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Selected endothelial hemostatic markers in patients with peripheral arterial disease after endovascular revascularization and restenosis formation*

Wybrane śródbłonkowe markery hemostazy u pacjentów z miażdżycą tętnic kończyn dolnych po wewnątrznaczyniowej rewaskularyzacji i po powstaniu restenoz

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: Surgical and endovascular revascularization of ischemic legs in patients with peripheral arterial disease (PAD) can damage the arterial wall (endothelial and smooth muscle cells). Hemostatic factors released during endothelial dysfunction can lead to restenosis.

Aim: 1. Determination of selected endothelial hemostatic factors in PAD patients and a reference group.
2. Prospective observation of new restenosis appearance in PAD patients after endovascular revascularization.
3. Comparison of selected endothelial hemostatic factors between non-restenotic and restenotic PAD patients.

Patients & methods: 150 PAD patients after endovascular revascularization – 90 men and 60 women, aged 44-88 (mean 65.5) years – were examined. During one-year observation after the revascularization procedures in 38 PAD patients restenosis occurred, when blood samples were also collected. 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% sodium citrate at a ratio of 9:1. Tissue factor (TF), tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), von Willebrand factor (vWF) and tissue plasminogen activator (t-PA) were measured in plasma with commercial tests using the enzyme immunoassay.

Results: In the plasma of PAD patients after revascularization, the concentrations of TF and vWF were significantly higher, TM lower, TFPI and t-PA similar compared to the reference group. Six months after revascularization the level of TF had increased and vWF had significantly decreased. The endothelial hemostatic factors before and after restenosis did not significantly differ except TF, which after restenosis was higher.

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Increased TF and vWF levels in PAD patients indicate arterial endothelial cell damage, by atherosclerotic and revascularization processes. In PAD patients with restenosis compared to these patients before restenosis the determined endothelial hemostatic factors, except TF level, did not significantly differ. Perhaps TF participates in restenosis formation.

Keywords: endothelial hemostatic factors • endovascular revascularization • restenosis

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Introduction

In patients with peripheral arterial disease (PAD) of the legs, increased coagulation and thromboembolic complications occur [2,25,28]. Surgical and endovascular revascularization procedures increase this thrombogenic state, sometimes leading to restenosis [19,22]. Vascular endothelium is located at the interface between vascular tissue and blood. It is pivotal for protecting against vascular injury and maintaining blood fluidity. Injury of endothelium is accompanied by loss of protective molecules, procoagulant activities and mitogenic factors, leading to endothelial and smooth muscle cell proliferation and migration and to development of atherosclerosis and thrombosis in PAD [31].

Endothelium releases nitric oxide and prostacyclin, potent vasodilators and inhibitors of platelet activation. Injury of the arterial wall induces a hemostatic response and release of: tissue factor (TF), tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), von Willebrand factor (vWF) and tissue plasminogen activator (t-PA). TF released from the damaged endothelial, smooth muscle cells and monocytes induces proliferation and migration of these cells. TF leads to an inflammatory process and induces blood coagulation, thrombin generation and fibrin formation. This process involves controlled interaction between different hemostatic proteins [28]. TF and TFPI with other clotting factors were found in the structure of atherosclerotic plaques [15,16]. TF is the principle initiator of the extrinsic blood coagulation and the major factor inducing fibrin deposition *in vivo*. The TF/VIIa complex is assembled on the cell surface with the strongest natural plasma inhibitor TFPI [10,27]. TFPI inhibits TF and TF/VIIa complex and also participates in a ternary complex with factor X and factor VIIa bound to tissue factor [13]. TM serves as a binding site for thrombin, forming a TM/thrombin complex, in which thrombin depreciates its possibility to activate factors V, VIII and XIII, blood platelets and conversion of fibrinogen to fibrin. The TM/thrombin complex activates proteins C and S and also inhibits fibrinolysis, blocking the activation of thrombin activatable fibrinolysis inhibitor (TAFI) [7]. Recombinant human thrombomodulin inhibits arterial neointimal hyperplasia after balloon injury [12]. Endothelium produces and secrets vWF, which mediates platelet adhesion to bind platelets at the site of vascular damage. VWF is also a carrier of factor VIII, an important risk factor for venous thrombosis [3,26]. Normal endothelium also secrets t-PA, which activates plasminogen to plasmin and breaks fibrin to fibrin degradation products, e.g. D-dimers. This process is called fibrinolysis [18]. Different surgical and endovascular revascularization methods exist for treatment of PAD patients. Currently, percutaneous transluminal angioplasty (PTA) with or without stenting is the best procedure to improve blood flow in narrowed arteries. These procedures are minimally invasive, but sometimes again can cause an artery stenosis (restenosis) or occlusion. When a 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 [5,6,23].

