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REVIEW

Coagulation and fibrinolysis in thyroid dysfunction

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Abstract Various abnormalities of hemostasis, ranging from subclinical laboratory abnormalities to clinically significant disorders of hemostasis, and rarely major hemorrhage or thromboembolism, may occur in patients with thyroid diseases. The objective of this review is to discuss the relationships between thyroid dysfunction and hemostasis (primary hemostasis and coagulation/fibrinolytic system). According to the recent literature, most of the hemostatic abnormalities associated with thyroid dysfunction are the consequences of direct effects of thyroid hormones on the synthesis of various hemostatic parameters. Thyroid autoimmunity may also modify the processes of primary and secondary hemostasis. We have concluded that hyperthyroidism is generally associated with hypercoagulability and hypofibrinolysis, whereas the hemostatic profile in hypothyroidism depends on the severity of the disease. As few data are available on hemostasis in subclinical thyroid disease, further studies on this subject are needed.

Keywords Hemostasis · Coagulation · Fibrinolysis · Hyperthyroidism · Hypothyroidism

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Introduction

The clinical relationship between thyroid diseases and the hemostatic system was first defined in 1913 by Kaliebe et al. [1]. Authors have reported an episode of central vein thrombosis in a thyrotoxic patient. Both thyroid dysfunction and thyroid autoimmunity may cause thrombosis or hemorrhage by affecting primary and secondary physiologic hemostasis [2].

Various hemostatic disorders, ranging from subclinical laboratory abnormalities to clinically important hemostasis disorders, and rarely major hemorrhage and thromboembolism, may occur in thyroid diseases [2–4]. Contradictory results regarding hemostasis disorders have been obtained in previous studies. In addition, the mechanisms of these disorders are not clearly understood. Although the patients with hypothyroidism are under the risk of bleeding, patients with hyperthyroidism show a tendency toward thromboembolic complications (8–40%), including major emboli which account for 18% of deaths associated with thyrotoxicosis [3]. In recent studies, it has been reported that a hypercoagulability state may also be in question, besides a tendency toward bleeding in patients with hypothyroidism [5].

Direct and indirect effects of excessive or insufficient of thyroid hormones on thrombocyte maturation and function, on the synthesis and action of coagulation factors, and on changes in blood viscosity may play a role in the pathogenesis of coagulopathies that accompany thyroid diseases [3]. According to recent knowledge, the relationship between thyroid diseases and hemostasis is more complex than assumed. There are some studies on this subject in the literature. However, appropriate and adequate studies of high quality are lacking. In most of the studies, there are important methodological shortcomings, such as lack of control groups, small number of cases, heterogeneity in etiology, and

severity of thyroid dysfunction and utilization of different laboratory methods. In addition, approximately two-thirds of the studies are case–control, whereas one-third are interventional cohort studies. Most of the studies are based on laboratory measurements; molecular pathogenesis-oriented experimental and molecular studies are few in number [2].

Hemostasis in hyperthyroidism

Thrombocytes

Clinically important thrombocytopenia (platelet count $<100{,}000/mm^3$) are almost always seen in patients with Graves' disease among thyrotoxicosis patients, and in the majority of the patients, the platelet count is <150,000. However, the clinical findings of thrombocytopenia and other coagulation disorders rarely become manifest [6]. In a study by Kurata et al. [7], it was demonstrated that the platelets count are low and their lifespan short in almost one-half of 214 patients with Graves' disease. These alterations have returned to normal ranges with antithyroid drug therapy. Panzer et al. [8] also reported a low platelet count, a shortened platelet lifespan, and an increase in mean platelet volume (MPV) in 15 patients with hyperthyroidism [8]. Researchers considered these abnormalities as a metabolic consequence of thyroid hormone elevation, rather than an immune-mediated phenomenon, as platelet-associated immunoglobulins (Ig) were present in only three of the patients. Nevertheless, the relationship between autoimmune thrombocytopenic purpura and hyperthyroidism is well known [9–12]. In a study by Cordiano et al. [13], platelet autoantibodies were demonstrated in 83% of patients with hyperthyroidism and thrombocytopenia. In the study by Marshall et al. [14], it was determined that hyperthyroidism had developed in 14% of the patients during a follow-up of 42 patients with autoimmune thrombocytopenic purpura.

