## ORIGINAL PAPER

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

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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 hypothyroidism. Also, the influence of hypothyroidism on hemostasis is controversial; both hypocoagulable and hypercoagulable states have been reported. The levels of plasma thrombin-activatable fibrinolysis inhibitor (TAFI) antigen and tissue factor pathway inhibitor (TFPI) have been investigated only once in patients with hypothyroidism. Therefore, the main purpose of this study was to evaluate the profile of coagulation and fibrinolytic parameters including TAFI and TFPI in patients with hypothyroidism. Fifteen patients with untreated hypothyroidism and 15 age-matched healthy controls were included in the study. Factors V(FV), VII (FVII), VIII (FVIII) activities, von Willebrand factor (vWF), protein C, protein S, thrombomodulin (TM), TFPI, and TAFI were measured. The relationships between serum thyroid hormones and these hemostatic parameters were examined. Compared with the control subjects, FVII activity, and TM Ag and TAFI Ag levels were significantly increased in patients with hypothyroidism, whereas FV, FVIII, vWF, protein C and protein S activities, and TFPI Ag levels were significantly

decreased. We did not find any significant correlation between serum thyroid hormones and the hemostatic parameters that we measured. In conclusion, we found some important differences in the hemostatic parameters between the patients with hypothyroidism and healthy controls. Increased FVII, TM, and TAFI and decreased FV, FVIII, vWF, protein C, protein S, and TFPI in these patients represent a potential hypercoagulable and hypofibrinolytic state, 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 hypothyroidism.

 $\begin{tabular}{ll} Keywords & Hemostasis \cdot Thrombin-activatable \\ fibrinolysis inhibitor \cdot Tissue factor pathway inhibitor \cdot \\ Hypothyroidism \end{tabular}$ 

# 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]. Although it has been generally agreed that hypothyroid patients have a bleeding tendency [7, 8], the more recent literature findings have evidenced that the interaction between thyroid dysfunction and hemostasis is more complex than initially believed [9].

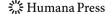
The influence of hypothyroidism on hemostasis is controversial; both hypocoagulable and hypercoagulable states have been reported [2]. Increased levels of fibrinogen, fibrinopeptide A, antithrombin III (ATIII), tissue factor

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pathway inhibitor (TFPI), and factors VII, VIII, IX, X, XII, XIII, von Willebrand factor antigen (vWF Ag), vWF ristocetin co-factor (vWF: RCo), and decreased fibrinolytic activity (increased tissue plasminogen activator inhibitor-1 (PAI-1),  $\alpha$ 2-antiplasmin and decreased D-dimer levels (DDI)) in moderate hypothyroidism and increased fibrinolytic activity (lower tissue plasminogen activator (t-PA), PAI-1 and  $\alpha$ 2-antiplasmin levels and higher DDI levels) in severe hypothyroidism have been shown in previous studies [2, 4–7, 9–14].

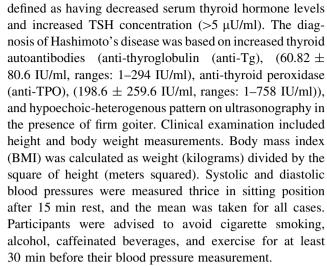
The thrombin-activatable fibrinolysis inhibitor (TAFI), an enzyme that may act as a link between coagulation and fibrinolysis, inhibits fibrinolysis by removing carboxyterminal residues from partially degraded fibrin, thus decreasing plasminogen binding on the surface of fibrin [15, 16]. Increased TAFI levels have been associated with several thrombotic conditions like venous thromboembolism [17, 18] and ischemic stroke [19, 20]. Tissue factor pathway inhibitor (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 (TF)/factor VIIa complexes in an inactive quaternary complex [22]. Low plasma TFPI levels have been reported in patients with ischemic stroke [23] and thrombotic thrombocytopenic purpura [24] as well as in women taking combine oral contraceptives [25].

Although several studies indicate that coagulation and fibrinolytic system is disturbed in the patients with hypothyroidism, the levels of plasma TAFI antigen and TFPI have been only once investigated in patients with hypothyroidism [10, 26]. Therefore, in a case–control study, we determined the profile of coagulation/fibrinolytic and vascular endothelial cell function parameters including TAFI and TFPI in patients with hypothyroidism. We also investigated the relationships between serum thyroid hormones and hemostatic parameters in these patients.

