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Tissue Factor and Other Hemostatic Parameters in Patients with Advanced Peripheral Artery Disease After Endovascular Revascularization – Search for Hemostatic Factors which Indicate Restenosis*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. In patients with peripheral artery disease (PAD) a hypercoagulable state and thromboembolic complications occur. Revascularization procedures increase this state, sometimes leading to restenosis. Restenosis following balloon angioplasty (PTA)and stent implantation is ≥ 50% of artery stenosis.
Objectives. To determine the concentration of tissue factor (TF), tissue factor pathway inhibitor (TFPI), thrombin–antithrombin (TAT) complexes, fibrinogen and D-dimers in the blood of patients with PAD after peripheral endovascular revascularization of the lower legs and in PAD patients with restenosis.
Material and Methods. The study included 150 patients with PAD, 90 men and 60 women, aged 44–88 (mean 65.5) years, after successful peripheral angioplasty (PTA) and/or with stenting. During the 6 months after the revascularization procedures, restenosis occurred in 27 patients. The reference group consisted of 53 healthy persons (44 men and 9 women, aged 20–56 years). Blood was drawn in the morning into 3.2% natrium citrate at a ratio of 9 : 1. The concentration of TF, TFPI, TAT complexes and D-dimers were measured in plasma with commercial tests using an enzyme immunoassay. Fibrinogen was determined with coagulometer.
Results. In the plasma of patients with PAD after endovascular revascularization, the concentrations of TF, TAT complexes, fibrinogen and D-dimers were significantly higher compared to the reference group. During the six months of observation, 27 patients developed restenosis. The results of hemostatic factors in patients with restenosis were compared with the same patients before restenosis and the group of 123 PAD patients after endovascular revascularization. TF and fibrinogen levels in the 27 patients with restenosis were significantly higher than in the group of PAD patients before restenosis.
Conclusions. Statistically significantly higher levels of tissue factor (TF) and fibrinogen in PAD patients with new restenosis, compared to those without restenosis after endovascular revascularization, indicate they can participate in the formation of restenosis (**Adv Clin Exp Med 2015, 24, 1, 93–98**).

Key words: PAD, endovascular revascularization, restenosis, hemostasis.

Peripheral artery disease (PAD) of the lower legs with its symptomatic manifestations: intermittent claudication or critical leg ischemia (rest pain, ulceration, gangrene) is associated with significant morbidity and mortality. In PAD patients, many activation markers of blood coagulation and fibrinolysis with several hemostatic parameters were determined to investigate the relation between the

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extension and main localization of atherosclerosis, risk factors and disturbances within the blood coagulation and fibrinolysis system. Compared to a healthy control group, PAD patients had elevated TAT complexes, prothrombin fragments 1 + 2 (PF 1 + 2), D-dimers, fibrinogen, von Willebrand factor (vWF), tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) as well as proteins C (PC) and S (PS) [1–3]. PAD patients exhibit a prothrombotic or thrombogenic state of blood and thromboembolic complications. These plasma clotting and fibrinolytic parameters together with tissue factor (TF) and tissue factor pathway inhibitor (TFPI) can be found in the structure of atherosclerotic plaques [4, 5]. TF is the principal initiator of the extrinsic blood coagulation pathway and the major factor inducing fibrin deposition *in vivo*. Complex TF/VIIa is assembled on the cell surface with the strongest natural plasma inhibitor TFPI [6, 7]. According to Ross's theory, the primary event in the development of atherosclerotic plaques in the arterial wall is the damage of endothelial and smooth muscle cells by various pathological factors including high blood pressure, oxygenated LDL, homocysteine, viruses, bacteria, immune or mechanical factors and others [8]. After the lesion, the arterial wall exposes TF, a receptor for plasma factor VII. Subsequently, TF/VIIa complexes activate the extrinsic coagulation process, which results higher thrombin generation and an increase in the concentration of TAT-complexes [7]. The high level of TF and TAT-complexes in PAD can indicate a hypercoagulable state and formation of thromboembolic complications. Similar to in other forms of atherosclerosis (i.e. cardiovascular diseases and the PAD), the release of TF is a response of the tissues after arterial wall damage. In the formation of atherosclerotic plaques, an interaction of endothelial and smooth muscle cells with macrophages, blood platelets and T-lymphocytes take part with many growth factors and cytokines forming during the inflammation process [8]. The plaques narrow or occlude the lower legs arteries. Different surgical and endovascular revascularization methods exist for treatment of PAD patients [9–11]. Currently, percutaneous transluminal angioplasty (PTA) with or without vascular stenting are the best procedures to improve blood flow in narrowed arteries. These procedures are minimally invasive; however angioplasty and stenting can sometimes cause another artery stenosis (restenosis) or occlusion. Restenosis following balloon angioplasty (PTA) and stent implantation is ≥ 50% of artery stenosis. When restenosis appears, this procedure can be repeated. The effects are less successful when multiple leg arteries are narrowed or occluded and when very small vessels have to be opened [10–12].