Aim

1. Determination of selected endothelial hemostatic factors in PAD patients and reference group,
2. Prospective observation of new restenosis appearance in PAD patients after endovascular revascularization.
3. Comparison of selected endothelial hemostatic factor levels between non-restenotic and restenotic PAD patients.

Patients and methods

The study included 150 PAD patients – 90 men and 60 women, aged 44 to 88 (mean 65.5) years – 1-18 months after successful peripheral endovascular revascularization, mainly PTA with stenting and stent implantation. The time between revascularization and blood drawing was divided into three periods: I) 1-3 months – 77 patients, II) >3-6 months – 30 patients, III) >6-18 months – 43 patients. In all PAD patients, medical interview, physical examination, hematological and biochemical tests and vascular examinations were performed. Ischemia of legs was diagnosed based on ultrasound examination (USG duplex Doppler). Before revascularization and after restenosis formation, computed tomography and/or arteriography were performed. Intermittent claudication and ankle brachial pressure index (ABPI) were also measured. Of the patients included in the study, 101 (66%) had various forms of ischemic heart disease, 126 (82%) arterial hypertension, 120 (78.4%) dyslipidemia, 90 (58.7%) were ex-smokers, 41 (26.8%) patients were current smokers, and 19 (12.6%) never smoked. Type 2 diabetes was observed in 91 (60.1%), overweight and obesity in 115 (75.1%). PAD patients, except those in whom restenosis occurred, were examined every 3 months, 5 times during 1 year with USG and blood collection. The reference group consisted of 53 healthy persons, who were qualified for their first blood donation at the Blood Donation Centre – 44 men and 9 women aged 20-56 years. In the healthy subjects, medical history and physical examination as well as laboratory tests including blood type identification, blood cell count and viral tests were performed. The reference group was younger than the patients with PAD, but some literature data suggest that in healthy persons sex and age do not influence TF, TFPI, TM, and t-PA but vWF depends on age.

4.5 ml blood samples for laboratory tests were drawing 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 minutes. Subsequently, 0.2 ml of the plasma to be tested was pipetted into Eppendorf tubes and stored at -80°C until measurements. The plasma concentration of endothelial hemostatic factors was measured with commercial enzyme immunoassay tests from American Diagnostica Inc. The manufacturer has not specified the normal range of results, but recommends that each laboratory establish its own reference values.

- TF – Imubind TF ELISA Kit. This assay detects TF and TF/VIIa complexes.
- TFPI – Imubind Total TFPI ELISA Kit. This assay detects both full-chain and truncated TFPI complexes with either TF or factor VIIa. TFPI suppresses both factor Xa and TF/VIIIa complexes.
- TM – Imubind Thrombomodulin ELISA Kit. It is a sandwich ELISA employing a monoclonal antibody, which recognizes the EGF_1 and EGF_2 domains of TM. A second horseradish peroxidase (HRP) conjugated with monoclonal antibody specific for EGF_5 and EGF_6 was used.
- vWF – Imubind vWF ELISA Kit. It is a sandwich ELISA test using goat polyclonal antibody as the capture antibody.
- t-PA – Imubind t-PA ELISA Kit. In this test goat polyclonal antibodies directed against human t-PA were used.

