Prognostic value of tissue factor in patients with abdominal aortic and iliac arterial aneurysms – preliminary study

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Abstract

Introduction: The decision on the time and choice of strategy of treatment of abdominal aortic aneurysm must be especially carefully balanced. The aim of the study was to evaluate the tissue factor (TF) plasma level as a potential factor useful in anticipation of abdominal aortic aneurysm and/or iliac arterial aneurysm via comparison of plasma TF level in patients with ruptured and non-ruptured aneurysms.

Material and methods: The study included 33 patients with aneurysm (17 operated on electively because of non-ruptured aneurysm and 16 operated on emergently due to ruptured aneurysm), 33 claudicant patients with atherosclerosis of the abdominal aorta and iliac arteries with normal diameter of arteries, and 30 healthy controls. Plasma TF level was assessed by ELISA method using the IMUBIND Tissue Factor ELISA Kit (American Diagnostica Inc.).

Results: The study showed an increased TF level in patients with aneurysm (134 ±54 pg/ml) and in patients with atherosclerosis without concomitant aneurysm (91 ±30 pg/ml) in comparison with the control group (62 ±20 pg/ml), respectively $p < 0.001$ and $p = 0.008$. A significantly higher TF plasma level was observed in patients with ruptured abdominal aortic aneurysms (160 ±57 pg/ml) as compared to patients with non-ruptured aortic aneurysms (109 ±39 pg/ml) or peripheral arterial occlusive disease (91 ±30 pg/ml), respectively $p < 0.001$ and $p < 0.001$. The difference in TF level between the group with non-ruptured aortic aneurysms (109 ±39 pg/ml) and the patients with atherosclerosis without aneurysm (91 ±30 pg/ml) was not statistically significant.

Conclusions: No difference in TF level between patients with non-ruptured AAA/IAA and patients with aortic and iliac atherosclerosis without aneurysm indicates that an increased TF plasma level is not specific for any of the above-mentioned vascular pathologies.

Key words: tissue factor, ruptured, non-ruptured aneurysm, abdominal aorta, iliac artery.

Introduction

Abdominal aortic aneurysm (AAA) and iliac arterial aneurysms (IAA) are among the main reasons for vascular surgical procedures/interventions of

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Jan Skóra, Tomasz Dawiskiba, Patrycja Zaleska, Jacek Kurcz, Agnieszka Mastalerz-Migas, Rajmund Adamiec, Izabela Gosk-Bierska

aorta and iliac arteries. On the basis of previous epidemiological studies AAA/IAA was demonstrated in 4–10% of people over 75 [1, 2]. The result of treatment of AAA and/or IAA depends on many factors, e.g. sex, age, smoking, comorbidities, methods of treatment, experience of the vascular surgery center, as well as activity of the coagulation-fibrinolysis system [3]. Detailed analysis of such factors significantly facilitates prognosis of the postoperative clinical course including risk of death [1–3]. Determinant prognostic factors are aneurysmal size and localization. Elective surgical or endovascular treatment is indicated in the case of AAA of diameter more than 5.5 cm and in the case of rapidly growing (more than 0.6/7 cm per 6 months or more than 1 cm per year) so-called small aneurysms (size < 5 cm) [1, 2]. Surgical treatment of IAA is indicated in the case of aneurysm diameter exceeding 3.5 cm and/or rapid growth (more than 3 mm per year) [4]. Due to anatomical location the detection rate of IAA by means of abdominal ultrasound is much lower when compared with AAA.

