ORIGINAL PAPERS

Adv Clin Exp Med 2006, **15**, 2, 271–277
ISSN 1230-025X

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Thrombomodulin in the Blood of Patients with Acute Cerebral Ischaemia

Trombomodulina we krwi chorych na ostre niedokrwienie mózgu

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Abstract

Background. Thrombomodulin (TM) is a membrane-bound receptor for thrombin expressed by vascular endothelial cells.
Objectives. Determination of the blood levels of soluble TM (sTM) in patients with acute cerebral ischaemia.
Material and Methods. The sample consisted of 73 patients (36 female, 37 male) aged 42–90 (68.1 ± 11.6) with acute cerebral ischaemia. sTM concentration was determined using the Imubind® Thrombomodulin ELISA Kit assay from American Diagnostica Inc.
Results. sTM concentration was found to be significantly higher in all patients with acute cerebral ischaemia enrolled in the study compared to the control group. There were no significant differences in sTM concentration among patients with acute cerebral ischaemia (ACI) relative to the presence of selected risk factors for ACI. A comparison of sTM concentration in patients with ACI relative to gender, age (below or above 70) and the presence or absence of a CT-confirmed ischaemic lesion did not reveal any statistically significant differences. Patients with ACI but without co-existing brain stem failure (ICT) had higher sTM levels. There were no differences in sTM concentration between patients with atherosclerotic and lacunar strokes or between patients with embolic strokes and transient ischaemic attacks. However, significantly lower sTM concentrations were seen in patients with embolic strokes or transient ischaemic attacks compared to patients with atherosclerotic or lacunar strokes.
Conclusions. Elevated sTM concentration is the result of vascular endothelial injury in the course of atherosclerosis in patients with acute cerebral ischaemia (**Adv Clin Exp Med 2006, 15, 2, 271–277**).

Key words: soluble thrombomodulin, ischaemic stroke.

Streszczenie

Wprowadzenie. Trombomodulina (TM) jest receptorem błonowym dla trombiny obecnym na powierzchni komórek śródbłonka naczyń.
Cel pracy. Oznaczenie stężenia rozpuszczalnej TM (sTM) we krwi chorych z udarem niedokrwiennym mózgu.
Materiał i metody. Do badań włączono 73 chorych (36 kobiet i 37 mężczyzn) w wieku 42–90 lat (68,1 ± 11,6) z ostrym niedokrwieniem mózgu. Stężenie sTM oznaczano za pomocą testu Imubind® Thrombomodulin ELISA Kit firmy American Diagnostica Inc.
Wyniki. W całej analizowanej grupie chorych na ostre niedokrwienie mózgu stężenie sTM było istotnie większe niż w grupie kontrolnej. Nie stwierdzono istotnych statystycznie różnic stężenia sTM między chorymi na ostre niedokrwienie mózgu w zależności od występowania wybranych czynników ryzyka tej choroby. Porównując stężenie sTM u chorych na ostre niedokrwienie mózgu w zależności od płci, wieku > 70. lub < 70. r.ż. oraz od stwierdzanego w tomografii komputerowej ogniska niedokrwiennego, nie stwierdzono istotnych statystycznie różnic. U chorych na ostre niedokrwienie mózgu bez współistniejącej niedomogi pnia mózgu stwierdzono większe stężenia sTM. Nie stwierdzono różnic stężenia sTM między chorymi z udarem o etiologii miażdżycowej a lakunarnej oraz między chorymi z udarem o etiologii zatorowej a przemijającym niedokrwieniem mózgu. Zaobserwowano natomiast istotnie mniejsze stężenia sTM u chorych z udarem mózgu o etiologii zatorowej lub TIA w porównaniu z chorymi z udarem o etiologii miażdżycowej lub lakunarnej.
Wnioski. Zwiększone stężenie sTM jest wynikiem uszkodzenia śródbłonka naczyniowego przez proces miażdżycowy u chorych na ostre niedokrwienie mózgu (**Adv Clin Exp Med 2006, 15, 2, 271–277**).

Słowa kluczowe: rozpuszczalna trombomodulina, udar mózgowy.

Human thrombomodulin is a integral membrane protein made up of 557 amino acids that bears some structural resemblance to the LDL receptor. Expressed by vascular endothelial cells and functioning as a thrombin receptor, thrombomodulin is one of the factors responsible for the anticoagulant properties of the vascular endothelium [1, 2].

