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ORIGINAL ARTICLE

Increased thrombin-activatable fibrinolysis inhibitor and decreased tissue factor pathway inhibitor in patients with hyperthyroidism

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Abstract Various abnormalities of coagulation-fibrinolytic system have been reported in patients with thyroid dysfunction. Several studies indicate that coagulation and fibrinolytic system is disturbed in the patients with hyperthyroidism. The levels of plasma thrombin-activatable fibrinolysis inhibitor (TAFI) antigen and tissue factor pathway inhibitor (TFPI) have been very rarely investigated in patients with hyperthyroidism. Therefore, the main purpose of this study was to evaluate the profile of coagulation and fibrinolytic parameters including TAFI and TFPI in patients with hyperthyroidism. We also investigated the relationships between serum thyroid hormones and hemostatic parameters in these patients. Thirty patients with untreated hyperthyroidism and 25 age- and sex-matched healthy controls were included in the study. Factor V (FV), protein C, protein S, TFPI, and TAFI were measured. The relationships between serum thyroid hormones and these hemostatic parameters were examined. Compared with the control subjects, TAFI Ag levels were increased significantly in patients with hyperthyroidism [mean ± SD (ranges)] [177.03 ± 20.37 (131–206%) versus 145.9 ± 23.0 (89–169%)] ($P < 0.001$), whereas FV [89.8 ± 21.02 (49–124%) versus 116.1 ± 31.4 (56.4–200%)], protein C [72.8 ± 46.22 (2–149%) versus 144.0 ± 26.3 (74–158%)] and protein S [60.06 ± 42.82 (9–156%) versus 151 ± 33 (76–231%)] activities and TFPI Ag levels [69.56 ± 17.63 (39–140 ng/ml) versus 87.5 ± 15.9 (64–121 ng/ml)] were decreased significantly ($P < 0.001$ for all of them). We did not find a significant difference between Graves' disease and toxic nodular goiter for hemostatic parameters. In patients with Graves' disease, serum-free T_3 levels were inversely correlated with TFPI Ag levels (r: −0.57, $P < 0.05$). In conclusion, we found some important differences in the hemostatic parameters between the patients with hyperthyroidism and healthy controls. Increased TAFI and decreased FV, protein C, protein S, and TFPI in these patients represent a potential hypercoagulable and hypofibrinolytic state, which might augment the risk for atherosclerotic and atherothrombotic complications. Thus, disturbances of the hemostatic system may contribute to the excess mortality due to cardiovascular disease seen in patients with hyperthyroidism.

Keywords Hemostasis · Thrombin-activatable fibrinolysis inhibitor · Tissue factor pathway inhibitor · Hyperthyroidism

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Introduction

Various abnormalities of coagulation-fibrinolytic system have been reported in patients with thyroid dysfunction [1–6]. These abnormalities range from subclinical laboratory findings to clinically significant coagulopathies and, more rarely, major hemorrhagic fatal thromboembolic events [3–6]. It seems that hyperthyroid state is associated with hypercoagulability, hypofibrinolysis, and endothelial dysfunction [1], the more recent literature findings have evidenced that the interaction between thyroid dysfunction

and hemostasis is more complex than initially believed [7]. Thus, hyperthyroid patients are at risk of thromboembolic events [4, 8].

The incidence of arterial thromboembolism in thyrotoxic patients with atrial fibrillation is higher than in patients with non-thyrotoxic atrial fibrillation [9, 10]. Increased levels of fibrinogen, fibrinopeptide A, thrombomodulin, tissue factor pathway inhibitor (TFPI), and factors VIII, IX, von Willebrand factor antigen (vWF Ag), vWF ristocetin co-factor (vWF: RCo), and decreased fibrinolytic activity [increased tissue plasminogen activator inhibitor-1 (PAI-1) and decreased tissue plasminogen activator (t-PA) and plasminogen] in hyperthyroidism have been shown in previous studies [1, 4–7, 11–14].

The thrombin-activatable fibrinolysis inhibitor (TAFI), an enzyme that may act as a link between coagulation and fibrinolysis, inhibits fibrinolysis by removing carboxyterminal residues from partially degraded fibrin, thus decreasing plasminogen binding on the surface of fibrin [15, 16]. Increased TAFI levels have been associated with several thrombotic conditions like venous thromboembolism [17, 18] and ischemic stroke [19, 20]. TFPI is secreted by the endothelium and stored in platelets [21]. TFPI binds directly and inhibits the earliest steps in extrinsic pathway activation by binding factor Xa (which involved in the activation of prothrombin to thrombin) and tissue factor/factor VIIa complexes in an inactive quaternary complex [22]. Low plasma TFPI levels have been reported in patients with ischemic stroke [23], thrombotic thrombocytopenic purpura [24], and in women taking combined oral contraceptives [25].