The etiology of aneurysms is not well known. Histologically the wall of AAA is characterized by chronic inflammation, reduction in the number of smooth muscle cells, destruction of elastin fibers and remodeling of extracellular matrix, activation of platelets and plasmatic coagulation [5–8]. An atherosclerotic component is present in most cases of AAA. An association between atherosclerosis of both coronary arteries and peripheral arterial vessels and the presence of AAA was demonstrated; nevertheless the mechanism of the phenomenon is not well researched [9, 10]. Some studies indicate the occurrence of AAA in response to the atherosclerotic process and vascular wall remodeling [11, 12]. Rupture of AAA is equivalent to extensive vascular wall damage and release of a large amount of tissue factor. Tissue factor (TF, thromboplastin) is crucial in induction and enhancement of the coagulation process. It also plays a role as a cofactor essential to activate factor VII. Complex TF/VIIa activates factors IX and X, thus initiating the cascade of proteolytic reactions that lead to generation of thrombin and clot formation [13]. Apart from a key role in the coagulation process, TF participates inter alia in inflammatory reactions and angiogenesis [14, 15]. The physiologically low level of TF is increased in clinical conditions associated with damage of vessel endothelium and other tissues depending on the degree of vascular wall damage [16]. The utilization of TF level as a potential marker for progression and/or risk of rupture of AAA could be of significance in early diagnosis of AAA rupture. Previous studies have demonstrated the increase of TF in the course of traumas, infections, cardiovascular disorders, diabetes, venous thrombosis and neoplasms [17–21]. The atherosclerotic process involving the aorta and peripheral arteries resulting in chronic lower limb ischemia seems to be a factor independent from diabetes, arterial hypertension, obesity, lipid disorders, age and sex that contributes to an increase in plasma TF level [18]. A few reports on TF and its physiological inhibitor tissue factor pathway inhibitor (TFPI) in patients with AAA point to their participation in formation of perimural thrombus in the aneurysmal lumen [22–24].

The purpose of the study was to evaluate TF level as a potential factor useful in anticipation of AAA and/or IAA rupture via comparison with plasma TF concentration in patients with ruptured and non-ruptured aneurysms. Considering that most of the patients with AAA demonstrate atherosclerotic lesions in both the abdominal aorta and iliac arteries and the atherosclerotic process is a factor causing increase in TF concentration, it was planned to compare the parameter (TF level) between patients with AAA and/or IAA and patients with atherosclerosis of the abdominal aorta and iliac arteries presenting symptoms of chronic lower limb ischemia (stage 2 according to Fontaine classification) and with normal vessel diameter.

Material and methods

The analyzed group included: 33 patients with AAA and/or IAA treated operatively between 2009–2012 in the Department of Vascular, General and Transplantation Surgery of Wroclaw Medical University; 33 patients with atherosclerosis of the abdominal aorta and iliac arteries with normal diameter of arteries, presenting symptoms of peripheral arterial occlusive disease (PAOD) grade II according to Fontaine and treated medically in the Department of Angiology, Hypertension and Diabetology of Wroclaw Medical University; and the control group of 30 healthy volunteers, selected from among employees of Wroclaw Medical University. Among 33 patients with AAA and/or IAA treated surgically, 17 patients were operated on electively because of non-ruptured aneurysm and 16 patients were operated on emergently due to ruptured aneurysm. The protocol of this study was approved by the Commission of Bioethics at the Wrocław Medical University.

The diagnosis of AAA and/or IAA was established based on CT-angiography. The diagnosis of chronic lower limb ischemia in the course of atherosclerosis of the aorta and iliac arteries was made on the basis of history of claudication, physical examination, segmental blood pressure measurements (ankle-brachial index < 0.8) and duplex-Doppler examination.

In all the patients plasma TF level was measured. In healthy controls and in subgroups treated electively, blood samples were taken after overnight fasting. In patients with ruptured AAA blood samples were taken at admission to hospital.

The 5 ml blood samples were drawn from an antecubital vein and transferred to a test tube with 3.2% sodium citrate in the proportion 9 : 1, and centrifuged at 3,000 × g for 15 min. Plasma was stored at 80°C. Plasma TF level was assessed by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit: IMUBIND Tissue Factor ELISA Kit no. 845 (American Diagnostica Inc., Stamford).

Statistical analysis

The collected data were analyzed statistically using the Statistica 10 software package (StatSoft, Poland). Statistical significance of between-group differences was assessed using Student's t-test (quantitative variables) and χ^2 analysis (qualitative variables).