There are several causes of thrombocytopenia in patients with hyperthyroidism. Thrombocytopenia caused by antiplatelet antibodies is called autoimmune thrombocytopenic purpura (idiopathic thrombocytopenic purpura [ITP]). The incidence of ITP is high among patients with Graves' disease, and it may occur prior to thyrotoxicosis. Other possible causes for thrombocytopenia in these patients are TSH receptor antibodies, as well as acceleration in thrombocyte degradation, which results from the binding of other thyroid antibodies to actin-binding proteins, which are located on the thrombocyte membrane [15]. Actin-binding protein is a Fc receptor in glycoprotein structure which shows high affinity for IgG.

Another factor that contributes to thrombocytopenia in Graves' patients is thyrotoxicosis itself. Thyrotoxicosis may increase the phagocytic activity of the reticuloendothelial system (RES) and may cause splenomegaly. The clearance of thrombocytes from plasma by degradation increases in both conditions as well. This situation is balanced with the increase in thrombocyte production in the bone marrow. For compensation, the number of megakaryocytes and circulating young thrombocytes increase. As the young thrombocytes are bigger than mature ones, an increase in MPV is also observed [7, 15].

After antithyroid therapy, an increase in the number of thrombocytes and a decrease in their dimensions as well as a decline in the level of platelet-associated IgG are usually observed. In patients with severe thrombocytopenia, glucocorticoid therapy together with antithyroid medications has also been applied. In this way, improvement in thrombocytopenia has been attempted. Antithyroid agents have immunosuppressive effects as well as antithyroid effects. There may be a reduction in the production of IgG, which is bound to thrombocytes due to this effect [6].

Thyrotoxicosis may also change the function of the thrombocyte. Thrombocyte aggregation which occurs as a response to adenosine diphosphate (ADP), collagen, and ristocetine decreases. These changes might be related to the inhibition of myosin light chain kinase, which stimulates the contractile proteins within the thrombocyte [3, 6]. These abnormalities also improve after antithyroid therapy [3, 6].

Coagulation factors

Despite the aforementioned changes in thrombocytes, patients with hyperthyroidism are under the risk for major thromboemboli, which causes high mortality due to the hemostatic and nonhemostatic (increase in erythrocyte mass and cardiac arrhythmias) factors [3, 4, 6]. Various coagulation parameter abnormalities, which lead to hypercoagulability, including elevation in anticardiolipin antibodies, have been determined in patients with hyperthyroidism [16, 17]. A relationship between Graves' disease and antiphospholipid antibody syndrome has been demonstrated [16, 17]. The incidence of thyroid autoantibody in patients with primary antiphospholipid syndrome has increased [18]. The following factors contribute to the hypercoagulability that is observed in hyperthyroidism [3, 6, 19]:

1. An increase in blood volume (as a consequence of increased erythropoietin production in response to increased oxygen needs).
2. An increase in hepatic protein synthesis and an increase in the levels of acute phase reactants.
3. A hyperfunctioning thyroid gland can produce large amounts of "tissue factor." This factor is the major trigger for the extrinsic pathway of coagulation.
4. An increase in thrombin and plasmin activity. Plasma fibrinopeptide A (FPA) levels, which are a sensitive

indicator of thrombin activity, and Bβ 15–42 peptide levels, which are a sensitive indicator of plasmin activity, increase in hyperthyroidism. The fibrinolysis activity is a secondary phenomenon to the increase in fibrin production.

5. Thyroid hormones increase the indicators of endothelial damage by affecting endothelial functions. High levels of thyroid hormones cause a shift to procoagulant state which is one of the physiological antithrombotic properties of the endothelium.
6. Hypermetabolism results in excess fluid loss because of an increase in respiratory rate and sweating. Despite this excess fluid loss, blood volume has increased as a consequence of an increased red blood cell mass in patients with hyperthyroidism.

The incidence of arterial thromboembolism in patients with hyperthyroidism is approximately 8–40% [19]. The risk for cerebral thromboemboli is increased in the presence of accompanying risk factors, such as age, atrial fibrillation, heart failure, left atrial dilatation, and (pre-existing) mitral valve dysfunction [19]. However, the risk of thromboembolism independent of these risk factors is also increased.