The aim of our study was to determine the concentration of TF, TFPI, TAT complexes, fibrinogen and D-dimers in the blood of patients with PAD after peripheral endovascular revascularization of the lower legs; to observe the appearance of new restenosis within 6-months in some of these patients; to compare these hemostatic factors in both groups of PAD patients before and after new restenosis, to search for hemostatic factors indicating restenosis.

Material and Methods

The study included 150 PAD patients, 90 men and 60 women aged 44–88 years, 1 week to 18 months after endovascular revascularization: 21 with PTA (percutaneous transluminal angioplasty), 49 with stent implantations and 80 with PTA and stenting. Patients were recruited from August 2010 to June 2012. Seventy seven PAD patients were 1 week to 3 months after treatment, 30 were more than 3 to 6 months after and 43 patients were more than 6 to 18 months after. Revascularization was performed on following arteries: iliac – 65, femoral superficial – 69, popliteal and crural – 38 (together 172 extremities). Before revascularization, 132 PAD patients had ischemic rest pain acc. Rutherford degree II, category 4 and 18 PAD patients had degree III and category 5 (acc. Fontaine – stages III and IV). In all 150 patients with PAD, a medical interview, physical examination, hematological and biochemical tests and vascular examinations were performed. Ischemia of the lower extremities was diagnosed based on ultrasound examinations (USG duplex Doppler) and before revascularization also with computer tomography and arteriography. Intermittent claudication and ankle brachial index (ABI) were also measured. In all PAD patients, ABI was < 0.9. 18 patients had small leg ulceration with stable low inflammation (C-reactive protein – CRP = 5.2 ± ± 3.7 mg/L). All revascularization procedures were successful. No amputations were performed. During a further 6 months, the patients remained under angiological care. In 27 PAD patients, restenosis occurred within 6 months. The demographic dates of these PAD patients are shown in Table 1.

Because the test producers did not present normal laboratory results, we examined a reference group consisting of 53 healthy subjects who had qualified for their first blood donation at the Blood Donation Center – 44 men and 9 women, aged 20–56 years. In these healthy persons, a medical

Table 1. Demographics of PAD patients after endovascular revascularization

PAD patients		n	%
		150	100
Men/Women		90/60	60/40
Age – years	mean	65.5 44–88	
CAD and infarction		101	67.3
Stroke		17	11.3
Hypertension		126	84.0
Dyslipidemia		120	80.0
Overweight and obesity BMI > 25		115	76.6
Type 2 diabetes		91	61.0
Smokers former/current		131/41	76.6

PAD – peripheral artery disease; CAD – coronary artery disease.

history and physical examination as well as laboratory tests including blood type identification, blood cell count and viral test were performed. The reference group was younger than the PAD patients, but literature data suggests that sex and age do not influence the assessed parameters [7, 14].

