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Relationship of serum angiogenin, adiponectin and resistin levels with biochemical risk factors and the angiographic severity of three-vessel coronary disease

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Abstract

Background: *Patients with advanced coronary artery disease (CAD) have an unfavorable prognosis. Therefore, early identification of this high-risk group is important. The aim of this study was to assess the usefulness of clinical, electrocardiographic and echocardiographic parameters supported by novel atherogenesis and angiogenesis markers in identifying patients with stable, three-vessel coronary artery disease.*

Methods: *The study group comprised 107 patients suffering from three-vessel CAD and a control group of 15 patients presenting with typical angina, a positive exercise stress test and abnormal segmental contractility, but no hemodynamically significant coronary stenosis in their angiograms. In each patient, we characterized a biochemistry test panel including novel markers: angiogenin, resistin, adiponectin, IL-8 and a TNF-α. The angiographic severity of CAD was expressed as a Gensini score.*

Results: *There were significant differences between three-vessel CAD patients and control groups with respect to the serum levels of: hsCRP (2.8* vs *1.4 mg/L, p = 0.01), HDL-cholesterol (45* vs *54 mg/dL, p = 0.04), LDL-cholesterol (102* vs *95 mg/dL, p = 0.04), NT-proBNP (392* vs *151 pg/mL, p = 0.008) and a marker of angiogenetic activity, angiogenin (414* vs *275 ng/mL, p = 0.02), However, no significant differences were found between three-vessel CAD and the control group with respect to the serum level of adiponectin (8.08* vs *7.82 μg/mL), resistin (17.5* vs *21 ng/mL), IL-8 (20.7* vs *26.8 pg/mL) and TNF-α (4.1* vs *4.3 pg/mL). Angiogenin tended to be higher in patients with higher Gensini scores (p = 0.06) but no influence of ejection fraction was noted.*

Conclusions: *Angiogenin is a novel marker of three-vessel coronary disease showing a relationship with the angiographic severity of the disease.* (Cardiol J 2010; 17, 6: 599–606)

Key words: three-vessel heart 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 mortality is still very high, exceeding seven million in 2002 [2]. Multivessel coronary artery disease (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]. According to various sources, it has been estimated that it accounts for up to 50% of all cases of CAD. The severity of atherosclerosis and numerous complications, with a concomitant lack of clear classification systems and diagnostic criteria, bring about an exceptionally high mortality rate in this population, which in five-year follow-ups ranges from 10% to as much as 60%, depending on the advancement of atherosclerotic lesions and other risk factors [3].

Considering the widespread unfavorable clinical course and poor prognosis of the discussed disease, based on interpretation of some diagnostic tests it would be very useful for clinicians to be able to initially group patients into those at high risk of severe CAD. A central aim of current cardiological research is finding markers which would allow for early diagnosis of MCAD with high specificity. Factors affecting this quest include adipocytokines and angiogenesis.

Adipose tissue is now recognized as an endocrine organ. Adiponectin, an adipocytokine, is a recently discovered protein that seems to play an anti-inflammatory role and regulates inflammatory responses in atherosclerotic lesions [4]. Hypoadiponectinemia has been observed in patients with metabolic syndrome, diabetes mellitus and coronary artery disease [5–7]. Published data supports a strong association between plasma adiponectin levels and atherosclerotic burden [8]. That is why hypoadiponectinemia is considered an independent risk factor and some recent studies have shown that plasma adiponectin levels in patients with MCAD were significantly lower than those in patients with single vessel coronary artery disease [9].

Resistin belongs to a novel family of cysteine-rich proteins called resistin-like molecule or found in inflammatory zones proteins [10]. Resistin appears to be involved in inflammatory pathways, activating vascular endothelial cells, and stimulating smooth muscle cell proliferation; which suggests a potential role in atherosclerosis [11, 12]. Recently, resistin mRNA and protein have been reported to be present in atherosclerotic lesions [13]. This is supported by the fact that levels of circulating resistin increase in patients who have CAD, and it is an inflammatory marker of atherosclerosis in humans.