The clearance rate of most of the coagulation factors is increased in thyrotoxicosis. The turnover of factor (F) II, FVII, and FIX is increased and the effect of oral anticoagulants is prolonged [19]. The levels of FVIII, FIX, and fibrinogen have been observed to be high in patients with hyperthyroidism or in patients who were given endogenous thyroid hormone in the previous studies; thus, these factors were considered to be produced as acute phase reactants [19–22]. Rogers et al. [20] reported that the levels of FVII:C, Willebrand factor-antigen (vWF:Ag), and vWF:RCo were increased in 95% of patients with newly untreated diagnosed hyperthyroidism [20]. Also a relationship has been identified between Graves' disease and acquired hemophilia A caused by factor VIII inhibitors [23].

There is strong evidence showing that hyperthyroidism affects endothelial function. The levels of thrombomodulin (TM) and vascular adhesion molecules increase regardless of the etiology of hyperthyroidism [24, 25]. It has been reported that plasma vWF concentrations are high in patients with hyperthyroidism and return to normal levels when euthyroidism is achieved with antithyroid therapy [19, 20, 26]. vWF primarily originates from the endothelium, and its high plasma levels are considered as an important indicator for endothelial dysfunction [19]. Burggraff et al. [24] have assessed endothelial marker proteins (vWF:Ag, TM, t-PA, PAI-1, cellular fibronectin, vascular cell adhesion molecule-1, and E-selectin), functional coagulation/fibrinolytic markers (t-PA activity, plasmin–antiplasmin complexes, thrombin fragment 1 + 2, tumor necrosis factor-α, and interleukin-6), and inflammatory markers (plasminogen, α2-antiplasmin, plasma fibronectin, fibrinogen, and C-reactive protein) in patients with hyperthyroidism, and they demonstrated an increase in most of the endothelium-associated proteins and in some proteins (plasma fibronectin and fibrinogen) synthesized in the liver; however, they observed no activation in the coagulation/fibrinolytic system. Researchers have suggested that thyroid hormones may affect the synthesis of many proteins originating from the liver and endothelium by altering gene expression. However, it should be kept in mind that thyroid hormones enhance the biological response to catecholamines and may increase vWF synthesis, which is induced by catecholamines [23, 24]. In one of our studies which we performed on 41 untreated, newly diagnosed hyperthyroidism patients (20 with Graves' disease and 21 patients with toxic nodular goiter [16 multinodular and 5 toxic adenoma]), the levels of fibrinogen, FIX, vWF, antithrombin III (AT-III), and PAI-1 were observed to be high, whereas the levels of FX and t-PA were low in the patient group compared to the euthyroid healthy control group [19]. In a most recent study, we determined that thrombin-activatable fibrinolysis inhibitor (TAFI) increased, whereas FV, protein C, protein S, and tissue factor pathway inhibitor (TFPI) decreased in patients with hyperthyroidism [27]. It was observed that FV, vWF, TM, and AT-III decreased when shifted from the hyperthyroid to the euthyroid state. In correlation analyses, we have demonstrated that there was a positive correlation between free T_4 (fT_4) and factor VIII, vWF, and PAI-1, and between fT_3 and vWF, and a negative correlation between TSH and PAI-1. As a result, it was suggested that there was increased coagulability (hypercoagulability), decreased fibrinolysis (hypofibrinolysis), and endothelial dysfunction in hyperthyroidism regardless of the etiology, suggesting that the factors mentioned above might contribute to the increased risk of thromboembolism [19].

Moreover, Morikawa et al. [28] reported an increase in serum TM levels in patients with Graves' disease in addition to a positive correlation between fT_4 and TM and a negative correlation between TSH and TM. Ozcan et al. [29] reported an increase in t-PA, PAI-1, and TFPI, and a positive correlation between fT_4 and TFPI in the hyperthyroid state compared to the euthyroid state. The findings of the researchers with respect to TFPI conflict with our results. Contrary to our results, Akinci et al. [30] determined low TAFI levels in patients with hyperthyroidism compared to control group. It was suggested that the inverse relationship between PAI-1 and TAFI, which were determined in the same study, might be caused by the activation of the TAFI pathway. Hemostasis disorders determined in patients with hyperthyroidism are summarized in Table 1 [2, 4, 6–11, 13–25, 27–32].