A 4.5 mL blood sample for laboratory tests was drawn in the morning after night fasting from an antecubital vein to a test tube with 3.2% sodium citrate at a ratio of 9 : 1. The plasma was obtained by centrifugation of blood samples at 2500 g for 15 min. Subsequently, 0.2 mL of the plasma to be tested was pipetted into Eppendorf tubes and stored at –80°C until analysis. The plasma concentration of hemostatic factors TF, TFPI, TAT complexes and D-dimers were measured with commercial tests with enzyme immunoassay. Blood was drawn in all PAD patients after endovascular revascularization and in PAD patients with restenosis formation. The following reagents were used:

TF – Imubind TF Elisa Kit (American Diagnostica Inc.). This assay detects TF and TF/VIIa complexes.

TFPI – Imubind Total TFPI Elisa Kit (American Diagnostica Inc.). This assay detects both full-chain and truncated TFPI complexes with either TF or factor VIIa. TFPI suppresses both factor Xa and TF/VIIa complexes.

TAT complexes – Enzygnost TAT micro – Siemens.

D-dimer – Innovance D-dimer Siemens.

Fibrinogen was measured using the Fibrintimer coagulometer (LAbor Germany). The manufacturer has not specified the normal range of hemostatic factors, but recommends that each laboratory establish its own reference values.

In tables, we describe 5 groups of patients:

1. Group A – all 150 PAD patients,
2. Group A1 – 123 PAD patients (Total Group A – 27 with restenosis),
3. Group B – 27 PAD patients before restenosis,
4. Group C – 27 PAD patients with new restenosis,
5. A reference group consisting of 53 healthy persons.

The protocol of the study was approved by the Bioethical Committee at the Regional Specialist Hospital in Wrocław.

Statistical Analysis

The results are presented in tables as mean value (M), standard deviation (SD), median (Me) and interquartile range (lower Q1 and upper Q3). Normality of distribution was assessed using the D'agostino-Pearson test. The statistical significance of differences between groups was analyzed with a nonparametric Mann-Whitney test (in case of non-normal data: TF, TFPI, TAT complexes and D-dimers), only fibrinogen was analyzed with the Student's *t*-test. The level of statistical significance was adopted at $p < 0.05$.

The correlations between the measured parameters characterized by non-normal data distribution were calculated using the Spearman rank correlation coefficient (r_s) with significance level p. Statistical analysis was performed with R for Windows (The R Foundation for Statistical Computing, Vienna, Austria) and MedCalc for Windows (MedCalc Software, Mariakerke, Belgium).

Results

Elderly PAD patients after endovascular revascularization had many risk factors and accompanied diseases.

The mean and median levels of TF, TAT complexes, fibrinogen and D-dimers in elderly PAD patients after endovascular revascularization were significantly higher than in the younger reference group. But TFPI concentration was similar in both groups.

Spearman's correlations between determined clotting factors in PAD patients exhibit a positive but weak interaction. Significant moderate correlation exists between tissue factor and TAT complexes only in the group of PAD patients with restenosis, which indicates a common interaction.

Only TF and fibrinogen levels were significantly higher in PAD patients with new restenosis compared to the same group of patients before restenosis and with the 123 PAD patients after endovascular revascularization

Table 2. Some hemostatic factors in PAD patients after successful peripheral endovascular revascularization and in the reference group

	All PAD patients (Group A) (n = 150)	**Reference group (n = 53)**	**Significance level**
Assessed parameters	M ± SD Me Q 1–Q 3	M ± SD Me Q 1–Q 3	p – value
TF pg/mL	194 ± 119 158 112–249	144 ± 71 135 92–192	0.013
TFPI ng/mL	59 ± 28 50 40–68	54 ± 14 55 41–62	0.78
TAT complexes ng/mL	6.4 ± 14.9 3.2 2.4–3.9	3.0 ± 5.3 1.4 0.6–2.4	0.0001
Fibrinogen g/L	3.67 ± 0.95 3.5 3.0–4.1	 2.82* 1.8–3.5*	0.01
D-dimers ng/mL	731 ± 736 515 347–832	275 ± 220 183 140–342	0.0001

n – number; M – mean; SD – standard deviation; Me – median; Q – quartils; PAD – peripheral artery disease; TF – tissue factor; TFPI – tissue factor pathway inhibitor; TAT complexes – thrombin–antithrombin complexes.