# Design and methods

Patients and study design

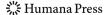
The study was performed at Karadeniz Technical University Medical Faculty, Department of Internal Medicine. We prospectively evaluated 15 untreated patients with hypothyroidism (ten women and five men; mean age,  $43.3 \pm 12.1$  years); nine patients with Hashimoto's thyroiditis, and six patients with postoperative hypothyroidism. The mean duration of hypothyroidism was  $27.3 \pm 43.0$  months  $(10.7 \pm 11.6$  months for Hashimoto's thyroiditis and  $39.8 \pm 55.9$  months for postoperative hypothyroidism). Each patient was clinically and biochemically hypothyroid,



Patients did not receive a medical treatment (e.g., estrogen therapy) or did not have any known disease (e.g., diabetes, coronary heart disease, collagen disease, liver cirrhosis, atrial fibrillation, morbid obesity, familial hyperlipidemia, or renal disease) that might affect blood coagulation/fibrinolysis and endothelial function, at the time of the study. At diagnosis, risk factors of coagulation and thromboembolism, including known cancer, pregnancy, known thrombophilia, recent childbirth, and use of oral contraceptives, were excluded from patient group. Also, no medication known to influence the serum lipid concentration was administered. Fifteen healthy age and sex-matched subjects (seven women and eight men, mean age  $41.9 \pm 10.52$  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 no 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 h after an overnight fast to avoid the differences of diurnal variation, especially for hormonal and hemostatic parameters. Serum-free  $T_3$  (FT<sub>3</sub>), free  $T_4$  (FT<sub>4</sub>), and TSH concentrations were measured by automated chemiluminescence system (Bayer Corporation, Tarrytown, NY, USA). Normal ranges are 1.8–4.6 pg/ml for FT<sub>3</sub>, 0.9–1.7 ng/dl for FT<sub>4</sub>, and 0.27–4.2  $\mu$ U/ml for TSH. Thyroid autoantibodies were measured by an enzyme-linked immunusorbent assay (ELISA) (Synelisa, Pharmacia,



Germany). Normal ranges are <34 IU/ml for anti-TPO antibodies and <40 IU/ml for anti-Tg antibodies. The intra-assay coefficients of variation (CV) were as follows:  $FT_3$  2.5%,  $FT_4$  2.6%, TSH 3.2%, anti-TPO 5.2%, anti-Tg 4.9% and inter-assay CV were as follows:  $FT_3$  2.0%,  $FT_4$  1.8%, TSH 2.7%, anti-TPO 7.2%, anti-Tg 5.7%.

For coagulation and fibrinolysis, a venous blood sample (9 vol) was collected into Vacutainer tubes (Becton Dickinson, Mountain View, CA) containing 0.129 mol/l trisodium citrate (1 vol). Platelet-poor plasma was obtained by centrifugation 3,500g at 10°C for 20 min. Factors V, VII, and VIII measurements were performed immediately. Aliquots of plasma were transferred into plastic tubes without delay and frozen at -80°C until assays for determination of protein C and protein S. Factors V, VII and VIII activities were measured with coagulometer (Diagnostica Stago) using commercial kits of Diagnostica Stago. Normal ranges are 50-150% for factors V, FVII, and FVIII. Protein C and Protein S activity assays were performed with ELISA method using commercial kits of Biopool International. vWF activity was determined by ELISA method using commercial kits of Imtec Immundiagnostica Gmbh. According to the manufacturer's instruction, normal ranges are 70-150% for vWF, 72-160% for protein C activity, and 60-150% for protein S activity. Thrombomodulin (TM) antigen (Ag), TAFI Ag, and TFPI Ag assays were performed with ELISA using commercial kits of American Diagnostica. According to the manufacturer's instruction, normal ranges are 2.7-5.4 ng/ml for TM, 40-250% for TAFI, and 75-120 ng/ml for TFPI Ag. The intra-assay CV were follows: FV 2.4%, FVII 2.4%, FVIII 6.4%, vWF 2.5%, protein C 6%, protein S 7.8%, TM 4%, TFPI (for 1.25 ng/ml) 6.2%, TAFI <10% and inter-assay CV were as follows: FV 2.7%, FVII 2.7%, FVIII 11.8%, vWF 5%, protein C 7.5%, protein S 11%, TM 5.2%, TFPI 6.7%.

# 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 analysis. Results are cited as mean  $\pm$  standard deviation, P < 0.05 was accepted significantly.