Table 1 Hemostatic abnormalities observed in hyperthyroidism

	References
Thrombocytes	
Platelet count and lifespan ↓, MPV ↑, platelet plug formation ↑	[7, 8]
Idiopathic thrombocytopenic purpura	[9–12]
Coagulation	
Turnover of FII, FVII, FIX, and FX ↑	[19, 24]
Fibrinogen, FPA, FVIII, FIX, vWF:Ag, vWF:Rco, TM ↑	[19–22, 24–26, 28]
AT-III ↑, = , protein C and S ↓	[19, 27]
FV and FX ↓	[19, 27]
TFPI ↓, ↑	[27, 29]
Fibrinolysis	
t-PA ↓, ↑, plasminogen ↓	[19, 24, 29]
PAl-1 ↑	[19, 24, 29, 30]
TAFI ↑, ↓	[27, 30]

MPV mean platelet volume, *F* factor, *FPA* fibrinopeptide A, *vWF:Ag* von Willebrand factor antigen, *vWF:Rco* von Willebrand factor ristocetin cofactor, *TM* thrombomodulin, *AT-III* antithrombin-III, *TFPI* tissue factor pathway inhibitor, *t-PA* tissue plasminogen activator, *PAl-1* plasminogen activator inhibitor type-1, *TAFI* thrombin-activatable fibrinolysis inhibitor, ↑ increased, ↓ decreased, = the change is not significant

Table 2 Recommendations for antithrombotic therapy in patients with AF based on thromboembolic risk category [31, 35]

Risk category		Recommended treatment
No risk factor (RF)		Aspirin, 81–325 mg/day
1 moderate RF		Aspirin, 81–325 mg/day or warfarin (INR target 2.5)
Any high RF or more than 1 moderate RF		Warfarin (INR target 2.5)
Less validated or weaker RFs	Moderate RFs	High RFs
Female	Age ≥ 75 years	Previous stroke, TIA, or embolism
Age, 65–74 years	Hypertension	Mitral stenosis
CAD	Heart failure	Prosthetic heart valve
Thyrotoxicosis	LV EF ≤ %35, DM	

INR International Normalized Ratio, *CAD* coronary artery disease, *LV EF* left ventricular ejection fraction, *DM* diabetes mellitus, *TIA* transient ischemic attack

Anticardiolipin antibodies

Anticardiolipin antibodies have been detected in 30% of patients with Graves' disease, particularly in the sera of patients with ophthalmopathy. However, primary antiphospholipid syndrome and recurrent pregnancy losses are rarely encountered among patients with Graves' disease [3, 6]. These antibodies are, especially, in the form of IgG, and may be related with hypercoagulability states. Antibody concentrations decrease with antithyroid treatment. The presence of these antibodies may be the nonspecific indicator of immune system activation [6].

Thyrotoxicosis, atrial fibrillation (AF), and anticoagulant treatment

Cardioembolic risk increases in patients with hyperthyroidism and AF [31, 33, 34]. While no complication developed in patients with sinus rhythm, cardioembolic events were encountered in 40% of thyrotoxic patients with AF. However, in 60% of the patients with hyperthyroidism-associated AF, heart rhythm returns to sinus rhythm without any specific antiarrhythmic treatment in 8–10 weeks, after they reach the euthyroid state with antithyroid treatment. For this reason, anticoagulant treatment is still controversial in such patients. In addition, while the risk for embolus related to pharmacologic or electrical cardioversion without anticoagulant treatment is 5–7%, it decreases to 0–1.6% with anticoagulant treatment. Therefore, according to the recommendations of the national and international guides, thyrotoxic patients with AF should initially be evaluated for cardioembolic risk factors, and then the treatment should be planned according to these risk factors [31]. Antithrombotic and anticoagulant treatment indications in thyrotoxic patients with AF are shown in Table 2 [31, 35]. If anticoagulant treatment is planned, concomitant oral anticoagulants should be started with

antithyroid treatment and continued at least three additional months after the patient returned to sinus rhythm. The initiation dose for warfarin is 2.5 mg/day. Sensitivity to the anticoagulant effects of warfarin increases in thyrotoxic patients [6]. This is probably related to the rapid clearance of coagulation factors and the decrease in binding of the drug to plasma proteins [6]. For this reason, lower doses may be required for thyrotoxic patients who are being treated with warfarin.