There are 30 000–50 000 thrombomodulin molecules expressed on an endothelial cell, representing 50–60% of all thrombin binding sites. Thrombomodulin is present on all endothelial cells except the sinusoidal hepatic lining cells and postcapillary endothelial cells in lymph node veins. It is also found in the mucosal mesothelium and lining of body cavities, blood plasma, platelets, monocytes, neutrophils, urine and placenta [2–6].

Thrombomodulin antigen (TM Ag) has been found in all blood vessels in the CNS: capillaries supporting the spinal cord, the white and grey matter of the medulla oblongata, pons, mesencephalon, cerebellum, diencephalon and telencephalon. Membranes and large arteries responded to exposed TM much more strongly than veins and capillaries. A strongly positive response in blood vessels did not depend on the organ investigated, but was related to the quality of blood flow [4, 7].

Thrombomodulin complexed with thrombin is a co-factor in protein C activation, accelerating this reaction more than 1000-fold. As an enzyme responsible for the proteolytic degradation of factors Va and VIIIa, activated protein C, aided by protein S, is a major inhibitor of coagulation [8–10]. Also, protein C inhibits the formation of new thrombin molecules by binding factor Xa [9] and has profibrinolytic properties since it inhibits the tissue plasminogen activator inhibitor (PAI-1). Thus, owing to its ability to catalyse protein C activation, TM plays a major role in maintaining blood in a liquid state and preventing intravascular coagulation. Moreover, thrombin complexed with thrombomodulin loses its pro-coagulation properties (the proteolytic effect) in the conversion of fibrinogen into fibrin, activation of factors V, VIII and XIII, inactivation of protein S and induction of platelet aggregation. Thus, TM also acts to inhibit intravascular coagulation [11]. TM is also known to bind factor Xa, thus inhibiting the activation and conversion of prothrombin into thrombin. It also speeds up thrombin-mediated activation of factor XI and inactivation of urokinase. TM also accelerates thrombin inactivation by antithrombin III [6–8]. The thrombomodulin-thrombin complex has also both profibrinolytic (PAI inactivation) and antifibrinolytic (activation of the thrombin-activable fibrinolysis inhibitor TAFI) properties [12]. TM is metabolised in the liver and eliminated via renal route [6].

Clinical studies have shown elevated levels of soluble thrombomodulin in various pathological conditions, such as the diffuse intravascular coagulation syndrome, pulmonary embolism, lung failure syndrome, chronic renal failure, acute liver failure, diabetic microangiopathy, systemic lupus erythematosus, peripheral and coronary atherosclerosis [6, 13–16], thrombotic thrombopenic polycythaemia, Schönlein-Henoch purpura, vasculitis [17], in malignancies such as lymphomas, leukaemias, carcinomas and other conditions [14, 18, 19].

Even though the clinical significance of elevated TM levels has not been ascertained to date, in view of the nature of conditions in the course of which this abnormality is seen, it is assumed that TM elevation is mostly associated with damage to the vascular endothelium and endothelial activation. In view of this, TM is regarded as a specific indicator of endothelial injury. The term soluble or circulating TM (sTM, cTM) refers to thrombomodulin released into the blood as a result of endothelial damage or activation [6, 8, 11, 13].

Since the main underlying condition in ischaemic stroke is atherosclerosis-associated endothelial injury, it may be supposed that TM is released into the blood in this condition.

In view of the paucity of data on changes in TM activity in ischaemic disease, the aim of our study was to evaluate the concentration of soluble TM in the blood of patients with ischaemic cerebral stroke and assess the effect of risk factors on TM concentration.

Material and Methods

The study was carried out from September 1999 to February 2000. The sample consisted of 73 patients (36 women, 37 men) aged 42–90 (68.1 ± 11.6) with first-ever episodes of acute anterior cerebral ischaemia treated at the Department of Neurology of the J. Biziel Memorial Voivodship Hospital in Bydgoszcz.

Case histories were obtained from all patients. Questions included exposure to risk factors for cerebral ischaemia, such as arterial hypertension, hypercholesterolaemia, cigarette smoking, diabetes mellitus, ischaemic heart disease and atrial fibrillation. Laboratory studies included the determination of blood glucose, total cholesterol and soluble thrombomodulin (TM) levels as an indicator of vascular endothelial activity. The diagnosis of acute cerebral ischaemia was based on history, neurological examination and a CT scan of the head.