## Results

Table 1 summarizes the clinical characteristics and laboratory parameters in patients with hypothyroidism and

Table 1 Clinical and biological parameters of controls and patients with hypothyroidism

	Controls	Hypothyroidism	P
Number of subjects	15	15	_
Age (years)	$41.9 \pm 10.5$	$43.27 \pm 12.08$	NS
BMI (kg/m <sup>2</sup> )	$26.6 \pm 3.2$	$27.1 \pm 5.6$	NS
SBP (mmHg)	$126.6 \pm 16.3$	$125.3 \pm 15.8$	NS
DBP (mmHg)	$81.3 \pm 10.6$	$80.3 \pm 12.31$	NS
FT <sub>3</sub> (pg/ml)	$3.45 \pm 0.76$	$2.33 \pm 0.71$	< 0.001
FT <sub>4</sub> (ng/dl)	$1.31 \pm 0.1$	$0.56 \pm 0.2$	< 0.001
$TSH (\mu U/ml)$	$1.52 \pm 0.67$	$41.09 \pm 34.49$	< 0.001
Factor V (%)	$127.0 \pm 32.73$	$85.33 \pm 18.06$	< 0.001
Factor VII (%)	$120.1 \pm 17.08$	$148.27 \pm 42.16$	< 0.05
Factor VIII (%)	$133.53 \pm 27.96$	$106.07 \pm 36.67$	< 0.05
vWF (%)	$159.8 \pm 29.0$	$73.0 \pm 30.57$	< 0.001
Protein C (%)	$155.0 \pm 1.81$	$55.8 \pm 35.3$	< 0.001
Protein S (%)	$165.13 \pm 29.17$	$40.53 \pm 21.35$	< 0.001
TM (ng/ml)	$2.12 \pm 0.19$	$2.45 \pm 0.44$	< 0.01
TFPI Ag (ng/ml)	$88.67 \pm 15.57$	$71.07 \pm 13.76$	< 0.01
TAFI Ag (%)	$148.6 \pm 24.3$	$184.13 \pm 15.43$	< 0.001

NS non significant (P > 0.05), BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, vWF von Willebrand Factor, TM Thrombomodulin, TFPI tissue factor pathway inhibitor, TAFI thrombin activatable fibrinolysis inhibitor

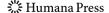
control subjects. There were no significant differences between the groups for mean age, BMI, and systolic and diastolic blood pressures.

Compared with the control subjects, FVII activity, and TM Ag and TAFI Ag levels were significantly increased in patients with hypothyroidism (P < 0.05, P < 0.01, and P < 0.001, respectively), whereas FV, FVIII, vWF, protein C and protein S activities, and TFPI Ag levels were significantly decreased (P < 0.001, P < 0.05, P < 0.001, P < 0.001, and P < 0.001, respectively). We did not find any significant correlation between serum thyroid hormones and the hemostatic parameters that we measured.

## Discussion

The influence of hypothyroidism on hemostasis has been studied but is still not well understood. Conflicting results (both bleeding tendency and hypercoagulability) have been reported [2, 7, 12, 26, 27]. In our previous study, we reported that hypofibrinolytic state in hypothyroidism, thus supporting the evidence of an increased risk of cardiovascular events in patients with hypothyroidism [2].

Factor VIII and vWF have been found to be decreased [7, 8, 28, 29], resembling acquired von Willebrand disease [30–32]. In other studies, however, these parameters have been described as normal [2, 33]. In the present study, we



found a significant decrease in FVIII and vWF activity in patients with hypothyroidism. In hypothyroidism, the most probable explanation for this condition is a decrease of FVIII and vWF protein synthesis in the absence of adequate levels of thyroxine [5]. Decreased FVIII and vWF activities may lead to a tendency to bleeding.

Factor VII is a vitamin-K-dependent zymogen that is converted to its active form FVIIa in the presence of tissue factor. The FVIIa/tissue factor complex converts factors IX and X into their active forms, leading to thrombin generation and fibrin clot formation [34]. The Northwick Park Heart Study (NPHS) in London was the first large-scale population study to report a significant correlation between increased plasma FVII levels and the risk for subsequent coronary heart disease (CHD) [35]. In other studies, elevated plasma FVII levels have been shown to be associated with arterial thrombosis and CHD [36, 37]. Ruddock and Meade suggested that FVII activity may be more strongly related to fatal events of CHD than to nonfatal events [38]. Müller et al. [14] reported that FVII:C and the FVII:C/ FVII:Ag ratio were higher in hypothyroid patients than in the euthyroid controls. These results suggested that the presence of a hypercoagulable state with hypothyroid patients. These findings confirmed the previous results of Chadarevian et al. [12], who found increased FVII activity and D-dimer levels in overt hypothyroid patients. In the present study, we found a significant increase in FVII activity in patients with hypothyroidism. Increased FVII activity may lead to a tendency to develop hypercoagulable state and arterial thromboembolism.