Angiogenin is a soluble protein belonging to angiogenic factors which are committed in the creation of capillaries, which leads to the formation of new vessels from pre-existing vascular structures [14]. Several studies have suggested that angiogenin, and other angiogenic factors, could promote atherosclerosis and potentially destabilize coronary plaques by promoting intralesional angiogenesis [15, 16]. Moreover, angiogenin has been shown to be an independent predictor of prognosis in coronary heart disease [17].

The aim of this study was to determine the clinical characteristics extended by the determination of novel atherogenesis markers, as well as angiogenesis factors in patients with severe, stable MCAD.

Methods

Study group

The study involved a group of 107 patients hospitalized at the 2nd Department of Cardiology, Medical University in Lodz in 2007 who met the following criteria: (1) Coronary artery disease with ≥ 75% diameter stenosis in three main coronary branches (right coronary artery, circumflex branch and left anterior descending branch of left coronary artery) as confirmed on coronary angiography. Stenosis of the left main coronary artery exceeding 50% represented an exlusion criterion due to the need for urgent revascularization; (2) Stable coronary heart disease (CCS I–III); (3) Absence of significant acquired valve disease resulting in predicted survival below one year.

The control group consisted of 15 patients with a history of typical, exercise-induced stenocardial symptoms, a clinically or electrographically positive exercise stress test, segmental contractility disturbances on echocardiography, with CAD confirmed on angiography but with non-significant coronary artery lumen narrowings (< 50%).

Following discharge from the Department, all patients remained under the care of the Cardiology Outpatient Clinic and were treated according to the guidelines of the European Society of Cardiology. Patients included in the study signed an informed consent form to participate; the study was also approved by the Bioethics Committee at the Medical University in Lodz (Poland).

Biochemical tests

All patients had additional tests performed in order to evaluate disease severity and possible dysfunctions of other organs: 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), CK-MB, urea, creatinine, hepatic transferases, C-reactive protein and NT-proBNP levels. Apart from standard biochemical parameters, we examined novel markers such as adiponectin, resistin, TNF-α, interleukin-8 (IL-8) and angiogenin, which are useful in the assessment of the severity of pathophysiological processes promoting atherogenesis.

Methodology of cytokine measurement

To assess the serum level of novel atherosclerosis markers, the ELISA method applying ready tests manufactured by the Biocom (angiogenin) and Biker (adiponectin, resistin, TNF-α and IL-8) companies was performed.

Electrocardiography, echocardiography, exercise stress test and coronary angiography

Transthoracic echocardiography, resting electrocardiography, and electrocardiographic exercise test were performed at baseline in all patients. Based on coronary angiographic results, the severity of atherosclerotic changes was semiquantified with the Gensini score. Lesions formed (involving lesion severity and location) in 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.

Statistical analysis

The Shapiro-Wilk test was used for determining the normality of distribution of the analyzed variables. Continuous variables showing normal distribution are presented as means ± standard deviations, whereas constant variables of distribution different from normal and ordinal variables are expressed as medians (25^{th}–75^{th} percentile). Variance analysis and the Wilcoxon non-parametric test were applied to compare the differences in the presence of particular features in patient groups. The relationship between continuous variables of normal distribution was analyzed using linear Pearson's correlation analysis. If at least one variable showed other than normal distribution, or was of ordinal type, Spearman rank correlation analysis was applied. The results were considered statistically significant if the p value was < 0.05.