All patients had given their consent to undergo the examinations.

A control group was formed consisting of 40 people (25 women, 15 men) aged 32–63, who were healthy and without the clinical indicators of arteriosclerosis.

The Regional Ethical Committee for Scientific Research in Bydgoszcz gave its consent to carry out the study.

Neurological examinations of the patients with acute cerebral ischaemia revealed paresis of various intensity in 59 patients (81%), paralysis in 14 patients (19%) and additional signs and symptoms of brain stem failure in 7 patients (10%). The patients were divided on the basis of the clinical picture into those suffering from: atherosclerotic stoke (38–51%), lacunar stroke (15–21%), embolic stroke (15–21%) and transient ischaemic attack (5–7%). A CT scan performed within 24 hours of the onset of ischaemia revealed areas of infarction in 19 (26%) patients.

The number of patients with acute cerebral ischaemia and co-existing risk factors for arteriosclerosis and embolus formation is presented in Table 1.

Blood samples for examination were obtained from the patients (within 24 hours of admission) and healthy controls in the morning (between 7 and 8 a.m.) into a 3.2% solution of sodium citrate at a ratio of 9 : 1. Platelet-poor plasma was obtained by centrifuging the citrated blood at 3000 rpm for 20 minutes at 4°C. Following centrifugation, the citrated plasma was refrigerated at –20°C for no longer than 3 months.

The concentration of thrombomodulin (TM) was determined using the Imubind® Thrombomodulin ELISA Kit assay from American Diagnostica Inc. This assay is able to recognize the intact and partially degraded forms of thrombomodulin (reference values: women – age-dependent: 2.73 ng/ml for those aged 21–30, then increases up to 4.79 ng/ml for those aged 61–70; men – age-independent: 4.00–5.35 ng/ml).

The results were then processed using Microsoft® Excel 2000 and StatSoft® STATISTICA for WINDOWS 5.0. The significance level was determined at $p < 0.05$. The Kolmogorov-Smirnov test was used to test for goodness of fit to the normal distribution. TM concentrations following a non-normal distribution were tabulated as medians and the upper and lower quartiles. The significance of differences between parameters was determined using the Mann-Whitney *U* test for independent groups. The incidence of risk factors for atherosclerosis in the subgroups was compared using the chi-squared distribution goodness of fit test. Spearman's method was used to determine correlations between parameters with non-normal distributions. The level of significance of the defined coefficient of correlation was also tested.

Table 1. Incidence of risk factors for atherosclerosis and embolus formation

Tabela 1. Występowanie czynników ryzyka miażdżycy tętnic oraz powstawania materiału zatorowego

Risk factor (Czynnik ryzyka)	Number of patients (Liczba chorych) n (%)
Arterial hypertension (Nadciśnienie tętnicze)	53 (73)
Hypercholesterolaemia (Hipercholesterolemia)	53 (73)
Cigarette smoking (Palenie papierosów)	16 (22)
Type 2 diabetes mellitus (Cukrzyca typu 2)	19 (26)
Ischaemic heart disease (Choroba niedokrwienna serca)	
– without atrial fibrillation (bez migotania przedsionków)	19 (26)
– with atrial fibrillation (z migotaniem przedsionków)	10 (14)

Results

Table 2 presents TM concentrations in the patients with acute cerebral ischaemia and in the controls. TM concentration was consistently and significantly higher in all patients compared to the control group.

There were no statistically significant differences in TM concentration in the patient group relative to the presence of risk factors for acute cerebral ischaemia, such as arterial hypertension, hypercholesterolaemia, cigarette smoking, diabetes mellitus, ischaemic heart disease and atrial fibrillation.

A comparison of TM concentration in patients with acute cerebral ischaemia relative to gender,

Table 2. TM levels in patients with acute cerebral ischaemia and normal controls

Tabela 2. Stężenia TM u chorych na ostre niedokrwienie mózgu i u osób zdrowych

Study group (Grupa badana) (n = 73)* TM ng/ml	Control group (Grupa kontrolna) (n = 40)* TM ng/ml	p
4.72 (4.0; 5.48)	4.32 (3.64; 4.68)	0.0349

* – median (1st quartile; 3rd quartile)

* – (mediana (kw I; kw III).