Hemostasis in hypothyroidism

Hypothyroidism is generally associated with a tendency toward bleeding [2, 3, 23, 31, 36]. In most cases, a primary hemostasis defect is the only coagulopathy. Usually, mild bleeding, such as easy bruising, nasal or gingival bleeding, and menorrhagia, and rarely serious bleeding after trauma or surgery, might be observed [3, 36]. Nevertheless, the pathogenesis of the tendency toward bleeding in patients with hypothyroidism is not understood [5]. Both hypercoagulable and hypocoagulable states have been reported in hypothyroidism. Hypothyroidism has also been found to be related with the changes in lipid metabolism and atherosclerosis. This is also a risk factor for thromboembolic disease in addition to hypercoagulability in hypothyroid patients. It has been demonstrated that the risk for arterial disease is increased in patients with hypothyroidism [5].

Thrombocytes

Although the platelet count is usually normal in patients with hypothyroidism, megakaryocytopoiesis may be inhibited due to the myxedema of bone marrow in rare cases [23]. In autoimmune hypothyroidism, thrombocytopenia may occur as a result of autoimmune-associated peripheral thrombocyte degradation, but this situation is mostly related to Graves' disease. The MPV is generally normal. Qualitative thrombocyte abnormalities have also been reported [3, 23, 36]. Hypothyroidism may change thrombocyte function by increasing ADP- and collagen-induced platelet aggregation. On the other hand, ristocetin-stimulated thrombocyte aggregation is deteriorated in patients with hypothyroidism. Ristocetin induces aggregation by facilitating the interaction between FVIII and thrombocyte. The low plasma FVIII level in patients with hypothyroidism is responsible for the decrease in ristocetin response. All these abnormalities improve after T4 therapy [36].

It was reported that easy bruising and bleeding are increased in a few patients with hypothyroidism. The bleeding time is increased in the majority of patients. There is a close relationship between bleeding time and both the duration and the severity of hypothyroidism. In patients with normal plasma FVIII activity, prolongation of the bleeding time is observed. Patients with severe hypothyroidism are more sensitive to aspirin. Therefore, the bleeding time is prolonged after aspirin administration. Abundant bleeding has been reported after aspirin use in patients with untreated or partially treated hypothyroidism. For this reason, care should be taken while using aspirin in patients with hypothyroidism [36].

Coagulation factors

The half-life of FII, FVII, FIX, and FX is prolonged in patients with hypothyroidism. It has been demonstrated that plasma concentrations of either these or other coagulation factors are normal or slightly low [3, 36]. The low levels of these factors are attributed to the decrease in protein synthesis in the liver. The most conspicuous abnormalities seen in patients with hypothyroidism are the decrease in FVIII concentration and the prolongation of activated partial thromboplastin time (aPTT) [36]. In early studies, prothrombin time (PT) was found to be normal or slightly low [3, 23].

Acquired von Willebrand disease (vWD) might be seen in patients with hypothyroidism because of the decreased plasma FVIII coagulant (C) activity, vWF Ag activity, and a decrease in vWF:RCo levels. The pathogenesis of hypothyroidism-associated vWD is still unknown. It was thought to be associated with the decrease in protein synthesis or the decreased response to adrenergic stimulation, which stimulates the release of FVIII activity from endothelial cells due to thyroid hormone deficiency. In hypothyroidism patients with acquired vWD, prolonged bleeding, nasal bleeding, and easy ecchymotic formation are seen after dental procedures. However, the diagnosis of this coagulopathy is very difficult because it cannot be assessed via routine laboratory analyses [3, 23, 31]. Since the course of hypothyroidism is quite slow and insidious, a tendency toward bleeding appears as major bleeding following trauma or a surgical procedure. Acquired vWD improves after T4 therapy [3, 31, 36]. This probably is related to two effects [31, 36]: (1) increase in the release of vWF from endothelial cells because of the increase in the sensitivity to epinephrine after thyroid hormone therapy and (2) nonspecific stimulation of protein synthesis in the liver with thyroid hormone. Hypothyroidism should be investigated in these patients since acquired vWH may be the first sign of hypothyroidism.

The relationship between hypothyroidism and acquired hemophilia is rarely identified. In a patient with autoimmune hypothyroidism, Meiklejohn and Watson [37] identified a high titration of the FVIII inhibitor.