Statistical analysis

Results are presented in tables as mean values (M) and standard deviation (SD) or medians (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 in the case of non-normal data with the nonparametric Mann-Whitney test and with Student's t-test in patients with normal data. The correlations between the measured parameters characterized by non-normal data distribution were calculated using the Spearman rank correlation coefficient (r). The level of statistical significance was adopted as $p < 0.05$. Statistical analysis was performed with R for Windows (the R Foundation for Statistical Computing, Vienna, Austria) and MedCalc for Windows (MedCalc Software, Mariakerke, Belgium).

This protocol of the study was approved by the Bioethical Committee at the Regional Specialist Hospital, no. KB/2/2008.

Results

Risk factors and comorbidities in PAD patients after endovascular revascularization with and without restenosis are presented in table 1.

No significant differences between the two groups were observed.

Table 2 presents measured concentrations of TF, TFPI, TM, vWF and t-PA in plasma of patients with PAD after endovascular revascularization compared to the reference group.

As demonstrated by our study, TF and vWF concentrations were significantly higher, TM lower, but TFPI and t-PA similar compared to the reference group.

Table 3 presents correlations between endothelial hemostatic factors: TF, TFPI, TM, vWF, tPA and age of PAD patients.

Except TFPI, all factors depend in a weak but significant manner on PAD patients' age. Similar correlations also exist between TF/TFPI, TF/vWF, TM/vWF, and t-PA/vWF.

We divided the time of 1-18 months from endovascular revascularization to blood collection into three periods:

Table 1. Distribution of risk factors and comorbilities in PAD patients

Risk factors	PAD patients without restenosis n=112		PAD patients with restenosis n=38		p-value
	n	%	n	%	
Men	72	64.3%	19	50%	0.18
Women	40	35.7%	19	50%	
Mean age / years	65.5		65.0		0.73
	44-88		47-84		
Body Mass Index (BMI) > 25	78	69.6%	30	78.9%	0.43
Dyslipidemia	67	59.8%	24	63.2%	0.96
Hypertension	89	79.5%	32	84.2%	0.83
Diabetes	62	55.4%	26	68.4%	0.26
Coronary heart disease	50	44.6%	15	39.5%	0.7
Stroke	15	13.4%	2	5.3%	0.28
Current smokers	25	22.3%	12	31.6%	0.51
Former smokers	94	83.9%	32	84.2%	0.94
ASA 75-150 mg	108	96.4%	38	100.0%	0.72
Ticlopidine	29	25.9%	6	15.8%	0.28
Clopidogrel	33	29.5%	20	52.6%	0.019
Acenocoumarol	3	2.7%	1	2.6%	0.58

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

Determined parameters	PAD patients n=150 M ± SD Me Q1 – Q3	Reference group n=53 M ± SD Me Q1 – Q3	p-value
TF pg/ml	191.1 ± 118.4 156.0 110.1-224.8	144.4 ± 71.0 135.0 92.5-192.0	**0.013**
TFPI ng/ml	58.0 ± 28.5 50.0 40.0-68.6	54.0 ± 14.1 62.0 49.0-76.0	0.78
TM ng/ml	3.0 ±1.5 2.6 2.2-3.4	4.2 ± 1.9 4.0 3.3-4.8	**0.0001**
vWF U/ml	2.080 ± 0.791 2.018 1.593-2.608	0.907 ± 0.332 0.908 0.663-1.032	**0.0001**
t-PA ng/ml	8.8 ± 14.1 7.0 4.9-9.5	6.6 ± 2.6 5.9 4.4-8.9	0.18

n – number, M – mean, Me – median, PAD - peripheral arterial disease, p-value - significance level of statistical test, Q – quartiles, SD - standard deviation, TF - tissue factor, TFPI - tissue factor pathway inhibitor, TM – thrombomodulin, t-PA - tissue plasminogen activator, vWF - von Willebrand factor