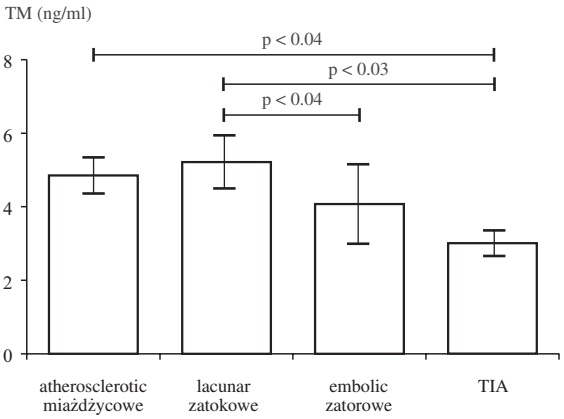

Fig. 1. TM levels in patients with acute cerebral ischaemia relative to type of ischaemia

Ryc. 1. Stężenia TM u chorych na ostre niedokrwienie mózgu w zależności od typu niedokrwienia

age (below or above 70 years) and the presence or absence of an ischaemic lesion in a CT scan did not reveal any statistically significant differences. Higher TM concentrations were seen in patients with acute cerebral ischaemia but without co-existing brain stem failure.

The differences in TM concentration in patients with acute cerebral ischaemia of different aetiology are charted in Figure 1.

There were no differences in TM concentration between patients with atherosclerotic and lacunar strokes or between patients with embolic strokes and transient ischaemic attacks. However, significantly lower TM concentrations were seen in patients with embolic strokes or transient ischaemic attacks compared to patients with atherosclerotic or lacunar strokes.

Discussion

Pathological processes in the vascular endothelium disturb the coagulation system and may thus be a major factor underlying acute cerebral ischaemia. These disturbances are associated with the response of endothelial cells to pathological processes in vessel walls e.g. in the course of atherosclerosis.

Thrombomodulin is chiefly present in the vascular endothelium and contributes considerably to its anticoagulant properties. TM circulating in the blood is in a soluble form. Soluble TM probably forms as a result of cell-bound TM having been split by one (or more) proteolytic enzymes present in the blood or endothelial cells. It is assumed that this process is intensified under pathological conditions following damage to the vascular endothelium [13, 20]. Consequently, elevated TM concentration is regarded as a sign of endothelial damage [18].

Table 3. Effect of risk factors on TM concentration in patients with acute cerebral ischaemia

Tabela 3. Wpływ czynników ryzyka na stężenia TM u chorych na ostre niedokrwienie mózgu

Risk factor (Czynnik ryzyka)	n	TM ng/ml *
Arterial hypertension (Nadciśnienie tętnicze)	53	4.96 (4.08; 5.48)
Without arterial hypertension (Bez nadciśnienia tętniczego)	20	4.28 (3.76; 5.22)
Cholesterol level > 200 mg/dl (Poziom cholesterolu)	53	4.76 (4.08; 5.56)
Cholesterol level ≤ 200 mg/dl (Poziom cholesterolu)	20	4.48 (3.76; 5.4)
Smokers (Palący papierosy)	16	4.48 (4.16; 5.04)
Non-smokers (Niepalący papierosów)	57	4.88 (3.88; 5.56)
Diabetes mellitus (Cukrzyca)	19	4.72 (3.84; 5.96)
Without diabetes mellitus (Bez cukrzycy)	55	4.8 (4.0; 5.4)
Ischaemic heart disease (Choroba niedokrwienna serca)	19	4.24 (3.84; 5.96)
Without ischaemic heart disease (Bez choroby niedokrwiennej serca)	54	4.96 (4.08; 5.48)
Atrial fibrillation (Migotanie przedsionków)	10	5.2 (3.44; 6.2)
Without atrial fibrillation (Bez migotania przedsionków)	63	4.64 (4.0; 5.4)

* – median (1st quartile; 3rd quartile)

* – mediana (kw I; kw III)

Our study demonstrated that TM levels are elevated in patients with acute cerebral ischaemia. A search through available data bases did not reveal any studies specifically designed to determine TM levels in the blood of patients with acute cerebral ischaemia. Still, our findings concur with reports by other authors, who found elevated TM in disorders associated with vessel wall injury and increased coagulation. This finding suggests that the release of soluble TM into circulating blood is intensified by proteolytic action on the surface of damaged endothelium [6, 13, 14, 17].