Table 3. Spearman's correlation coefficient between the determined clotting factors in PAD patients

Examined parameters	**PAD patients n = 150**	
	r_s	**p**
TF/TFPI	0.196	p < 0.016
TFPI/fibrinogen	0.167	p < 0.043
TAT complexes/D-dimers	0.184	p < 0.026
Fibrinogen/D-dimers	0.265	p < 0.001
	PAD patients with restenosis n = 27	
TF/TAT complexes	0.458	p < 0.002

r_s – Spearman correlation coefficient; n – number; p – significance level; PAD – peripheral artery disease; TF – tissue factor; TFPI – tissue factor pathway inhibitor; Fibrinogen; TAT complexes – thrombin–antithrombin complexes.

Discussion

Peripheral Artery Disease (PAD) is the major manifestation of atherosclerosis and is commonly found in elderly patients. It is well established that mainly hypertension, smoking, diabetes mellitus and hypercholesterolemia play a major role in the manifestations of atherosclerosis although the prognostic potency of each of these factors in atherosclerosis differ in the various arterial beds. The data of our PAD patients agrees with these observations. The occurrence of CAD in our PAD patients was higher than 67%, while in PAD in the literature it ranges between 43 and 90%. [13]. The causative role of inflammation in the atherosclerosis process was established by Russel Ross [8]. Many articles exist on this theme. We also observed, in PAD patients after endovascular revascularization and in patients with restenosis increased inflammatory factors: CRP, fibrinogen and interleukin 6 and 10 [14]. The mean or median levels of TF, TAT complexes, fibrinogen and D-dimers in PAD patients after endovascular revascularization were significant higher than in the younger reference group (Table 2). This observation agrees with the literature on blood clotting factors in PAD patients [15–18]. But TFPI levels in our PAD patients and the reference group were similar independently of age. The mean concentration of TF in the group with PAD was 194 ± 120 pg/mL and was significantly higher than in the reference group (p < 0.013). This result was similar to Radziwon et al., who acquired a level of TF = 217 pg/mL in patients with intermittent claudication, but they did not find any difference between PAD patients and the control group [15]. Our results of TFPI level in PAD after endovascular revascularization did not agree with the results of Radziwon et al., who observed very high level of TFPI (333.3 ± ± 10.2 ng/mL) in PAD with intermittent claudication [15]. In our examination, PAD patients compared to the reference group also had significantly increased TAT complexes. Many reports about TAT complexes in different stages of PAD also had significantly higher TAT complexes [1–3]. In our patients, higher fibrinogen level is not only a clotting factor, but also an inflammatory mediator. In group A of the patients, the mean level of CRP was 4.35 mg/L [14]. Schillinger et al. suggested that CRP better predicts the inflammatory process than fibrinogen [18]. Higher D-dimers in PAD (group A) illustrate activation of fibrinolysis moderately higher than in the reference group. In the past

Table 4. Comparison of the examined parameters in 123 PAD patients after successful peripheral endovascular revascularization (group Al) and patients with restenosis: before (group B) and after newly-created restenosis (group C) within a 6-month observation

Assessed parameters	PAD patients after endovascular revascularization (n = 123) (group A1)	Patients with restenosis (n = 27)		Significance level p-value		
		before restenosis	after restenosis	group A1-C	group A1-C	group B-C
	M ± SD Me QI–Q3	M ± SD Me QI–Q3	M ± SD Me Q1–Q3			
TF pg/mL	186.6 ± 116.9 153.0 108.5–237.6	215.1 ± 126.7 177.0 123.4–309.0	245.0 ± 133.0 215.0 178.0–304.0	0.28	0.014 x	0.048 x
TFPI ng/mL	57.9 ± 28.7 50.7 39.6–69.5	58.4 ± 28.1 49.4 43.9–65.9	58.4 ± 26.6 51.9 42.4–65.5	0.89	0.78	0.67
TAT complexes ng/mL	6.0 ± 13.4 3.3 2.5–4.3	8.3 ± 20.3 3.2 2.5–4.8	4.0 ± 3.3 3.0 2.3–3.8	0.88	0.32	0.16
Fibrinogen g/L	3.7 ± 0.8 3.5 3.2–4.1	3.5 ± 0.9 3.5 2.9–4.2	4.0 ± 1.0 3.6 3.4–4.6	0.38	0.14	0.008x
D-dimer ng/mL	755 ± 768 526 390–837	624 ± 563 422 313–803	690 ± 664 513 329–832	0.18	0.54	0.14

