. These findings are consistent with other published data [19, 25]. In addition, there is a strong correlation between angiogenin concentration and risk level in CAD. Raised angiogenin levels are independently associated with more adverse events in short- and long-term observations [19, 26]. This is why the decreased concentration of circulating angiogenin observed in our study group, achieved mostly due to complete revascularisation in surgically treated patients, is indirectly associated with a better prognosis (40% reduction of MACE in the surgical group compared to the medical group).

It is very important to clarify the link between adipocytokine level and vascular disease. Adiponectin, an adipocyte-derived plasma protein with anti-diabetic and anti-atherogenic properties, may be a key molecule in the pathogenesis of metabolic syndrome, diabetes mellitus and CAD [27, 28]. Many positive molecular actions (e.g. suppression of macrophage to foam cell transformation, increase in the expression of tissue inhibitor of metalloproteinase-1) suggest that adiponectin contributes to the stabilisation of atherosclerotic plaque [29]. On the other hand, there is strong evidence that patients with HF symptoms have significantly higher adiponectin concentrations than healthy controls, and that patients with the highest adiponectin levels have significantly increased risk of death, irrespective of other baseline clinical or laboratory findings. This is probably a result of robust neurohormonal and inflammatory activation seen in HF patients, but also a consequence of resistance at the level of the adiponectin receptor — a mechanism potentially akin to that seen in diabetics with elevated insulin levels [8, 30, 31]. We believe that the significant lowering of plasma adiponectin concentrations after 12 months (more strongly expressed in the surgical group), observed in our study, might be the result of the improvement of the systolic left ventricular function and HF symptoms, and thus reflect positive effects of the treatment.

There is no clear explanation of the absence of changes in resistin serum concentrations observed in our study. This new, recently discovered inflammatory marker, closely related to atherosclerosis, is elevated in CAD, which reflects the severity of the inflammatory response associated with atherogenesis [32]. There have been many reports showing a strong relationship between resistin levels and the progression, severity and prognosis of CAD [33, 34]. The fact that there was no change in resistin serum concentrations after 12 months in our study is difficult to explain. We can only speculate that a longer follow-up may be required to observe the positive effects of the treatment on circulating resistin level.

Limitations of the study

Two main study limitations need to be acknowledged and addressed. The first concerns choice of treatment strategy, with no randomisation. The second limitation is associated with the relatively small study group and differences in risk profiles within the study group. Finding a more homogenous group of patients, especially regarding their functional class of HF, might help to elucidate the chain of complex relationships between inflammation, atherosclerosis and angiogenesis.

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Wpływ metody leczenia na dynamikę stężeń adiponektyny, rezystyny i angiogeniny w surowicy u pacjentów z wielonaczyniową chorobą wieńcową w trakcie 12-miesięcznej obserwacji*

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Streszczenie

Wstęp: Adiponektyna, rezystyna oraz niedawno odkryty czynnik stymulujący angiogenezę — angiogenina są zaangażowane w patogenezę procesu zapalnego, w tym aterogenezę. Dostępne są tylko ograniczone dane na temat zależnej od przyjętej strategii terapeutycznej dynamiki zmian stężeń tych substancji w surowicy u pacjentów z chorobą wieńcową.

Cel: Celem pracy było porównanie dynamiki zmian stężeń adiponektyny, rezystyny i angiogeniny w surowicy oraz ich wpływu na zdarzenia sercowo-naczyniowe u pacjentów z wielonaczyniową chorobą wieńcową (MCAD) leczonych kardiochirurgicznie lub zachowawczo.

Metody: Do badania włączono 107 pacjentów z MCAD (80 mężczyzn, średni wiek 63 ± 8 lat); 55 (51%) osób leczono kardiochirurgicznie (CABG), a 52 (49%) pacjentów przydzielono do grupy terapii zachowawczej. Stężenia adiponektyny, rezystyny i angiogeniny w surowicy mierzono na początku badania i po 12-miesięcznej obserwacji. Złożony punkt końcowy (MACE) zdefiniowano jako zgon z przyczyn sercowo-naczyniowych, zawał serca niezakończony zgonem, udar mózgu i hospitalizację z przyczyn sercowo-naczyniowych.

Wyniki: W trakcie 12-miesięcznej obserwacji zmarło 9 (8%) osób, wszyscy z przyczyn sercowo-naczyniowych. U 34 (32%) pacjentów stwierdzono MACE. Po 12 miesiącach w grupie CABG udokumentowano istotny spadek stężenia angiogeniny ($p < 0,0001$) i adiponektyny ($p = 0,03$), podczas gdy w grupie osób leczonych zachowawczo zaobserwowano jedynie zmniejszenie stężenia adiponektyny ($p = 0,003$) bez istotnych zmian w stężeniach rezystyny i angiogeniny.

Wnioski: W trakcie 12-miesięcznej obserwacji przyjęta strategia terapeutyczna (optymalna farmakoterapia *v.* CABG) u pacjentów ze stabilną MCAD wpływa na profil cytokin w surowicy na przykładzie angiogeniny i adiponektyny. Ocena dynamiki stężeń tych biomarkerów w tak wyselekcjonowanej grupie chorych może być bardzo przydatna w codziennej praktyce klinicznej.

Słowa kluczowe: adipocytokiny, angiogenina, wielonaczyniowa choroba wieńcowa, rokowanie

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