Activated protein C (APC) cleaves and inhibits coagulation cofactors FVIIa 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 [39]. Protein C deficiency is weakly associated with arterial ischemic stroke [40]. Deficiency of protein S increases the risk of thrombosis and associated with cerebral arterial ischemia [40, 41]. However, protein S deficiency is not a major risk factor for ischemic stroke [40]. Thus, although there is conflicting evidence, deficiency of protein S appears to have a mild association with arterial stroke [40]. Müller et al. [14] reported that no differences were found in protein C and protein S activities between subclinical hypothyroid patients and control group. In the present study, we found a significant decrease in protein C, protein S and FV activities in patients with hypothyroidism. This condition in the patients may lead to a tendency to thrombosis and coagulation which is crucial in cardiovascular events.

Thrombomodulin (TM) is an endothelial cell surface glycoprotein. It acts as a thrombin receptor [42]. When thrombin binds to TM, clotting activity of thrombin is

neutralized. Thrombin–TM complex accelerates protein C activation. Serum TM is regarded as a new marker of generalized endothelial cell damage [42]. It was reported that the TM concentration in hypothyroidism did not differ from than in control group in the literature [43, 44]. In the present study, we found that serum TM levels were significantly higher in the hypothyroid patients than those in the normal healthy subjects. Increased TM levels in hypothyroidism may be related to generalized vascular endothelial injury or decreased clearance of TM. Endothelial dysfunction may lead to a tendency to develop atherosclerosis in the patients.

Tissue factor pathway inhibitor (TFPI) regulates FX activation. Low TFPI is a risk factor for a first venous thrombosis, recurrent venous thromboembolism, and stroke [23, 45, 46]. To our knowledge, this is the second study to determine TFPI levels in hypothyroid patients. In previous study, Ozcan et al. [10] reported that there was no significant difference for free TFPI levels between the control and study groups. In the present study, we found a significant decrease in TFPI levels in patients with hypothyroidism. Thus, decreased TFPI levels in patients with hypothyroidism may lead to a tendency to thrombosis and coagulation in these patients.

Thrombin-activatable fibrinolysis inhibitor (TAFI), also known as procarboxypeptidase B, is a plasma zymogen that potently inhibits fibrinolysis [47, 48]. It protects the fibrin clots from breakdown by removing C-terminal lysine residues from partially degraded fibrin which are necessary for t-PA-mediated plasmin regeneration [48]. Increased activation of TAFI might exacerbate a prothrombotic disposition [17]. Increased plasma TAFI Ag levels were 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 [49]. On the other hand, high TAFI levels were reported to be associated with an increased risk of first ischemic stroke [19]. Silveiro et al. [50] 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 [50-52]. In another study, increased TAFI activity was associated with an almost 4 times higher risk of CAD [53]. To our knowledge, there is only one study to evaluate TAFI Ag levels in patients with hypothyroidism [26]. In this study, Akinci et al. [26] reported increased TAFI Ag levels in patients with overt and subclinical hypothyroidism compared to controls. Elevated plasma TAFI Ag levels were inversely correlated with free thyroid hormone levels and positively correlated with serum TSH levels. They also showed that high TAFI levels were correlated with the degree of thyroid failure. In



the present study, we found higher TAFI Ag levels in patients with hypothyroidism. Thus, increased TAFI Ag levels in hypothyroidism may be related to generalized vascular endothelial damage and decreased clearance of TAFI [26]. Moreover, increased TAFI Ag levels may cause thromboembolic events by lowering fibrinolytic activity in patients with hypothyroidism.

In conclusion, we found some important differences in the hemostatic parameters between the patients with hypothyroidism and healthy controls. Increased FVII, TM, and TAFI and decreased factors V, VIII, vWF, protein C, protein S, and TFPI in these patients represent a potential hypercoagulable and hypofibrinolytic state, 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 hypothyroidism. However, our study comprised a small number of patients with hypothyroidism. A larger number of patients should be included in a prospective study to explain the association between hypothyroidism and TAFI.

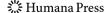
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