Although several studies indicate that coagulation and fibrinolytic system is disturbed in the patients with hyperthyroidism, plasma TAFI antigen and TFPI levels have been very rarely investigated in patients with hyperthyroidism. Therefore, in a case–control study, we determined the profile of coagulation and fibrinolytic parameters including TAFI and TFPI in patients with hyperthyroidism. We also investigated the relationships between serum thyroid hormones and hemostatic parameters in these patients. A hypercoagulable state might increase the risk for thromboembolic complications and predispose to an increased prevalence of vascular disease.

Design and methods

Patients and study design

The study was performed at Department of Internal Medicine, Faculty of Medicine, Karadeniz Technical University. We prospectively evaluated 30 untreated patients with hyperthyroidism (13 women and 17 men; mean age 46.6 ± 16.2 years); 15 patients with Basedow-Graves disease, and 15 patients with toxic nodular goiter (11 toxic multinodular and 4 toxic adenoma). Each patient was clinically and biochemically hyperthyroid, defined as having increased serum thyroid hormone levels, a suppressed TSH concentration (<0.1 mU/l). Only one case had T_3 toxicosis (FT_3: 5.2 pg/ml and FT_4: 1.45 ng/dl) and one case had T_4 toxicosis (FT_3: 3.26 pg/ml and FT_4: 1.9 ng/dl). The diagnosis of Graves' disease was based on the additional presence of a smooth goiter, increased thyroid autoantibodies [anti-thyroglobulin (anti-Tg), anti-thyroid peroxidase (anti-TPO), and anti-TSH receptor], or specific eye signs. The mean duration of hyperthyroidism since onset of symptoms was 3.3 ± 2.1 months. Any coagulopathy was not observed in our patients during the treatment of hyperthyroidism (e.g., anti-thyroid drug therapy, surgical therapy, or radioactive iodine therapy). Clinical examination included height and body weight measurements. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters squared). Systolic and diastolic blood pressures were measured thrice in sitting position after 15 min rest, and the mean was taken for all cases. Participants were advised to avoid alcohol, caffeinated beverages, and exercise for at least 30 min before their blood pressure measurement.

Patients neither received any medical treatments (e.g., estrogen therapy) nor had any known diseases (e.g., diabetes, coronary heart disease, collagen diseases, inflammatory diseases, liver cirrhosis, non-alcoholic fatty liver disease, atrial fibrillation, morbid obesity, familial hyperlipidemia, or renal disease) that might affect blood coagulation or fibrinolysis at the time of the study. At diagnosis, risk factors for coagulation and thromboembolism, including known cancer, pregnancy, known thrombophilia, recent childbirth, and use of oral contraceptives, were excluded from the patient group. Also, no medication known to influence the serum lipid concentration was administered. Twenty-five healthy age- and sex-matched subjects (12 women and 13 men, mean age 41.9 ± 11.1 years) were used as controls. Their biochemical values were within normal ranges. None of the controls were taking any drugs affecting the levels of serum thyroid hormones and hemostatic parameters. All participants including patients and control subjects were non-smokers, and there was no minor illness like viral infections or family history of clotting disorders in patients and controls. Informed consent was obtained in all cases and the study was approved by the local ethics committee of Karadeniz Technical University (No.: 2005/14).

Laboratory analysis

Blood was collected in the morning between 0800 and 0900 hours after an overnight fast to avoid the differences of diurnal variation, especially for hormonal and hemostatic

parameters. Serum-free T_3 (FT_3), free T_4 (FT_4), and TSH concentrations were measured by automated electrochemiluminescence system (Roche Diagnostics GmbH, Mannheim, Germany). Normal ranges are 1.8–4.6 pg/ml for FT_3, 0.9–1.7 ng/dl for FT_4, and 0.27–4.2 μU/ml for TSH. Thyroid autoantibodies were measured by a chemiluminescence immunoassay (Diagnostics Products Corp., Los Angeles, USA). Normal ranges are <34 IU/ml for anti-TPO antibodies, <40 IU/ml for anti-Tg antibodies, and 0–10 U/l for anti-TSH receptor Ab.

