Thrombin Activatable Fibrinolysis Inhibitor Antigen Levels Are Inversely Correlated with Plasminogen Activator Inhibitor-1 Antigen Levels in Hyperthyroid Patients

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Abstract. Both increased and decreased fibrinolytic activity have been reported in patients with hyperthyroidism. Elevated levels of plasma plasminogen activator inhibitor-1 (PAI-1) antigen have been found in hyperthyroid patients. Thrombin activatable fibrinolysis inhibitor (TAFI) is a novel plasma protein, which inhibits fibrinolysis through removal of C-terminal lysines from partially degraded fibrin. Previously, we showed that plasma TAFI antigen levels were increased in patients with overt and subclinical hypothyroidism. The aim of this study is to investigate plasma levels of TAFI and PAI-1 antigens in hyperthyroid patients. PAI-1 and TAFI antigen levels were measured in the plasma of 29 patients with hyperthyroidism (14 overt hyperthyroid and 15 subclinical hyperthyroid), and 26 healthy individuals. Although there were increased levels of PAI-1 antigen in hyperthyroid patients, plasma TAFI antigen levels were significantly lower compared to controls (80.79 ng/ml vs. 32.42 ng/ml, $p = 0.000$ for PAI-1; 10.42 $\mu\text{g/ml}$ vs. 12.24 $\mu\text{g/ml}$, $p = 0.009$ for TAFI). Elevated PAI-1 antigen levels were positively correlated with free thyroid hormones, although TAFI antigen levels were in negative correlation with free thyroxine. Furthermore, an inverse correlation between PAI-1 and TAFI antigen levels was found. Our study demonstrated that TAFI antigen levels were decreased in patients with hyperthyroidism. Inverse correlation with PAI-1 suggests that the decrease in TAFI antigen levels may be due to activation of TAFI pathway. Further studies evaluating the underlying mechanisms of low TAFI antigen levels in hyperthyroidism should be undertaken.

Key words: Thrombin activatable fibrinolysis inhibitor, Hyperthyroidism, Plasminogen activator inhibitor-1, Coagulation
(*Endocrine Journal* 54: 593–599, 2007)

THE imbalance between thrombotic and antithrombotic factors leads to pathological thrombus formation. A defect in the fibrinolytic system is sufficient for extended fibrin deposition and enhanced procoagulation [1–3]. Various coagulation abnormalities may be seen during the course of thyroid disorders. It is generally believed that there is a tendency to develop thrombosis in patients with hyperthyroidism [4]. The incidence of arterial thromboembolism in patients with thyrotoxic

atrial fibrillation is higher than in those with non-thyrotoxic atrial fibrillation [5]. Prolonged euglobulin lysis time, reduced fibrinolytic activity, and decreased plasminogen levels in hyperthyroidism have been shown in previous studies [4, 6]. The administration of levothyroxine in healthy subjects increases plasma vWF levels, an indicator of endothelial dysfunction and procoagulation [7]. Dorr and Volzke [8] showed that decreased serum TSH is an independent risk factor for elevated plasma fibrinogen levels. Li *et al.* [9] reported that serum thyroid hormone concentrations were strongly correlated with plasma PAI-1. Ozcan *et al.* [10] found that elevated PAI-1 antigen levels in hyperthyroid patients decreased after euthyroidism was restored.

Received: October 10, 2006

Accepted: March 5, 2007

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Although hyperthyroid patients are prone to developing thromboembolism, bleeding due to various coagulation defects are also reported [11–13]. Increased levels of a specific fragment of fibrinogen, which is degraded by plasmin, suggest hyperfibrinolysis in hyperthyroid patients [14]. Furthermore, hyperthyroid patients are sensitive to the anticoagulant effects of warfarin [15]. Kellett *et al.* [16] showed that hyperthyroidism was associated with lower activity of factor II, and a shorter partial thromboplastin time with kaolin.