The Mann-Whitney U-test was used to compare subgroups of patients. As the data were not normally distributed, Spearman's rank test was used to correlate TF concentration and clinicopathological variables. Value of $p < 0.05$ was considered statistically significant. All the data are presented in the tables as mean values ± standard deviation.

Results

Demographic and clinical data of analyzed groups are compared in Table I. Mean age in the subgroup with aortic and iliac arterial atherosclerosis was comparable with the control subgroup. However, mean age in patients with AAA and/or IAA was significantly higher in comparison with both the aortic/iliac atherosclerosis subgroup and healthy control. Males comprised at least 80% of patients in all the subgroups. Arterial hypertension was shown to be more frequent in the AAA/IAA subgroup than in the subgroup with aortic/iliac arterial atherosclerosis and normal arterial diameter. On the other hand, patients with aortic/iliac arterial atherosclerosis were often heavy smokers. No significant differences in incidence of diabetes and lipid disorders were demonstrated in analyzed groups.

The comparison of risk factors and clinical course between patients with ruptured and non-ruptured AAA and/or IAA is shown in Table II. No significant differences referring to the size of ruptured and non-ruptured aneurysms were demonstrated. Perimural thrombi were detected in the lumen of all the aneurysms.

Seventy-five percent of patients with ruptured AAA and/or IAA presented symptoms of circulatory insufficiency and/or hypovolemic shock. Myocardial infarction was the most common complication in the early postoperative period – 18.8%.

Table I. Demographic data and risk factors of atherosclerosis in analyzed groups

Parameter	AAA/IAA Total ($n = 33$)	AAA/IAA Non-ruptured ($n = 17$)	AAA/IAA Ruptured ($n = 16$)	PAOD ($n = 33$)	Control ($n = 30$)
Age, n (%) [years]					
Median	69.6 ±9.3	67.8 ±9.6	71.7 ±8.9	58.9 ±6.9	54.4 ±7.6
Range	52–89	52–84	57–89	48–78	46–71
Sex, n (%)					
Men	28 (84.8)	14 (82.4)	14 (87.5)	27 (81.8)	24 (80)
Women	5 (15.2)	3 (17.6)	2 (12.5)	6 (18.2)	6 (20)
Smoking, n (%)	19 (57.6)	12 (70.6)	7 (43.7)	32 (93.9)	0
Currently	7 (21.2)	5 (29.4)	2 (12.5)	18 (54.5)	
In the past	12 (36.4)	7 (41.2)	5 (31.2)	13 (39.4)	
Arterial hypertension, n (%)	29 (87.8)	17 (100)	12 (75)	20 (60.6)	0
Diabetes, n (%)	11 (33.3)	6 (35.3)	5 (31.2)	11 (33.3)	0
Lipid disorders, n (%)	20 (60.6)	11 (64.7)	9 (56.2)	19 (57.6)	0
Coronary disease, n (%)	9 (27.3)	5 (29.4)	4 (25.0)	12 (36.4)	0
Carotid artery disease, n (%)	7 (21.2)	5 (29.4)	2 (12.5)	19 (57.6)	0
Renal failure, n (%)	3 (9.1)	1 (5.9)	2 (12.5)	0 (0)	0
Pharmacotherapy, n (%)					
Calcium channel blockers	11 (33.3)	6 (35.3)	5 (31)	12 (36.4)	0
β-blockers	17 (51.5)	9 (53)	8 (50)	11 (33.3)	0
Statins	22 (66.7)	10 (58.8)	12 (75)	30 (90.9)	0
Antiplatelet drugs	20 (60.6)	11 (64.7)	6 (56.2)	29 (87.9)	0
Anticoagulants (warfarin)	4 (12.1)	3 (17.6)	1 (6.2)	3 (9.1)	0

Jan Skóra, Tomasz Dawiskiba, Patrycja Zaleska, Jacek Kurcz, Agnieszka Mastalerz-Migas, Rajmund Adamiec, Izabela Gosk-Bierska

Table II. Clinical profile of patients treated surgically due to non-ruptured and ruptured abdominal aortic and/or iliac arterial aneurysms