Elevated TM levels have been observed mainly in conditions associated with small vessel injury. Since it is not clear whether damage limited to major vessels would also result in increased production of sTM, some authors are not inclined to look at TM as an independent risk factor in all vascular disorders [6, 21]. Our study apparently supports their reservations as we found higher TM

Table 4. TM concentration in patients with acute cerebral ischaemia relative to gender, age (below or above 70 years), presence of an ischaemic lesion on CT scan and presence of signs of brain stem failure (ITC)

Tabela 4. Stężenia TM u chorych na ostre niedokrwienie mózgu w zależności od płci, wieku > 70. lub < 70. r. ż., obecności ogniska niedokrwiennego wykazanego w tomografii komputerowej i występowania objawów niewydolności pnia mózgu (ITC)

		n	TM ng/ml *	p
Gender (Płeć)	male (męska) female (żeńska)	37 36	4.52 (3.92; 5.48) 4.96 (4.08; 5.48)	ns.
Age (Wiek)	< 70 years < 70 (lat) > 70 years > 70 (lat)	35 38	4.64 (4.16; 5.32) 4.96 (4.08; 5.48)	ns.
CT (KT)	ischaemic lesion present (ognisko niedokrwienne) ischaemic lesion absent (bez ogniska niedokrwiennego)	19 54	5.22 (4.32; 5.56) 4.56 (3.84; 5.32)	ns.
ITC	ITC signs present (z objawami ITC) ITC signs absent (bez objawów ITC)	7 66	3.92 (3.44; 4.32) 4.96 (4.08; 5.52)	0.0344

* – median (1st quartile; 3rd quartile)

* – mediana (kw I; kw III).

Table 5. TM levels in patients with acute cerebral ischaemia relative to type of ischaemia

Tabela 5. Stężenia TM u chorych na ostre niedokrwienie mózgu w zależności od typu niedokrwienia

Defined types of ischaemia (Porównywane typy niedokrwienia)	n	TM ng/ml*	p
Atherosclerotic (Miażdżycowy) Lacunar (Lakunarny)	38 15	4.84 (4.12; 5.36) 5.24 (4.48; 5.96)	ns.
Atherosclerotic (Miażdżycowy) Embolic (Zatorowy)	38 15	4.84 (4.12; 5.36) 4.08 (3.44; 5.2)	ns.
Atherosclerotic (Miażdżycowy) TIA	38 5	4.84 (4.12; 5.36) 3.02 (2.68; 3.36)	0.0307
Lacunar (Lakunarny) Embolic (Zatorowy)	15 15	5.24 (4.48; 5.96) 4.08 (3.44; 5.2)	0.0359
Lacunar (Lakunarny) TIA	15 5	5.24 (4.48; 5.96) 3.02 (2.68; 3.36)	0.0254
Embolic (Zatorowy) TIA	15 5	4.08 (3.44; 5.2) 3.02 (2.68; 3.36)	ns.

* – median (1st quartile; 3rd quartile)

* – mediana (kw I; kw III).

concentrations in patients with atheromatous and lacunar strokes than in those with embolic strokes and TIAs.

In last years some studies appeared about presence of plasma haemostatic factors, among them TM, in human atherosclerotic carotid plaques.

These observations indicate that concentration of examined parameters in carotid plaques were much higher as in plasma, but no correlation between their concentration in plaques and plasma were observed [22–24].

The authors conclude that patients with acute cerebral ischaemia had elevated levels of TM, which may be the result of damage to the vascular endothelium. Higher TM concentrations were observed in patients with atherosclerotic and lacunar strokes or between patients with embolic strokes and transient ischaemic attacks. In patients without generalised signs of CNS damage (brain stem failure – ITC), TM levels were higher than in patients with ITC. Exposure to risk factors for cerebral ischaemia does not influence TM concentration in patients with acute cerebral ischaemia.

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Conflict of interest: None declared

Received: 8.07.2005
Revised: 16.09.2005
Accepted: 28.11.2005

Praca wpłynęła do Redakcji: 8.07.2005 r.
Po recenzji: 16.09.2005 r.
Zaakceptowano do druku: 28.11.2005 r.