n – number; M – mean; SD – standard deviation; Me – median; Q – quartils; PAD – peripheral artery disease; TF – tissue factor; TFPI – tissue factor pathway inhibitor; TAT complexes – thrombin–antithrombin complexes; x – significant.

decade, cytokines and other inflammatory markers have been extensively investigated in various diseases, including PAD with arterial thrombosis after revascularization [8, 18–22]. Performed correlations between the determined hemostatic factors in PAD patients indicate significant but weak correlations. More importantly, there is a moderate correlation between tissue factor (TF) and thrombin/antithrombin (TAT) complexes, which can indicate the activation of thrombin generation by complex TF/VIIa ($r_s = 0.458$, $p < 0.002$). In the literature there are only a few articles concerning TF and TFPI in PAD patients after endovascular revascularization and after formation of new restenosis [19]. Observation of the 150 PAD patients within 6 months after endovascular revascularization showed 27 subjects (18%) in which restenosis occurred. We compared the hemostatic factors TF, TFPI, TAT complexes, fibrinogen and D-dimers in 3 groups of PAD patients: group C with new restenosis (27), group B before restenosis (27) and group A1 – 123 patients, i.e. the total group minus those 27. Only tissue factor (TF) and fibrinogen were statistically significantly higher in PAD patients with new restenosis (group C) compared to group B before restenosis and the group A1 with PAD without restenosis. This view agrees with the observation of Mizuno et al., who after coronary angioplasty observed increased tissue factor expression in coronary circulation and thought that TF is a good prognostic factor for late restenosis [23]. The moderate correlation of TF and TAT complexes only in PAD patients with new restenosis indicated its participation in the formation of restenosis. Pärson et al. suggested that the prothrombotic state and increased fibrinolysis induced by surgical revascularization were still evident 30 days after a successful procedure. In PAD patients, the determined parameters, TAT complexes, PF 1+2, fibrinogen, CRP and D-dimers, were increased [16].

The results of Tschöpl et al. in PAD patients with extended atherosclerosis or after PTA, showed that high procoagulant factors such as the von Willebrand factor (vWF), PF 1+2, fibrinogen, CRP, D-dimers and thrombin generation were increased [17]. The authors confirmed that surgical and PTA procedures increased hypercoagulability and can promote thrombosis and restenosis [16–18].

The authors concluded that statistically significantly higher levels of tissue factor (TF) and fibrinogen in PAD patients with new restenosis compared to those without restenosis after endovascular revascularization indicate they can participate in the formation of restenosis.

References

[1] **Strano A, Hoppensteadt D, Walenga JM, Fareed J, Saba C, Berard E:** Plasma levels of the molecular markers of coagulation and fibrinolysis in patients with peripheral arterial disease. Semin Thromb Hemost 1996, 22 Suppl 1, 35–40.

[2] **Makin A, Silverman SH, Lip GY:** Peripheral vascular disease and Virchow's triad for thrombogenesis. QJM 2002, 95, 199–210.

[3] **Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J:** Markers of coagulation activation endothelial stimulation and inflammation in patients with peripheral arterial disease. Eur J Vasc Endovasc Surg 2005, 29, 171–176.

[4] **Migdalski A, Jawień A, Kotschy M, Knapik-Bieniek A:** Selected haemostatic factors in carotid bifurcation plaques of patients undergoing carotid endarterectomy. Eur J Vasc Endovasc Surg 2004, 27, 172–179.