Recently, a new plasma protein has been identified. This procarboxypeptidase is named thrombin activatable fibrinolysis inhibitor (TAFI) [17]. It is synthesized by the liver and has inhibitor role in fibrinolysis through the removal of C-terminal lysines from partially degraded fibrin [18]. TAFI also has a suppressor effect on conversion of inactive plasminogen to plasmin [19], thus leading to inhibition of fibrinolysis. Although several studies indicate that fibrinolytic system is disturbed in hyperthyroid patients, plasma TAFI antigen levels have not been investigated in patients with hyperthyroidism. Moreover, there is no data on simultaneous measurement of the circulating level of PAI-1 and TAFI antigen levels in patients with thyroid dysfunction.

The purpose of our study is to determine TAFI antigen levels in hyperthyroidism, and to investigate the relationship between plasma TAFI and PAI-1 antigen levels in hyperthyroid patients.

Material and Methods

Subjects

Twenty-nine hyperthyroid (21 females and 8 males) and 26 healthy control subjects (18 females, 8 males) were enrolled in the study. Overt hyperthyroidism was defined as TSH <0.35 mIU/L and elevated free thyroid hormone levels. Subclinical hyperthyroidism was defined as a low TSH (<0.35 mIU/L) in the presence of normal thyroid hormone levels. Informed consent was obtained in all cases and the study was approved by the local ethics committee of Dokuz Eylul University. Exclusion criteria were known atherosclerotic disease, diabetes, morbid obesity, familial hyperlipidemia, and coagulation disorders. Patients were excluded if they had been diagnosed with renal or hepatic dysfunction,

or if they had a history of malignancy or severe systemic disease. Patients taking lipid lowering drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin-2 receptor blockers, estrogen, oral contraceptives, and any other drugs which may influence coagulation system were also not included in the study.

Methods

Height (m) and weight (kg) were measured under fasting conditions with subjects in light clothing and without shoes. Measurements were taken with the subject standing upright. Body mass index (BMI) was calculated as body weight divided by square of height for each subject.

Fasting blood samples for TAFI and PAI-1 antigen assessment were obtained between 8:00 am and 9:00 am from the cannulated antecubital vein in tubes containing 3.2% buffered sodium citrate. Platelet-poor plasma was obtained by centrifugation at 2000 g for 15 minutes at 4°C. The plasma samples were stored at –80°C until use.

Plasma TAFI antigen levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits (Affinity Biologicals; Ontario, Canada). PAI-1 antigen levels were measured by ELISA (American Diagnostica; Stamford, CT, USA). Intraassay and interassay coefficients of variation were 5.8 and 8% for TAFI; and 4.0 and 4.3% for PAI-1, respectively. Triglycerides, total cholesterol and HDL were measured by Roche/Hitachi D/P Modular System Autoanalyzer (Roche Diagnostics, Basel, Switzerland). LDL cholesterol was calculated from Friedewald's formula. Free thyroid hormones were measured with immunoassay method (Diagnostic Products Corporation, Los Angeles, CA, USA). Anti thyroid peroxidase, anti thyroglobulin, anti TSH receptor antibodies (TRAb) and serum TSH levels were measured using solid phase chemiluminescent immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistical analysis

Data were analyzed using chi square, Kruskal Wallis and Mann Whitney U tests by the SPSS 11.0 for Windows software package. Correlation analyses were conducted by Spearman's test. Statistical significance was accepted at $p < 0.05$.

Results

The etiology of hyperthyroidism was diagnosed as Graves' disease in 15 cases (51.7%) and toxic nodular goiter in 14 cases (48.3%). Of the 29 hyperthyroid patients, 14 (48.3%) had overt and 15 (51.7%) subclinical hyperthyroidism. The median age was 45.5 (range: 24–68 years) in overt hyperthyroid group, 46 (range: 24–71 years) in subclinical hyperthyroid group, and 45.5 (range: 30–75 years) in control group. There was no significant difference in terms of age and BMI between hyperthyroid and control groups (Table 1).

Median values for FT₃, FT₄ and TSH in hyperthyroid patients and controls are shown in Table 1. Total cholesterol, HDL and LDL cholesterol levels were similar between hyperthyroid and control groups. Although overt and subclinical hyperthyroid patients had elevated serum triglycerides, the difference was not statistically significant ($p = 0.054$, Table 1).