Table 3. Correlations between age of PAD patients and determined endothelial hemostatic factors

Determined parametrs		Age	TFPI	TM	vWF
TF	r	**0.175** x	**0.167** x	-0.048	**0.283**x
	p	**0.035**	**0.045**	0.570	**0.0006**
TFPI	r	0.148		0.055	0.012
	p	0.075		0.507	0.883
TM	r	**0.189**x	0.055		**0.247**x
	p	**0.023**	0.507		**0.005**
vWF	r	**0.285**x	0.012	**0.247**x	
	p	**0.006**	0.882	**0.005**	
t-PA	r	**0.200**x	0.156	0.116	**0.180**x
	p	**0.016**	0.061	0.185	**0.029**

PAD - peripheral arterial disease, p-value - significance level of statistical test TF- tissue factor, r - Spearman rank correlation coefficient, TFPI - tissue factor pathway inhibitor, TM – thrombomodulin, t-PA - tissue plasminogen activator, vWF - von Willebrand factor, x - significant correlation

I) 1-3 months, II) > 3-6 months, III) >6-18 months. This is presented in table 4.

TF had the lowest value (167±106 pg/ml) in period 1 and after 6 months of revascularization significantly increased to 220±117 pg/ml (p<0.018). TFPI and t-PA levels were similar, not significant, in the three phases. VWF concentration was very high (2.213±0.763 U/ml) and after 6 months had decreased by about 20%. TM level after 3 months also decreased, but remained in the normal range for this factor.

Table 5 shows the comparison of endothelial hemostatic factors in 38 PAD patients after endovascular revascularization with new restenosis compared with the same group of 38 patients but without restenosis (< 3 months earlier) and with the whole group of 112 PAD patients without restenosis.

Only TF level was significant higher in PAD patients with new restenosis (p<0.013). Other endothelial factors did not significantly differ between PAD patients with and without restenosis.

Discussion

Atherosclerosis, surgical and endovascular revascularization damage arterial wall (endothelium and smooth muscle cells) in PAD patients. Can released from the tissue to blood endothelial hemostatic factors induce formation of new restenosis? In the present study we determined the concentration of TF, TFPI, TM, vWF and t-PA in the plasma of 150 PAD patients, 1 to 18 months after endovascular revascularization. The levels of TF (p<0.013) and vWF (p<0.0001) were significantly higher and TM significantly lower (p<0.0001) compared to the reference group. PTA with stenting had no influence in PAD patients on release of TFPI (p=0.78) and t-PA (p=0.18). Our results of TF concentration agree with the observation of Steffel et al. (2006) on increased TF level in cardiovascular diseases [27]. It seems that TF is released during PAD and also after a revascularization procedure. More than six months after revascularization TF increased from 167±106 pg/ml to 220±117 pg/ml (Table 4). A weak correlation exists between the age of PAD patients and TF level (r=0.175 p<0.035) and between TF and TFPI (r=0.167 p<0.045). TF concentration is significantly higher after restenosis (223 ± 127 pg/ml) compared to patients before restenosis (192 ± 120 pg/ml), and the difference was statistically significant (p<0.013). Perhaps TF can take place in the pathogenesis of restenosis. Mizuno et al. (2001) observed after percutaneous transluminal coronary angioplasty (PTCA) significantly higher levels of TF and TAT complexes in coronary sinus blood with late restenosis than in patients without restenosis.