For coagulation and fibrinolysis, a venous blood sample (9 vol.) was collected into Vacutainer tubes (Becton–Dickinson, Mountain View, CA, USA) containing 0.129 mol/l trisodium citrate (1 vol.). Platelet-poor plasma was obtained by centrifugation 3500 × *g* at 10°C for 20 min. Factor V (FV) measurement was performed immediately. Aliquots of plasma were transferred into plastic tubes without delay and frozen at −80°C until assays for determination of proteins C and S. FV activity was measured with coagulometer using commercial kits of Diagnostica Stago, Asnieres, France. Normal range is 50–150% for FV. Proteins C and S activity assays were performed with ELISA method using commercial kits of Biopool International, Westminster, CO, USA. TAFI Ag and TFPI Ag assays were performed with ELISA using commercial kits of American Diagnostica, CT, USA. According to our hematology laboratory, normal ranges are 72–160% for protein C activity, 60–150% for protein S activity, 40–250% for TAFI, and 75–120 ng/ml for TFPI Ag. Intraassay coefficients of variation were found to be <10% for TAFI and 7.1% for TFPI. All the samples were assayed at the same time.

Statistical analysis

Statistical analyses were performed by Student's *t*-test for normal distribution data and Mann–Whitney *U*-test for not normal distribution data. In patient group, correlations among biochemical parameters and thyroid hormones and coagulation were carried out using Pearson (normal distribution data) and Spearman (not normal distribution data) correlation analyses. Results are cited as mean ± standard deviation, $P < 0.05$ was accepted significantly.

Results

Table 1 summarizes the clinical characteristics and laboratory parameters in patients with hyperthyroidism and control subjects. There were no significant differences between the groups for mean age, gender, BMI, and systolic and diastolic blood pressures.

Compared with the control subjects, TAFI Ag levels were increased significantly in patients with hyperthyroidism [mean ± SD (ranges)] [177.03 ± 20.37 (131–206%) versus 145.9 ± 23.0 (89–169%)] ($P < 0.001$), whereas FV [89.8 ± 21.02 (49–124%) versus 116.1 ± 31.4 (56.4–200%)], protein C [72.8 ± 46.22 (2–149%) versus 144.0 ± 26.3 (74–158%)], and protein S [60.06 ± 42.82 (9–156%) versus 151 ± 33 (76–231%)] activities and TFPI Ag levels [69.56 ± 17.63 (39–140 ng/ml) versus 87.5 ± 15.9 (64–121 ng/ml)] were decreased significantly ($P < 0.001$ for all of them). We did not find a significant difference between Graves' disease and toxic nodular goiter for hemostatic parameters (Table 2).

In patients with Graves' disease ($n = 15$), serum FT_3 levels were inversely correlated with TFPI Ag levels (r: −0.57, $P < 0.05$) (Fig. 1). We did not find any significant correlation between serum thyroid hormones and the other hemostatic parameters that we measured. Also, we could not have found any correlation among pro- and anticoagulant state, and thyroid autoantibodies.

Discussion

Thyroid hormones exert effects on different levels of the hemostatic system, such as modulation of fibrinolytic activity and coagulation proteins [26]. The patients with hyperthyroidism have various abnormalities of hemostatic parameters [4–7]. In our previous study, we reported a hypercoagulable and hypofibrinolytic state and vascular endothelial dysfunction in hyperthyroid patients compared with euthyroid controls [1]. Thus, hyperthyroid patients display a tendency to develop thromboembolic complications, with major embolism accounting for up to 18% of deaths in patients dying from thyrotoxicosis [1, 27, 28]. Moreover, acute cerebral ischemia has been described in hyperthyroidism independent of thyrotoxic atrial fibrillation and cardioembolic stroke [29].

Activated protein C (APC) cleaves and inhibits coagulation cofactors FVIIIa and FVa, which result in downregulation of the activity of the coagulation system. The two cofactors, protein S and the intact form of FV, enhance the anticoagulant activity of APC [30]. Protein C deficiency is weakly associated with arterial ischemic stroke [31]. Deficiency of protein S increases the risk of thrombosis and associated with cerebral arterial ischemia [31, 32]. However, protein S deficiency is not a major risk factor for ischemic stroke [31]. Thus, although there is conflicting evidence, deficiency of protein S appears to have a mild association with arterial stroke [31]. In this study, we found a significant decrease in proteins C and S activities in patients with hyperthyroidism. This condition in the patients may be due to tendency to thrombosis and coagulation which is crucial in cardiovascular events.