Plasma PAI-1 antigen levels were significantly higher in hyperthyroid patients compared to controls (80.79 ng/ml, 25–75 percentiles: 60.45–94.64 vs. 32.42 ng/ml, 25–75 percentiles: 23.51–41.12, $p = 0.000$; Fig. 1). Both overt and subclinical hyperthyroid patients had significantly elevated plasma PAI-1 antigen levels ($p = 0.000$ for overt hyperthyroid patients, $p = 0.000$ for subclinical hyperthyroid patients; Table 2). Although overt hyperthyroid patients had higher PAI-1 antigen levels when compared with subclinical hyperthyroid patients, the difference was not statistically significant ($p = 0.326$).

Plasma TAFI antigen levels were found to be lower in hyperthyroid patients (10.42 μ g/ml, 25–75 percentiles: 9.26–11.83 vs. 12.24 μ g/ml, 25–75 percentiles:

10.68–15.01, $p = 0.009$; Fig. 1). Both overt and subclinical hyperthyroid patients had reduced TAFI levels; however, the difference between subclinical hyperthyroid and control groups was not statistically significant ($p = 0.016$ for overt hyperthyroid patients, $p = 0.058$ for subclinical hyperthyroid patients; Table 2). There was no significant difference between overt and subclinical hyperthyroid patients regarding plasma TAFI antigen levels ($p = 0.458$).

There was no significant difference in PAI-1 and TAFI antigen levels in terms of the etiology of hyperthyroidism, although hyperthyroid patients with Graves' disease had a slightly higher level of PAI-1 antigen compared to hyperthyroid patients with toxic

Fig. 1. TAFI and PAI-1 antigen levels of hyperthyroid patients and controls

Table 1. Characteristics of hyperthyroid patients and controls (* $p < 0.05$)

	Overt (n = 14)	Subclinical (n = 15)	Control (n = 26)	P value
Age	45.5 (26.75–54.75)	46 (35–62)	45.5 (33–53.5)	0.394
Gender (F/M)	4/10	4/12	18/8	0.961
BMI (kg/m ²)	23.29 (22.16–26.91)	24.17 (21.6–29.19)	25.12 (21.76–26.79)	0.983
FT ₃ (pg/ml)	6.66 (5.09–8.68)	3.25 (3.05–3.69)	2.76 (2.48–2.92)	0.000*
FT ₄ (ng/dl)	2.7 (2.07–3.72)	1.41 (1.28–1.45)	1.35 (1.27–1.42)	0.000*
TSH (mIU/L)	0.005 (0.004–0.03)	0.099 (0.023–0.2)	1.447 (0.98–2.16)	0.000*
Total cholesterol (mg/dl)	183.5 (152–214)	191 (173–210)	184 (166–203)	0.845
HDL-cholesterol (mg/dl)	53.5 (48–62)	53 (42–65)	54.5 (48–60)	0.762
LDL-cholesterol (mg/dl)	99.1 (70–131)	110 (69–132.8)	102 (87–123)	0.989
Triglyceride (mg/dl)	145 (101.5–167)	145 (120–182)	111.5 (80–144)	0.054

Data are expressed as median (25–75 percentiles); p-values are calculated using chi-square and Kruskal Wallis tests.

Table 2. Comparison of TAFI and PAI-1 antigen levels in overt and subclinical hyperthyroid patients, and controls

	Overt (n = 14)	Subclinical (n = 15)	Control (n = 26)	P value*	P value†	P value‡
PAI (ng/ml)	88.45 (64.15–104.59)	79.61 (60.39–88.48)	32.42 (23.51–41.12)	0.000*	0.000†	0.326‡
TAFI (µg/ml)	10.07 (9.09–11.53)	10.72 (9.14–11.98)	12.24 (10.68–15.01)	0.016*	0.058†	0.458‡

Data are expressed as median (25–75 percentiles); p-values are calculated using Mann Whitney U test.

* overt vs. control, † subclinical vs. control, ‡ overt vs. subclinical.