TF level can be a prognostic factor for late restenosis after PTCA [17]. We did not observe any differences between TFPI level in PAD patients and the reference group (p=0.78). In contrast, Radziwon et al. (2001) described a very high level of TFPI in non-operated PAD patients only with intermittent claudication [21]. Lears et al. also observed an increased level of TFPI and TM in elderly non-operated subjects with cardiovascular diseases and type 2 diabetes [11]. In our PAD patients compared to the reference group we observed significantly lower TM concentration (p<0.0001), but in the normal range of this factor. Tschöpl et al. (1999) observed increased concentration of TM and vWF in 71 PAD patients before PTA and a trend for higher TM at 6 months in 30 patients, those in whom restenosis developed [22]. We do not know how to explain the lower level of TM in our PAD patients after endovascular revascularization. It is known that endothelial and smooth muscle cell proliferation is the major pathophysiologic factor after injury, which can induce neointimal hyperplasia and recurrent stenosis. Li et al. demonstrated in rabbits that recombinant human thrombomodulin (TM) inhibits thrombin-induced arterial smooth muscle cell proliferation in vitro and in vivo [12]. Perhaps the decreased TM level in our PAD patients after revascular-

Table 4. Endothelial hemostatic factors in PAD patients in different time between endovascular revascularization and blood drawing.

Determined parameters	Time of revascularization to collections of blood			p-value
Months	I 1-3 mo	II > 3-6 mp	III > 6-18 mo	[KW test]
Number of PAD patients	n = 77	n = 30	n = 43	
	M ± SD Me Q1–Q3	M ± SD Me Q1–Q3	M ± SD Me Q1–Q3	I/II I/III II/III
TF pg/ml	167 ± 106 134.5 97.8-227.3	216 ± 137 173.5 144.5-284.0	220 ± 117 181.0 131.8-301.2	[0.008] 0.059 0.018 0.739
TFPI ng/ml	57.6 ± 29.6 48.2 38.7-65.5	52.1 ± 17.0 51.2 43.7-62.4	61.8 ± 24.8 54.6 42.8-79.8	[0.32]
TM ng/ml	3.3 ± 1.4 2.8 2.4-3.9	2,7 ± 1,2 2.4 2.1-3.0	2.7 ± 1.2 2.5 1.9-3.4	[0.009] 0.038 0.038 1.000
vWF U/ml	2.213 ± 0.763 2.159 1.743-2.731	2.003 ± 0.774 2.235 1.493-2.571	1.795 ± 0.814 1.751 1.333-2.480	[0,03] 0,421 0.025 0.421
t-PA ng/m	8.0 ± 3.6 7.5 5.8-9.7	6.6 ± 3.2 6.6 4.5-8.2	11.7 ± 27.1 5.8 4.5-9.5	[0,091]

mo – months, n – number, Me – median, M – mean, PAD - peripheral arterial disease, p-value - significance level of statistical test, [KW test] - Kruskall-Wallis test or in case of significant difference post-hoc pairwise comparison between subgroups, Q – quartiles, SD - standard deviation, TF - tissue factor, TFPI - tissue factor pathway inhibitor, TM – thrombomodulin, t-PA - tissue plasminogen activator, vWF - von Willebrand factor

ization can be caused by its consumption during inhibition of neointimal cell proliferation after arterial damage. TM can also be suppressed by TNF (tumor necrosis factor), IL-1 and endotoxin. To confirm this thesis further experiments must be performed. Our PAD patients compared to the reference group had a significantly increased vWF level: 2.080±0.791 U/ml) versus 0.907±0.332 U/ml (p<0.0001). Our results are difficult to compare with the literature, where the level of vWF is expressed as a percentage, while we calculate this factor in units. The concentration of vWF correlated with the age of PAD patients (r_s=0.285, p<0.006), with TF (r_s=0.283, p<0.0006), TM (r_s=0.247, p<0.005) and t-PA (r_s=0.180, p<0.029). More than six months after revascularization of PAD patients vWF had decreased by over 20%. We did not observe any difference in vWF concentration in PAD patients before and after the newly created restenosis. It was always high. Our observation of an increased vWF level in PAD patients agrees with the literature [3,20,24,30,32]. Smith et al. observed that the mean levels of fibrinogen and vWF were higher in patients developing PAD. However, vWF was not associated with progression of PAD [24]. Tsakiris et al. observed a trend to a higher level of vWF in patients who later developed restenosis [30]. Blann et al. demonstrated that also successful coronary intervention, e.g. stent implantation, is associated with endothelial damaged and concurrent vWF release [3]. Stenting with drug-eluting devices is associated with reduced inflammation and diminished vWF level in the coronary circulation. Tamburino et al. described early stenosis after drug-eluting stent implantation [29]. Bongeri et al. reported a higher vWF level in patients with stroke but did not observe any difference in vWF level in patients with and without restenosis [4]. t-PA level in PAD patients after endovascular revascularization was a little higher than in the reference group, but the difference was not statistically significant. t-PA weakly correlates with the age of patients (r_s=0.200, p <0.016) and with vWF (r_s=0.180, p<0.029). t-PA level does not statistically change from 1 to 18 months after revascularization. Also a similar level of t-PA was observed in PAD patients with a newly created restenosis and in these same subjects without restenosis. More than six months after revascularization of PAD patients the TF concentration significantly increased. It does not agree with the suggestion of Ariyoshi et al. that ePTFE grafts lose their thrombogenicity (TAT, D-dimers, CRP) 6 months after stent implantation [1].