Variable	Non-ruptured AAA/IAA (n = 17)	Ruptured AAA/IAA (n = 16)
Localization of aneurysms, n (%)		
Only abdominal aorta	12 (70.6)	8 (50)
Only iliac arteries	2 (11.8)	2 (12.5)
Both abdominal aorta and iliac arteries	3 (17.6)	6 (37.5)
Morphologic evaluation of an aneurysm, mean (range) [cm]		
Diameter of abdominal aortic aneurysm	6.26 (3.6–7.8)	6.77 (5–12.1)
Diameter of iliac arterial aneurysm	3.2 (2–62)	5.35 (1.8–13)
Thrombus in aneurysmal lumen, n (%)	17 (100)	100 (16)
Thickness of thrombus, mean (range) [cm]	2.94 (1.8–5)	2.59 (1–7)
Type of surgery, n (%)		
Straight prosthesis	10 (58.8)	7 (43.8)
Bifurcated prosthesis	4 (23.5)	6 (37.5)
Stent graft	2 (11.8)	2 (12.5)
Iliac-femoral bypass	1 (5.9)	1 (6.30)
Time of surgery, mean (range) [h]	2.35 (1.4–3.2)	2.28 (1.2–3.25)
Preoperative clinical condition, n (%)		
Hypovolemic shock	0	11 (68.8)
Circulation failure	0	12 (75)
Early postoperative complications, n (%)		
Death	0	7 (43.8)
Myocardial infarction	0	3 (18.8)
Renal failure	0	1 (6.3)
Acute lower limb ischemia	0	2 (12.5)
Intestinal necrosis	0	2 (12.5)
Paraplegia due to spinal cord ischemia	0	1 (6.3)

The other early postoperative complications in patients with ruptured AAA/IAA included acute kidney failure, acute lower limb ischemia, intestinal necrosis and paraplegia due to spinal cord ischemia – 6.3%, 12.5%, 12.5% and 6.3% respectively. Such complications were the causes of death in over 40% of the subgroup. None of the above-mentioned complications occurred in patients with non-ruptured aneurysms treated electively. The most common localization of aneurysms was the abdominal aorta; therefore implantation of a straight vascular prosthesis was the prevailing surgical management.

No correlation between smoking and risk of aneurysm rupture was demonstrated. No correlation between TF level and either aneurysmal size or perimural thrombus size was found.

The TF level was significantly higher both in patients with AAA/IAA (134 ±54 pg/ml) and in patients with atherosclerotic lesions (91 ±30 pg/ml) when compared with the control group (62 ±20 pg/ ml), respectively $p = 0.000107$ and $p = 0.008428$. Furthermore, the TF level was significantly higher in patients with AAA/IAA when compared with the subgroup with atherosclerotic aortic changes ($p < 0.001$). Further analysis demonstrated that the difference resulted from the very high TF level observed in patients with ruptured aneurysms. The level of TF in patients with ruptured aneurysms (160±57 pg/ml) was significantly higher in comparison with both the non-ruptured aneurysm subgroup (109 ±39 pg/ml) and the aortic atherosclerotic lesions subgroup (91 ±30 pg/ml), respectively $p < 0.001$ and $p < 0.001$. No significant difference in TF level was observed between patients with non-ruptured aneurysms (109 ±39 pg/ml) and patients with aortic/iliac arterial atherosclerotic lesions and normal arterial diameter (91 ±30 pg/ml).

The analysis of TF level in particular groups is shown in Tables III and IV.

Discussion

The decision on the time and choice of strategy of treatment of AAA and/or IAA must be especially carefully balanced, because both medical management burdened with the risk of aneurysm rupture, and invasive treatment associated with increased risk of myocardial infarction, cerebral stroke, renal failure, and perioperative bleeding, are related to a high risk of death. To improve the clinical course and to follow up the results of AAA surgery, studies are conducted in search of biological markers that evaluate the risk of postoperative complications [25, 26] and predict the aneurysmal size progression [27].