Table 3. Comparison of data in hyperthyroid patients with Graves' disease and toxic nodular goiter (*p<0.05)

	Graves' Disease (n = 15)	Toxic Nodular Goiter (n = 14)	P value
Age	46 (27–58)	49.5 (35–63.25)	0.451
Gender (F/M)	4/11	4/10	0.617
BMI (kg/m ²)	22.6 (21.6–26.6)	25.04 (22.87–28.2)	0.134
FT3 (pg/ml)	5.36 (3.65–7.39)	3.37 (3.04–4.96)	0.07
FT4 (ng/dl)	2.7 (2.07–3.72)	1.41 (1.28–1.45)	0.451
TSH (mIU/L)	0.02 (0.004–0.099)	0.043 (0.04–0.2)	0.425
TRAb (IU/L)	20 (7.4–33)	2.1 (1.6–2.5)	0.000*
PAI (ng/ml)	87.96 (65.99–95.65)	78.38 (55.24–94.67)	0.451
TAFI (µg/ml)	10.37 (8.2–11.16)	10.9 (9.47–12.1)	0.29

Data are expressed as median (25–75 percentiles); p-values are calculated using chi-square and Mann Whitney U tests.

nodular goiter. Furthermore, TAFI antigen levels of hyperthyroid patients with Graves' disease were significantly lower than controls, while the difference between toxic nodular goiter and control groups was not statistically significant (Table 3). Plasma TAFI and PAI-1 antigen levels were not associated with sex and menopausal status.

There were significant correlations between age, FT₄, TSH, and plasma TAFI antigen levels ($r = 0.278$, $p = 0.04$; $r = -0.365$, $p = 0.006$; $r = 0.355$, $p = -0.008$; $r = -0.35$, $p = 0.009$; respectively). Serum FT₃, FT₄, TSH and triglyceride levels were significantly correlated with PAI-1 levels ($r = 0.642$, $p = 0.000$; $r = 0.498$, $p = 0.000$; $r = -0.733$, $p = 0.000$; $r = 0.295$, $p = 0.029$; respectively). While there was no significant correlation between auto antibody titers and TAFI antigen levels, PAI-1 antigen levels were in positive correlation with serum anti thyroglobulin antibody ($r = 0.369$, $p = 0.049$) and TRAb ($r = 0.378$, $p = 0.043$) levels. Furthermore, PAI-1 antigen levels were in negative correlation with TAFI antigen levels ($r = -0.350$, $p = 0.009$; Fig. 2). Multiple regression analysis was performed to determine the best linear combination to predict plasma TAFI and PAI-1 antigen levels. Serum TSH was a significant predictor of plasma PAI-1 antigen levels ($p = 0.000$, $\beta = -0.558$). Although serum TSH levels were more strongly correlated with plasma

Fig. 2. Statistical significant correlation between plasma PAI-1 and TAFI antigen levels ($r = -0.35$, $p = 0.009$)

TAFI antigen levels than other studied parameters, they did not contribute as an independent predictor of plasma TAFI antigen levels ($p = 0.057$, $\beta = 0.338$).

Discussion

In this study, we found that PAI-1 antigen levels were elevated in patients with hyperthyroidism, similar to other studies [10, 20]. However, plasma TAFI antigen levels were decreased in hyperthyroid patients. Moreover, an inverse correlation was observed between both inhibitors of fibrinolysis. Decreased serum TSH was an independent predictor of elevated PAI-1 antigen levels. Both overt and subclinical hyperthyroid patients had increased plasma PAI-1 antigen levels and decreased TAFI antigen levels, although the difference regarding TAFI antigen levels between subclinical hyperthyroid and control groups was not statistically significant.

A decrease in fibrinolytic potential has been observed both in hyperthyroid and hypothyroid patients in various studies [4, 12, 21]. Similarly, increased levels of PAI-1 antigen have been reported in patients with both thyroid dysfunctions [20, 22]. Results from the few studies evaluating PAI-1 levels in hyperthyroid patients suggest that PAI-1 is elevated in hyperthyroidism [8–10, 20]. We found lower TAFI and elevated PAI-1 antigen levels in patients with hyperthyroidism. As PAI-1 and TAFI both are inhibitors of the fibrinolytic system, a reverse correlation between both inhibitors is a complex condition. Despite decreased levels of TAFI antigen in patients with hyperthyroidism, our study could not suggest increased fibrinolytic potential in hyperthyroidism. It is not clear whether plasma levels of TAFI antigen are reduced because of impaired synthesis, or increased metabolism in hyperthyroid patients. Hypermetabolic status due to hyperthyroidism may also be responsible for low TAFI levels [23]. Another explanation for inverse correlation between plasma levels of both fibrinolysis inhibitors may be a decrease in plasma antigen levels of TAFI secondary to activated TAFI pathway. In a study, decreased TAFI levels were found to be correlated with activation of some coagulation factors such as prothrombin in patients with sepsis [24]. Similarly, Zorio *et al.* [25] reported lower plasma TAFI antigen levels in young patients with myocardial infarction, although TAFI activity was significantly elevated and positively correlated with plasma PAI-1 antigen levels and activity. They also found a positive relationship between TAFI activity and activation of protein C system, and concluded that lower TAFI Ag levels in these patients are associated with overactivation of TAFI pathway, resulting in hypo-