Table 1 Clinical and biological parameters of controls and patients with hyperthyroidism [mean ± SD (ranges)]

	Controls	Hyperthyroidism	*P*
Number of subjects	25	30	–
Gender (F/M)	12 F/13 M	13 F/17 M	–
Age (years)	41.9 ± 11.1	46.6 ± 16.2	NS
BMI (kg/m^2)	26.4 ± 3.3	25.5 ± 4.8	NS
SBP (mmHg)	126.2 ± 14.9	133.1 ± 19.0	NS
DBP (mmHg)	80.8 ± 9.9	80.6 ± 10.5	NS
FT_3 (pg/ml)	3.49 ± 0.73 (1.35–4.33)	12.33 ± 8.87 (3.26–32.55)	<0.001
FT_4 (ng/dl)	1.31 ± 0.09 (1.1–1.53)	3.67 ± 2.13 (1.45–7.77)	<0.001
TSH (μU/ml)	1.50 ± 0.63 (0.58–2.93)	0.01 ± 0.008 (0.001–0.04)	<0.001
FV (%)	116.1 ± 31.4 (56.4–200)	89.8 ± 21.02 (49–124)	<0.001
Protein C (%)	144.0 ± 26.3 (74–158)	72.8 ± 46.22 (2–149)	<0.001
Protein S (%)	151 ± 33 (76–231)	60.06 ± 42.82 (9–156)	<0.001
TFPI Ag (ng/ml)	87.5 ± 15.9 (64–121)	69.56 ± 17.63 (39–140)	<0.001
TAFI Ag (%)	145.9 ± 23.0 (89–169)	177.03 ± 20.37 (131–206)	<0.001

NS non-significant ($P > 0.05$), *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TFPI* tissue factor pathway inhibitor, *TAFI* thrombin activatable fibrinolysis inhibitor

Table 2 Comparison of data in hyperthyroid patients with Graves' disease and toxic nodular goiter [mean ± SD (ranges)]

	Graves' disease	Toxic nodular goiter	*P*
Number of subjects	15	15	–
Gender (F/M)	6 F/9 M	7 F/8 M	–
BMI (kg/m^2)	25.3 ± 5.1	25.9 ± 4.82	NS
SBP (mmHg)	134 ± 14.1	142.3 ± 22.1	NS
DBP (mmHg)	80.3 ± 9.4	81.6 ± 10.4	NS
FT_3 (pg/ml)	13.5 ± 8.8	11.2 ± 9.14	NS
FT_4 (ng/dl)	4.2 ± 2.23	3.1 ± 2.0	NS
TSH (μU/ml)	0.013 ± 0.009	0.014 ± 0.008	NS
FV (%)	86.8 ± 22.1	92.8 ± 17.1	NS
Protein C (%)	65.3 ± 36.7	80.3 ± 49.2	NS
Protein S (%)	43 ± 28.4	77.1 ± 48.7	NS
TFPI Ag (ng/ml)	69.1 ± 10.4	70.0 ± 23.2	NS
TAFI Ag (%)	170.9 ± 22.8	183.2 ± 16.1	NS

NS non-significant ($P > 0.05$), *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TFPI* tissue factor pathway inhibitor, *TAFI* thrombin activatable fibrinolysis inhibitor

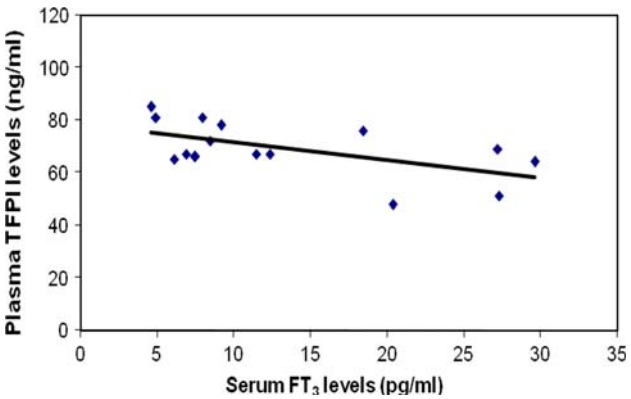

Fig. 1 Correlation between serum FT_3 and TFPI in patients with Graves' disease (r: −0.57, $P = 0.02$)