There is depression of various coagulation factors in hypothyroidism. In various studies, a decrease in FVII,

FVIII, FIX, FX, FXI, and FXII levels in patients with hypothyroidism was reported [38–40]. In contrast, opposite results were observed in some studies. Chadaverian et al. [41] have found an increase in FVII:C and D-dimer levels in patients with hypothyroidism. High FVII activity and increased D-dimer levels are risk factors for thromboembolism [23, 42]. In another study by the same researchers, it was reported that there was a decrease in fibrinolytic activity (an increase in alpha2-antiplasmin, t-PA, and PAI-1, and a decrease in D-dimer) in moderate hypothyroidism (TSH: 10–50 mU/l); thus, an increase in risk for cardiovascular disease was observed [43]. In severe hypothyroidism (TSH >50 mU/l), an increase in fibrinolytic activity was reported (a decrease in alpha2-antiplasmin, t-PA, and PAI-1, and an increase in D-dimer); thus, a tendency toward bleeding was observed [43]. Ozcan et al. [29] have reported that plasma TFPI levels were higher in patients with hypothyroidism compared to patients with subclinical hypothyroidism. Gullu et al. [44] have reported that there was a decrease in platelet count, a prolongation of the bleeding time, coagulation time, PT, and aPTT, and a decrease in FVIII and vWF activities. These abnormalities improved during the euthyroid period after levothyroxine therapy. In a very recent study, Akinci et al. [45] have demonstrated that TAFI antigen levels were markedly higher in patients with overt and subclinical hypothyroidism compared to controls. In that study, a positive correlation was determined between TAFI antigen levels and the degree of thyroid failure, and it was observed that TAFI antigen levels were significantly decreased in both groups after euthyroidism had been provided by thyroxine replacement. An increase in TAFI antigen levels in hypothyroidism is thought to be related with either a decrease in TAFI clearance or an increase in its production within the adipose tissue and endothelium. Consequently, it was concluded that increased TAFI levels might be related to hypofibrinolysis and an increased risk for the thrombosis seen in hypothyroidism [45]. In two different studies that we have conducted, an increase in fibrinogen, FVII, PAI-1, AT III, TM, and TAFI, and a decrease in FV, FVIII, vWF, protein C, protein S, and TFPI was determined in patients with newly diagnosed and untreated hypothyroidism compared to the control group. As a consequence, it was suggested that these changes might indicate endothelium dysfunction, hypofibrinolysis, and hypercoagulability rather than a tendency toward bleeding; thus, might lead to an increase in the risk for thrombosis [5, 46].

Patients with hypothyroidism are relatively refractory to the hypoprothrombinemic effect of warfarin since the clearance of coagulation factors is decreased in these patients. Therefore, the prolongation of PT with warfarin takes more time in patients with hypothyroidism compared to patients with euthyroidism. In the event of hypothyroidism in a woman treated with warfarin, the warfarin dose must be threefold the original dose for the maintenance of appropriate anticoagulation. The original warfarin dose becomes sufficient after the patient is treated with T4. Hypothyroidism should be considered in patients who are resistant to warfarin. Warfarin application more than 4–5 days may be required in patients in whom warfarin and heparin have been started [36]. The hemostatic disorders determined in patients with hypothyroidism are summarized in Table 3 [2–5, 23, 31, 36–41, 43–46].

Autoimmune effects

In a study in which 12 patients (2 with hypothyroidism and 10 with euthyroidism) with chronic autoimmune thyroiditis have been included, it was determined that thrombocyte binding IgG levels were elevated in 6 patients and thrombocytopenia was present in 2 patients. Autoimmune thrombocytopenic purpura is rarely associated with chronic autoimmune thyroiditis. In addition, reduced levels of anticardiolipin antibody in serum have been determined in two of five patients with chronic autoimmune thyroiditis, but antiphospholipid syndrome has not been reported in hypothyroidic or euthyroidic patients with autoimmune thyroiditis [6, 36].

Hemostasis in subclinical thyroid disease

The prevalence of subclinical hypothyroidism is between 1 and 10%, and the rate of progression to clinical hypothyroidism is approximately 4.3%/year [47]. Subclinical hypothyroidism is an independent risk factor for atherosclerosis of the aorta, coronary heart disease, and myocardial infarction [33, 34, 48]. In addition, it has been demonstrated that high TSH is associated with ischemic heart disease and an increase in mortality. The number of studies investigating hemostasis in subclinical hypothyroidism is limited. In all studies, except one [44], results concordant with hypercoagulability and hypofibrinolysis were observed, and it was suggested that subclinical hypothyroidism might cause an increase in risk for thrombosis [45, 49–51] (Table 4). In two different studies, which we performed and Ozcan et al. [29, 48], no significant change was observed for hemostasis parameters in patients with subclinical hypothyroidism compared to control group.