fibrinolysis. Similarly, the inverse relationship between elevated PAI-1 and decreased TAFI antigen levels in our study suggests that decreased TAFI antigen levels may be related to the activation of the TAFI pathway during the coagulation process.

On the other hand, plasma levels of PAI-1 and TAFI antigens may be affected by different factors in hyperthyroidism. Simultaneous measurements of the circulating levels of TAFI and PAI-1 antigen were performed in patients with various disorders, and the results from these studies were found not to be similar with each other [26–28]. Our observation of inverse correlation between TAFI and PAI-1 antigen levels in hyperthyroid individuals is an interesting finding. In one study, PAI-1 antigen levels were found to be associated with TAFI antigen levels in obese subjects [26]. Juhan-Vague *et al.* [27] found a significant correlation between TAFI and PAI-1 antigen levels only in women. In another study, Kitagawa *et al.* [28] found no significant correlation between plasma TAFI and PAI-1 antigen levels in non-obese diabetic subjects.

It has been shown that endothelial dysfunction and impaired fibrinolytic activity are present in hyperthyroid patients with Graves' disease [9]. To evaluate the effect of different etiologies of hyperthyroidism on PAI-1 and TAFI antigen levels, we divided hyperthyroid group into two subgroups, namely Graves' disease' and toxic nodular goiter. Although patients with Graves' disease had slightly higher PAI-1 and mildly lower TAFI antigen levels compared to patients with toxic nodular goiter, the difference between two subgroups did not reveal statistical significance. Furthermore, a weak correlation between PAI-1 levels and serum antithyroglobulin antibody and TRAb levels were found. However, this weak correlation was not statistically significant after adjustment for free thyroid hormones and TSH. In addition, a slight difference in free thyroid hormone and TSH levels between both subgroups was remarkable. Thus, we believe that alterations of PAI-1 and TAFI antigen levels in hyperthyroidism are associated with the presence of thyroid dysfunction, and not etiology of hyperthyroidism.

Recently, we investigated TAFI antigen levels in overt and subclinical hypothyroidism. Although hyperthyroid patients have decreased TAFI antigen levels in the present study, TAFI antigen levels were found to be elevated in our previous study including hypothyroid patients. Our previous results showed that elevated TAFI antigen in hypothyroidism could be decreased

by levothyroxine replacement. Additionally, a positive correlation between the degree of thyroid failure and plasma TAFI antigen levels was demonstrated. Low levels of free thyroxine were determined as an independent predictor of high plasma TAFI antigen levels in patients with hypothyroidism [29]. Significant correlations between free thyroxine, TSH and TAFI antigen levels in the present study also indicate that similar association between the degree of the thyroid dysfunction and TAFI antigen levels is partially present in patients with hyperthyroidism.

In conclusion, our study demonstrated that TAFI antigen levels are decreased in patients with hyperthyroidism. Despite low TAFI antigen levels in our study, elevated PAI-1 levels suggest that our results

could not provide definite evidence about hyperfibrinolysis in hyperthyroid patients. Furthermore, inverse correlation between TAFI and PAI-1 antigen levels may be associated with activation of TAFI pathway. It is also possible that plasma levels of PAI-1 and TAFI antigens may be affected by different factors in hyperthyroidism. However, our study comprised a small number of patients with hyperthyroidism, and did not evaluate TAFI activation or relationship with other components of fibrinolytic system. The underlying mechanism of low TAFI antigen levels in hyperthyroidism should be investigated. A larger number of patients should be included in a prospective study to clarify the association between hyperthyroidism and plasma TAFI levels.

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