On the basis of a meta-analysis of previous studies, Golledge *et al.* mentioned biomarkers associated with progression of AAA size (elastin peptides, N-terminal propeptide of type III procollagen (PIIINP), elastase, α1 antitrypsin, plasmin-antiplasmin complex, tissue plasminogen activator, homocysteine, urokinase plasminogen activator, osteopontin, interferon γ, macrophage migratory inhibitor factor, transforming growth factor, C-reactive protein) and biomarkers related to the clinical course, including aortic rupture (fibrinogen, α1-antitrypsin) [28]. There are no studies on evaluation of TF as a prognostic factor in relation to progression of size and risk of rupture of AAA. Previous studies devoted to the process of coagulation and fibrinolysis in patients with AAA related first of all to the pathomechanism of formation of lesions in the aneurysmal vascular wall, taking the susceptibility of formation of perimural thrombus into special consideration [9, 22, 23]. The conclusions concerning the correlation between activation of the coagulation/fibrinolysis process and the occurrence of AAA are based primarily on the preoperative assessment of non-ruptured aneurysms. Yamazumi *et al.* stated that TF level in 36 patients undergoing elective surgery due to non-ruptured aneurysms does not depend on the aneurysm size and does not correlate with other exponents of the hemostasis process. However, the researchers observed a correlation between TFPI level and aneurysmal size and levels of TAT, D-dimers, fibrinogen degradation products, and α2 plasminogen inhibitor [29]. Nomura *et al.* demonstrated significantly higher levels of TFPI, TAT, D-dimers, and sICAM-1 in 17 patients with non-ruptured AAA in comparison with a control group of healthy volunteers of comparable age. According to the authors, a positive correlation between AAA size and levels of TAT, D-dimers, and sICAM-1 indicates the possibility to make use of such parameters in diagnosis and follow-up of AAA progression [24]. According to Kotschy *et al.*, increase of TF and TAT levels without simultaneous increase of the TFPI level in patients with non-ruptured aneurysms may induce a proteolytic process

Table III. TF level in particular groups

Group	TF level [pg/ml]
AAA/IAA (*n* = 33)	134.6 ± 54.7
Ruptured AAA/IAA (*n* = 16)	160.7 ±57.7
Non ruptured AAA/IAA (*n* = 17)	109.9 ±39.3
PAOD (*n* = 33)	91.8 ±30.4
Control (*n* = 30)	62.2 ±20.9

Table IV. Statistical analysis of TF level in particular groups

Compared groups	Value of *p*
Control vs. AAA/IAA	< 0.001
Control vs. ruptured AAA/IAA	< 0.001
Control vs. non-ruptured AAA/IAA	0.001
Control vs. PAOD	0.008
Ruptured AAA/IAA vs. non-ruptured AAA/IAA	< 0.001
PAOD vs. AAA/IAA	< 0.001
PAOD vs. ruptured AAA/IAA	< 0.001
PAOD vs. non-ruptured AAA/IAA	Non-significant

in the vessel wall through an increase in thrombotic susceptibility and clot formation in the aneurysmal lumen [23].

There are only a few studies, additionally performed in small groups of patients, comparing the condition of the coagulation-fibrinolysis system between ruptured and non-ruptured aneurysms. Adam *et al.* stated that the occurrence of AAA is accompanied by an increase in thrombotic susceptibility expressed by activation of the coagulation process and inhibition of fibrinolysis, enhanced in the case of aneurysmal rupture. Significantly higher levels of thrombin-antithrombin complex (TAT), prothrombin fragment 1+2 (PF 1+2) and plasminogen activator inhibitor (PAI) and lower levels of tissue plasminogen activator (t-PA) were demonstrated in 10 patients with ruptured AAA in comparison with 9 patients with non-ruptured AAA [30]. This phenomenon was considered as a natural response to the condition of direct risk of severe bleeding. On the other hand, the authors concluded that the condition of hypercoagulation concurrent with aneurysm rupture is conducive to clot formation in micro- and macrocirculation and to thromboembolic complications and thus is a risk factor for infarction, stroke, multiple organ dysfunction syndrome (MODS) [30]. Only one study evaluating the influence of AAA rupture on TF level has been reported so far. Hobbs *et al.* performed a prospective study comparing 17 patients undergoing elective surgery due to AAA with 10 patients undergoing emergent surgery due to AAA rupture. The researchers observed a significantly higher preoperative TF level in the subgroup with ruptured AAA compared with