Results

Patients with three-vessel coronary artery disease (TVCAD) had a long history of angina (mean 52 months) and most of them (73%) had previous myocardial infarction. In the study group, the detection of obliterative atherosclerosis of the lower limbs, atrial fibrillation, a positive medical history, stroke and smoking were more common. The distribution of other CAD risk factors in the study group revealed no significant differences in comparison to the control group. Detailed data is shown in Table 1. All patients with TVCAD had ischemic changes on electrocardiography. In most cases, pathological Q waves, negative T waves and ST depression were observed. In patients with TVCAD, echocardiography showed much more aggravated segmental contractility disorders, and left ventricular ejection fraction was significantly lower than in controls (Table 2). Exercise test was more often electrographically positive in TVCAD patients ($p = 0.01$; Table 3). The mean Gensini score in TVCAD patients was 91 (66–132), with the proximal Gensini score being 45 (20–90) and the distal one 39 (20–70). There were significant differences between TVCAD patients and control groups with respect to serum levels of: hsCRP (2.8 *vs* 1.4 mg/L, $p = 0.01$), HDL-cholesterol (45 *vs* 54 mg/dL, $p = 0.04$), LDL-cholesterol (102 *vs* 95 mg/dL, $p = 0.04$), NT-proBNP (392 *vs* 151 pg/mL, $p = 0.008$) and angiogenin (414 *vs* 275 ng/mL, $p = 0.02$), However, no significant differences were found between the TVCAD and control groups with respect to the serum level of adiponectin (8.08 *vs* 7.82 μg/mL), resistin (17.5 *vs* 21 ng/mL), IL-8 (20.7 *vs* 26.8 pg/mL) and TNF-α (4.1 *vs* 4.3 pg/mL; Table 4).

In addition, a negative correlation between adiponectin and both triglyceride ($r = –0.2$, $p = 0.02$) and serum IL-8 levels ($r = –0.2$, $p = 0.03$) and a positive correlation between adiponectin and NYHA class ($r = 0.3$, $p = 0.0025$), NT-proBNP ($r = 0.4$, $p < 0.0001$) and LDL serum levels ($r = 0.4$, $p = 0.0001$) was documented in TVCAD patients. There was a positive correlation between angiogenin and NT-proBNP ($r = 0.3$, $p = 0.001$), resistin ($r = 0.3$, $p = 0.001$) and TNF-α serum levels ($r = 0.3$, $p = 0.005$) as well as resistin levels and NYHA class ($r = 0.2$, $p = 0.02$) levels (Table 5). Serum adiponectin concentration was significantly lower in males (7.38 *vs* 12.6 μg/mL, $p = 0.015$).

Table 1. Selected demographic data of patients with three-vessel coronary artery disease (TVCAD) and control groups.

	TVCAD group (n = 107)	Control group (n = 15)	p
Males	79 (74%)	8 (53%)	0.04
Age	63.1 ± 8.5	59.7 ± 10.8	NS
Duration of angina (months)	52 (20–98)	6 (1–10)	0.001
History of myocardial infarction	73 (68%)	0 (0%)	< 0.001
NYHA class	2 (1–2.5)	0 (0–0)	< 0.001
CCS class	2.5 (2–3)	1 (0–2)	0.01
Kidney failure	3 (3%)	1 (7%)	NS
Hypertension	104 (97%)	13 (87%)	NS
Diabetes mellitus	51 (48%)	6 (40%)	NS
Impaired glucose tolerance	34 (32%)	4 (27%)	NS
Obesity	37 (35%)	5 (33%)	NS
Body mass index	28.8 ± 3.9	28.8 ± 3.3	NS
Smoking	34 (32%)	2 (13%)	0.01
Positive family history	28 (26%)	1 (7%)	0.01
Atrial fibrillation	5 (5%)	0	0.05
Atherosclerosis of peripheral arteries	18 (17%)	0	0.002
Stroke	5 (5%)	0	0.05

NYHA — New York Heart Association; CCS — Canadian Cardiovascular Society

Table 2. Summary of echocardiography and resting electrocardiogram results in patients with three-vessel coronary artery disease (TVCAD) and in control groups.