TFPI regulates FX activation. Low TFPI is a risk factor for a first venous thrombosis, recurrent venous thromboembolism, and stroke [23, 33, 34]. To our knowledge, this is the third study to determine TFPI levels in hyperthyroid patients. In previous studies, Ozcan et al. [14] and Morishita et al. [35] reported that free TFPI levels were significantly higher hyperthyroid patients compared with the control group. Also, in hyperthyroid patients, there was a strong positive correlation between thyroid hormones and free TFPI [14]. Researchers suggested that thyroid hormones might influence the synthesis or metabolism of TFPI on the surface of endothelial cells in patients with Graves' disease. Thus, increased plasma-free TFPI levels could be a marker of the peripheral activity of thyroid hormones. In contrast to these studies, in this study, we found a significant decrease in TFPI levels in patients with hyperthyroidism. The discrepancy may be due to different pathophysiological mechanisms or duration of hyperthyroidism. Thus, decreased TFPI levels in patients with hyperthyroidism may be tendency to thrombosis and coagulation in these patients. Also, we found an inverse correlation between TFPI and serum FT_3 levels only in patients with Graves' disease (Fig. 1). This result indicates that extrinsic coagulation pathway is influenced by T_3. We speculate that decreased TFPI Ag levels may be related to the activation of the TFPI pathway during the coagulation process. Also, a cause of an inverse correlation between FT_3 and TFPI only seen in patients with Graves' disease and not in hyperthyroidism caused by toxic nodular goiter is not clear. It may be explained by an autoimmune mechanism for Graves' disease.

TAFI, also known as procarboxypeptidase B, is a plasma zymogen that potently inhibits fibrinolysis [36, 37]. It protects the fibrin clots from breakdown by removing C-terminal lysine residues from partially degraded fibrin which is necessary for t-PA-mediated plasmin regeneration [37]. Increased activation of TAFI might exacerbate a prothrombotic disposition [17]. Increased plasma TAFI Ag levels are associated with a mild risk for venous thrombosis [17]. One study reported that patients with a recent myocardial infarction presented lower TAFI Ag values and that increased TAFI levels were actually protective against myocardial infarction [38]. On the other hand, high TAFI levels were reported to be associated with an increased risk of first ischemic stroke [19]. Silveira et al. [39] demonstrated increased TAFI Ag levels in men with symptomatic coronary artery disease (CAD). High plasma TAFI levels were found in patients with stable angina pectoris and angiographically verified CAD [39–41]. In another study, increased TAFI activity was associated with an almost four times higher risk of CAD [42]. To our knowledge, there is only one study to evaluate TAFI Ag levels in patients with hyperthyroidism [9]. In this study, Akinci et al. [9] reported increased levels of PAI-1 and decreased TAFI Ag levels in patients with hyperthyroidism compared to controls. Elevated PAI-1 Ag levels were positively correlated with free thyroid hormones, although TAFI Ag levels were in negative correlation with free thyroxine. Furthermore, interestingly, there was in inverse correlation between PAI-1 and TAFI Ag levels. They also suggested that the decrease in TAFI Ag levels might be due to activation of TAFI pathway. In contrast to this study, in this study, whereas we found higher TAFI Ag levels in patients with hyperthyroidism, our results may be more reliable because of decreased TFPI and increased TAFI. Thus, increased TAFI Ag levels in hyperthyroidism may be related to increased production by hepatic cells and endothelial damage. Moreover, increased TAFI Ag levels may cause thromboembolic events by lowering fibrinolytic activity in patients with hyperthyroidism.

Interestingly, we very recently demonstrated a quite similar hypercoagulative status in hypothyroid patients (decreased TFPI and increased TAFI) [43]. A cause of the analogies between the results obtained in the two studies is not clear. It may be explained by similar or different mechanisms. Circulating thyroid hormones may directly or indirectly influence the synthesis, release, or clearance of coagulation/fibrinolytic parameters; or alter distribution among different intravascular pools [35].

In conclusion, we found some important differences in the hemostatic parameters between the patients with hyperthyroidism and healthy controls. Increased TAFI and decreased FV, proteins C and S, and TFPI in these patients represent a potential hypercoagulable and hypofibrinolytic state and possible endothelial dysfunction, which might augment the risk for atherosclerotic and atherothrombotic complications. Thus, disturbances of the hemostatic system may contribute to the excess mortality due to cardiovascular disease seen in patients with hyperthyroidism. In fact, recent studies performed in a very large population (more than 3,000 patients) demonstrated that the CVD related to the hyperthyroid status is mainly due to dysrhythmias and that the apparently there is no increase in general mortality risk in patients treated with thyroid disease [44]. However, our study comprised a small number of patients with hyperthyroidism. In addition, an another limitation of this study is that patients were not followed after euthyroid state. Thus, a larger number of patients should be included in a further prospective study to explain the association between hyperthyroidism and TAFI.

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