Jan Skóra, Tomasz Dawiskiba, Patrycja Zaleska, Jacek Kurcz, Agnieszka Mastalerz-Migas, Rajmund Adamiec, Izabela Gosk-Bierska

patients with non-ruptured AAA. However, no difference in TFPI level was demonstrated between the preoperative period and soon after the surgery. The TFPI level in patients with ruptured AAA was observed just after 24 h and 48 h following surgery. The authors consider that preoperative lack of increase in TFPI level simultaneous with increase in TF level in patients with ruptured AAA means an increase in thrombotic susceptibility and constitutes a mechanism that reduces the risk of severe bleeding complications [31].

We found in our study a significant increase in plasma TF level both in patients with AAA and in patients with aortic and peripheral arterial atherosclerosis compared to the control group. The results are similar to those obtained in previous studies [18, 23]. The further analysis demonstrated that increase in TF level in the AAA subgroup in comparison with aortic atherosclerotic patients without AAA is associated with aneurysm rupture. In the subgroup with ruptured AAA, the tissue factor level was significantly higher than in other subgroups, including patients with non-ruptured aneurysms undergoing elective surgery. The rupture of the aneurysmal wall and enhanced release of TF into the bloodstream might be one of the reasons for this phenomenon. An additional factor that might stimulate increase in TF level might be the damage of tissues located in the retroperitoneal space and the root of the mesentery due to blood extravasated from the ruptured aneurysm [31, 32]. No difference in TF level between the subgroup with non-ruptured aneurysm and patients with atherosclerotic lesions without pathological dilatation of both aorta/iliac arteries suggests a similar degree of damage of the vascular wall that is responsible for release of thromboplastin both in the course of occlusive atherosclerosis and in the course of aortic aneurysm formation. The fact indicates that the increase in TF level in relation to the control group is not specific for either aortic atherosclerosis or aortic aneurysms and does not differentiate between these pathologies. The results of performed studies unambiguously demonstrate that high serum TF level accompanies ruptured AAAs. Due to this fact, the assessment of TF level can be used as an additional parameter to confirm the rupture of AAA. However, on the basis of our results it is difficult to evaluate unambiguously whether the observed significantly higher TF level in patients with ruptured AAA/IAA as compared with the non-ruptured AAA/IAA subgroup can be adopted as a useful predictor of aortic aneurysm rupture or as a proof of occurrence of rupture of the vascular wall.

Hence further prospective randomized studies in larger groups of patients with AAA are needed.

The limited number of patients with ruptured AAA/IAA does not allow us to answer the question whether TF level correlates with complications in the form of bleeding, circulatory failure, myocardial infarction, renal failure, lower limb and visceral ischemia, and finally death. In the discussed reports TF level was evaluated at the moment of admission to hospital.

In conclusion, increased TF levels are observed both in patients with abdominal aortic aneurysm and/or iliac arterial aneurysm and in patients with abdominal aortic and iliac arterial atherosclerosis without concomitant aneurysm in comparison with the control group. At the same time, the lack of difference in TF level between patients with non-ruptured aortic and/or iliac arterial aneurysm and patients with aortic and iliac atherosclerosis without aneurysm indicates that increase of TF level is not specific for any of the above-mentioned vascular pathologies. A significantly higher TF level was observed in patients with ruptured abdominal aortic aneurysms as compared to patients with non-ruptured aortic aneurysms or peripheral arterial occlusive disease. Further studies are needed to evaluate whether an increase in TF level in patients with abdominal aortic and/or iliac arterial aneurysm can be considered as a predictor of aneurysmal rupture or rather as a result of vascular wall rupture.

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