	TVCAD group (n = 107)	Control group (n = 15)	p
Ejection fraction (%)	45 ± 11	55 ± 6	0.005
Left atrium diameter [mm]	42 ± 5	40 ± 4	NS
Aorta diameter [mm]	34 ± 4	33 ± 4	NS
LVDD [mm]	49 (48–55)	46 (44–47)	0.007
LVSD [mm]	35 (30–42)	30 (27–36)	0.004
Heart rate [hbm]	69 (62–79)	68 (62–85)	NS
ST elevation > 1 mm	10 (9%)	0 (0%)	0.001
ST depression >1 mm	30 (28%)	4 (27%)	NS
Negative T waves	63 (59%)	9 (60%)	NS
Pathological Q wave	62 (58%)	0 (0%)	< 0.001
LBBB	3 (3%)	1 (7%)	NS
Left anterior hemiblock	7 (7%)	2 (13%)	NS
RBBB	4 (4%)	1 (7%)	NS
Non corrected QT [ms]	388 ± 38	363 ± 33	NS

LVDD — Left ventricular diastolic diameter; LVSD — left ventricular systolic diameter; LBBB — left bundle branch block; RBBB — right bundle branch block

Moreover, angiogenin tended to be higher in patients with higher Gensini scores (357 ng/mL in the group with a Gensini score of < 90 and 417 ng/mL in the group with a Gensini score of > 90; p = 0.06) but no influence of the ejection fraction was noted (374 ng/mL in the group with ejection fraction < 40% and 421 ng/mL in the group with ejection fraction > 40%, p = 0.1).

Discussion

An initial selection of patients with a high risk of multivessel CAD, made on the basis of interpretation of some biochemical and imaging tests, would allow for a much earlier qualification for invasive procedures, thus limiting the frequency of cardiovascular adverse events in this group. Medical his-

Table 3. Characteristics of the three-vessel coronary artery disease (TVCAD) group and the control group regarding exercise test results.

	TVCAD group (n = 90)	Control group (n = 15)	p
Workload [METS]	5.5 (4–7)	6 (4.8–8)	NS
Significant ST depression	67 (74%)	7 (47%)	0.02
Significant ST elevation	4 (4%)	0 (0%)	NS
Left bundle branch block	3 (3%)	0 (0%)	NS
Electrographically positive test	74 (83%)	7 (47%)	0.01
Non diagnostic test	11 (12%)	6 (40%)	0.03
Electrographically negative test	5 (5%)	2 (13%)	NS

METS — metabolic equivalents

Table 4. Selected laboratory test results in the three-vessel coronary artery disease (TVCAD) group and the control group

	TVCAD group (n = 107)	Control group (n = 15)	p
Adiponectin [μg/mL]	8.08 (5.8–12.9)	7.82 (4.6–8.9)	NS
Resistin [ng/mL]	17.5 (12.5–25.4)	21 (16.6–24.3)	NS
Interelukin-8 [pg/mL]	20.7 (12–30)	26.8 (12.6–40.1)	NS
TNF-α [pg/mL]	4.1 (2.3–4.9)	4.3 (4–4.4)	NS
Angiogenin [ng/mL]	414 (326–521)	275 (127–447)	0.02
Hemoglobin [g/dL]	14.5 ± 1.3	14.6 ± 1.5	NS
WBC [$\times 10^3/\mu$L]	7.5 (6.4–9.6)	7.4 (6.6–7.9)	NS
PLT [$\times 10^3/\mu$L]	251 ± 67	239 ± 48	NS
Total cholesterol [mg/dL]	171 (148–210)	185 (169–199)	NS
HDL [mg/dL]	45 (39–52)	54 (43–63)	0.04
LDL [mg/dL]	102 (79–128)	96 (84–116)	0.04
Triglycerides [mg/dL]	131 (94–184)	150 (115–202)	NS
hsCRP [mg/L]	2.8 (1.6–5.4)	1.4 (1.1–2)	0.01
Urea [mg/dL]	34 (29–42)	28 (24–39)	0.025
Creatinine [mg/dL]	0.91 ± 0.13	0.89 ± 0.18	NS
Uric acid [mg/dL]	6 ± 1.2	5.3 ± 1.3	NS
GFR [mL/min/1.73 m^2]	92 (79–118)	113 (70–122)	NS
NT-proBNP [pg/mL]	392 (162–850)	151 (83–221)	0.008
HbA1c (%)	6 (5.6–7.1)	5.8 (5.7–6.2)	NS
Fibrinogen [mg/dL]	385 (335–440)	360 (315–455)	NS