Table 5. Endothelial hemostatic factors in PAD patients without and with restenosis (<3 months before restenosis and after restenosis)

Determined parameters	Without restenosis (n=112) A	With restenosis (n=38) B before	With restenosis (n=38) C after	p-value A/B A/C B/C
	M ± SD Me Q1 - Q3	M ± SD Me Q1 - Q3	M ± SD Me Q1 - Q3	
TF pg/ml	192 ± 120	192 ± 120	223 ± 127	0.86
	156	166	196	0.14
	116-253	95-267	126-293	**0.013**
TFPI ng/ml	60 ± 29	58 ± 28	59 ± 27	0.74
	53	49	52	0.99
	42-71	43-64	43-66	0.68
TM ng/ml	3.0 ± 1.6	3.0 ± 1.0	3.1 ± 1.3	0.22
	2.5	2.7	2.8	0.15
	2.1-3.8	2.5-3.0	2.5-3.3	0.24
vWF U/ml	2.078 ± 0.836	2.090 ± 0.662	1.953 ± 0.614	0.88
	2.122	2.093	1.933	0.45
	1.499-2.640	1.812-2.562	1.623-2.357	0.89
t-PA ng/ml	9.0 ± 16.2	8.3 ± 4.0	8.9 ± 4.8	0.21
	6.9	7.7	7.4	0.15
	4.7-9.4	5.8-9.5	5.5-11.2	0.57

n- number, M – mean, Me – median, PAD - peripheral arterial disease, p-value - significance level of statistical test, SD - standard deviation, TF - tissue factor, TFPI - tissue factor pathway inhibitor, TM – thrombomodulin, t-PA - tissue plasminogen activator, vWF - von Willebrand factor

Hoshiba et al. (2006) observed co-localization of vWF with platelet thrombi, TF with fibrin and consistent presence of inflammatory cells in coronary thrombi obtained by an aspiration device from patients with acute myocardial infarction [8]. Probably such a picture appears in thrombi and restenosis in legs of PAD patients.

According to Juni et al. (2013), oxidative stress greatly influences the pathogenesis of various cardiovascular disorders. Coronary interventions, including balloon angioplasty and coronary stent implantation, are associated with increased vascular levels of reactive oxygen species in conjunction with altered endothelial and smooth muscle cell function. These alterations potentially lead to restenosis [9].

Conclusions

Increased TF and vWF level in advanced PAD patients after endovascular revascularization compared to the reference group indicates endothelial damage due to atherosclerotic and revascularization processes. More than 6 months after revascularization of PAD patients a significant increase of TF concentration appeared. Except for TF level, no significant differences of other endothelial hemostatic factors – TFPI, TM, vWF and t-PA – between PAD patients with and without restenosis were observed. Perhaps TF takes part in restenosis formation.

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