[5] **Migdalski A, Kotschy M, Jawień A:** Tissue factor, tissue factor pathway inhibitor and vascular endothelial growth factor-A in carotid atherosclerotic plaques. Eur J Vasc Endovasc Surg 2005, 30, 41–47.

[6] **Lwaleed BA, Bass PS:** Tissue factor pathway inhibitor: structure, biology and involvement in disease. J Pathol 2006, 208, 327–339.

[7] **Kotschy M, Kotschy D, Witkiewicz W:** Rola czynnika tkankowego i jego inhibitora w procesie krzepnięcia krwi oraz w powikłaniach zakrzepowych. Kardiol Pol 2010, 10, 1158–1162.

[8] **Ross R:** The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993, 362, 801–809.

[9] **Rowe VL, Lee W, Weaver FA, Etzioni D**: Patterns of treatment for peripheral arterial disease in the United States: 1996–2005. J Vasc Surg 2009, 49, 910–917.

[10] **Gabrusiewicz A, Słowiński P, Krosny T, Staszkiewicz W:** The present state of the art of the pathophysiology, diagnosis and treatment of the superficial femoral artery occlusion based on own results. Post N Med 2012, 25, 612–616.

[11] **Bennett MR:** In-stent stenosis: pathology and implications for the development of drug eluting stents. Heart 2003, 89, 218–224.

[12] **Goodney PP, Beck AW, Nagle J:** National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. J Vasc Surg 2009, 50, 54–60.

[13] **Brevetti G, Schiano V, Chiariello M:** Endothelial dysfunction: a key to the pathophysiology and natural history of peripheral arterial disease. Atherosclerosis 2008, 197, 1–11.

[14] **Kotschy D, Kotschy M, Masłowski L, Socha P, Kwapisz J, Czyżewska-Buczyńska A, Karczewski M, Witkiewicz W:** Inflammatory markers in peripheral arterial diseases patients after endovascular revascularization with new restenosis. Acta Angiol 2014, 20, 47–59.

[15] **Radziwon P, Bielawiec M, Kłoczko J, Giedrojć J, Mazgajska K, Galar M:** Tissue factor pathway inhibitor (TFPI) in patients with occlusive arterial diseases in consideration with risk factors and conservative treatment of the disease. Acta Angiol 2001, 7, 43–54.

[16] **Pärsson H, Holmberg A, Siegbahn A, Bergqvist D:** Activation of coagulation and fibrinolytic systems in patients with CLI is not normalized after surgical revascularisation. Eur J Vasc Endovasc Surg 2004, 27, 186–192.

[17] **Tschöpl M, Tsakiris DA, Marbet GA, Labs KW, Jäger K:** Role of hemostatic risk factors for restenosis in peripheral arterial occlusive disease after transluminal angioplasty. Arterioscler Thromb Vasc Biol 1997, 17, 3208–3214.

[18] **Schillinger M, Exner M, Mlekusch W, Rumpold H, Ahmadi R, Sabeti S:** Vascular inflammation and percutaneous transluminal angioplasty of the femoropopliteal artery: association with restenosis. Radiology 2002, 225, 21–26.

[19] **Steffel J, Lüscher TF, Tanner FC:** Tissue Factor in Cardiovascular Diseases. Circulation 2006, 113, 722–731.

[20] **Joseph L, Fink LM, Hauer-Jensen M:** Cytokines in coagulation and thrombosis: a preclinical and clinical review. Blood Coagul Fibrinolysis 2002, 13, 105–116.

[21] **Nijm J, Wikby A, Tompa A:** Circulating levels of proinflammatory cytokines and neutrophil-platelet aggregates in patients with coronary artery disease. Am J Cardiol 2005, 95, 452–456.

[22] **Schillinger M, Exner M, Mlekusch W:** Endovascular revascularization below the knee: 6-month results and predictive value of C-reactive protein level. Radiology 2003, 227, 419–425.

[23] **Mizuno O, Ikeda U, Hojo Y:** Tissue factor expression in coronary circulation as a prognostic factor for late restenosis after coronary angioplasty. Cardiology 2001, 95, 84–89.

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