WBC — white blood count; PLT — platelets; hsCRP — high sensitivity C-reactive protein; GFR — glomerular filtration rate; HbA1c — hemoglobin A1c

tory, together with the interpretation of some selected routine imaging studies, appears to be the key aspect of management in this case. In light of the above, novel biochemical markers, such as the marker of angiogenetic activity (angiogenin), have shown promising results. However, we did not find that knowledge of the serum levels of selected adipocytokines (adiponectin and resistin), as well as novel inflammatory markers (IL-8 and TNF-α) made it possible to obtain additional information on the discussed aspect. Importantly, in this study we confirm many of the metabolic associations reported previously for resistin and adiponectin [11, 18, 19]. Specifically, in our study, lower levels of adiponectin were seen in association with hypertriglyceridemia and high HDL-cholesterol concentrations. We also report a strong positive correlation between adiponectin and resistin levels and heart failure symptoms as well as NT-proBNP serum concentration. In this regard, our findings are in accord with the literature and support the validity of our dataset.

Table 5. Correlations between selected parameters in the study group.

	Adiponectin	Resistin	Interleukin-8	TNF-α	Angiogenin
NYHA class	r = 0.3 p = 0.0025	r = 0.2 p = 0.02	r = –0.15 p = NS	r = –0.03 p = NS	r = –0.04 p = NS
NT-proBNP	r = 0.4 p < 0.0001	r = 0.04 p = NS	r = –0.04 p = NS	r = 0.2 p = NS	r = 0.3 p = 0.001
HDL-cholesterol	r = 0.4 p = 0.0001	r = 0.05 p = NS	r = –0.07 p = NS	r = 0.04 p = NS	r = –0.04 p = NS
Triglycerides	r = –0.2 p = 0.02	r = –0.04 p = NS	r = –0.05 p = NS	r = 0.04 p = NS	r = 0.06 p = NS
Adiponectin		r = –0.1 p = NS	r = –0.2 p = 0.03	r = 0.03 p = NS	r = –0.04 p = NS
Resistin	r = –0.1627 p = NS		r = 0.1 p = NS	r = 0.2 p = NS	r = 0.3 p = 0.001
Interleukin-8	r = –0.2 p = 0.03	r = 0.1 p = NS		r = 0.1 p = NS	r = 0.1 p = NS
TNF-α	r = 0.03 p = NS	r = 0.16 p = NS	r = 0.1 p = NS		r = 0.3 p = 0.005
Angiogenin	r = –0.04 p = NS	r = 0.3 p = 0.001	r = 0.1 p = NS	r = 0.3 p = 0.005	

Understanding mechanisms underlying the atherosclerotic process, from a pathologist's point of view being a form of inflammatory response to factors damaging the vessel wall, has made it possible to identify many markers of inflammatory response crucial in atherogenesis. A new, recently revealed inflammatory marker, closely connected to atherosclerosis, is the fat cell protein product, resistin. There are many studies showing elevated serum resistin levels in CAD patients which indicate the severity of the inflammatory response connected with atherogenesis [20]. The reports published so far on the relationship between resistin levels and progression, severity and prognosis of patients with CAD give contradictory information. Reilly et al. [20] demonstrated a relationship between resistin levels and the degree of coronary artery calcification ('calcium score') computed on the basis of the interpretation of imaging from computed tomography performed in asymptomatic patients. In addition, based on angiographic evaluation, Ohmori et al. [11] came to the conclusion that there is a correlation between the resistin level and the number of stenoses in coronary arteries. Hu et al. [21] also documented significantly different concentrations of resistin in stable and unstable CAD, thus confirming the role of resistin in risk stratification of atherosclerotic plaque destabilization in CAD patients. On the other hand, Pilz et al. [22] did not show any correlation between resistin levels and the severity of atherosclerosis in a group of 1,100 patients, though a high level of resistin was a strong and independent predictor of non-fatal cardiovascular events in this group. Similar conclusions follow from research conducted by Hoefle et al. [23], where in a group of 547 patients, there were no significant differences in serum resistin between patients with CAD and those in whom angiography did not show CAD, nor between patients with ≥ 50% coronary narrowings and those without such lesions.

Another substance recently detected and found to be useful in the risk stratification of multivessel CAD is adiponectin, the insulin-sensitizing, anti-inflammatory anti-atherosclerotic protein. The pleiotrophy of adipokine activity is the reason for performing a number of clinical studies investigating its usefulness in everyday medical practice. Our findings with respect to the lack of correlation between adiponectin levels and the severity of atherosclerosis in coronary vessels are in contrast to many other studies that have reaffirmed a strong relationship between a low serum level of adiponectin and the severity of CAD. According to Otsuka et al. [9], in a group of 207 patients with confirmed CAD, a level of adiponectin lower than 4 μg/mL is a strong and independent predictor of severe atherosclerosis of coronary arteries (OR 2.14, p = 0.027). Miłosz et al. [24] drew similar conclusions: mainly that hypoadiponectinemia and exacerbation of inflammatory processes, expressed by C-reactive protein and sVCAM-1 concentrations, were responsible for a greater escalation of atherosclerosis in coronary arteries. These conflicting observations may relate, at least in part, to the markedly different risk pro-

files of the populations in our study. Our study population consisted of a relatively high-risk cohort as manifested not only in the clinical, angiographic, and laboratory data, but also in the high incidence of heart failure. Indeed, it is well-established that patients with heart failure symptoms have higher baseline levels of adiponectin, which may be a consequence of resistance at the level of the adiponectin receptor, a mechanism potentially akin to that seen in diabetics with elevated insulin levels [25, 26].

The presence of coronary collateralization improves the prognosis of patients with advanced CAD. Collaterals improve ventricular function and overall perfusion in the ischemic myocardium [27]. The development of coronary collaterals appears to be initiated by ischemia 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 [16, 28]. That is why the role of angiogenesis remains highly contentious, and no consensus exists as to whether angiogenesis is the key causative factor in the pathogenesis of atherosclerotic plaque formation, or a way to treat CAD. Our data demonstrates that the serum level of angiogenin is about 35% higher in patients with multivessel coronary heart disease than in patients without significant narrowings in the coronary arteries. These findings are consistent with data coming from Tello-Montoliu et al. [17], where the authors demonstrated in a group of 516 patients that 'acute coronary syndrome' patients had significantly elevated plasma angiogenin levels as compared with both diseased controls (stable CAD) and healthy controls ($p < 0.001$). However, the authors did not find any correlation between angiogenin and the severity of atherosclerosis expressed as a Gensini score; raised angiogenin levels were independently associated with more adverse events at a six month follow-up. Other pro-angiogenic molecules have been studied in coronary heart disease, in particular VEGF, hepatocyte growth factor, and angiopoietin types 1 and 2. In all the studies, patients presenting with advanced atherosclerosis had significantly higher levels of pro-angiogenic effector molecules as compared to (usually healthy) controls [29–31].

Limitations of the study

This study is limited by the relatively small control group and the high variety of risk profiles in the study group. Finding a more homogenous group of patients (especially as regards heart failure symptoms) might help to better understand the chain of complex relationships between inflammation, atherosclerosis and angiogenesis.

Conclusions

The ability of each clinician to perform risk stratification of atherosclerosis severity in coronary arteries is very important. Angiogenin is a novel marker of three-vessel coronary disease, showing a relationship with the angiographic severity of the disease. This initial demonstration of the diagnostic potential of the marker warrants further studies on its practical usefulness and relationship to established clinical factors.

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