The prevalence of subclinical hyperthyroidism among the population is 0.7–12%, and the progression rate to overt hyperthyroidism is 5% per year [52]. The risk for cardiovascular disease is increased, and the risk for AF is increased up to 3- to 5-fold in patients with subclinical hyperthyroidism. The risk for AF during a 10-year follow-up period is approximately 10% in these patients. Compared to normal subjects, the risk for AF is 3.1-fold higher

Table 3 Hemostatic abnormalities seen in hypothyroidism

	References
Thrombocytes	
Peripheral platelet count ↓, N (megakaryocytopoiesis inhibition and ITP), deterioration in platelet reactivity (adhesion and aggregation ↓)	[3, 23, 36, 44]
Coagulation	
FV, FVII, FVIII, FIX, FX, FXI, FXII, vWF:Ag, and vWF:Rco ↓	[5, 38–40, 44, 46]
Fibrinogen, FPA, TF, FVII, and AT III ↑	[5, 41, 46]
Protein C and S ↓	[46]
TFPI ↑, ↓, TM =, ↑	[5, 25, 29, 46]
Acquired vWD	[2–5, 23, 31]
Acquired Hemophilia A	[37]
Prolongation of PT, aPTT, and coagulation time	[44]
Fibrinolysis	
In moderate hypothyroidism, fibrinolytic activity ↓ (alpha2-antiplasmin, t-PA and PAI-1 ↑, D-dimer ↓)	[5, 41, 43]
In severe hypothyroidism, fibrinolytic activity ↑ (alpha2-antiplasmin, t-PA and PAI-1 ↓, D-dimer ↑)	
TAFI ↑	[45, 46]

N normal, *vWD* von Willebrand Disease, *TF* tissue factor, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, ↑ increased, ↓ decreased, = the change is not significant

Table 4 Hemostatic abnormalities observed in subclinical hypothyroidism

Study	
Muller et al. [49]	F VIIc activity ↑ (hypercoagulability)
Ozcan et al. [29]	=
Cantürk et al. [50]	Fibrinogen, F VII, PAI-1 ↑
	AT III ↓ (Hypercoagulability, hypofibrinolysis)
Gullu et al. [44]	vWF, F VIII ↓ (hypocoagulability)
Guldiken et al. [51]	Global fibrinolytic capacity ↓ (relative hypercoagulability)
Erem [48]	=
Akinci et al. [45]	TAFI Ag ↑ (hypofibrinolysis → risk for thrombosis ↑)

↑ increased, ↓ decreased, = the change is not significant

in patients with low serum TSH (≤0.1 mU/l), and 1.6-fold higher in patients with slightly low TSH (0.1–0.4 mU/l) [33, 35, 48]. We performed the first study in the literature investigating hemostatic changes in subclinical hyperthyroidism relative to the euthyroid state [48]. Although many coagulation and fibrinolytic mechanisms were investigated, only an increase in FX activity in patients with subclinical hyperthyroidism was determined. This increase might be related to the increase in FX gene expression by thyroid hormones. For example, Shih et al. [53] has demonstrated that in vitro T3 induced FX gene expression. In another study, Akinci et al. [30] have reported that PAI-1 levels increased and TAFI levels decreased in patients with subclinical hyperthyroidism, but this decrease in TAFI levels was not significant.

Conclusion

Thyroid dysfunction changes the coagulation–fibrinolysis imbalances. An increase in the risk for thrombosis caused by hypercoagulability is seen in clinical hyperthyroidism. In clinical hypothyroidism, according to the severity of the disease, either an increase in the risk for bleeding caused by hypocoagulability or an increase in the risk for thrombosis caused by hypercoagulability might be seen. The main mechanism that affects the hemostatic balance is excess or deficiency of thyroid hormones. This balance is rarely affected by autoimmune mechanisms [2]. Hypercoagulability and hypocoagulability are probably independent of the pathophysiology of the underlying thyroid disease. A few coagulation–fibrinolytic test abnormalities have been identified in subclinical thyroid disease. The hypothesis that subclinical hypothyroidism causes hypercoagulability is not sufficiently corroborated. The role of the coagulation–fibrinolytic system in the pathophysiology of atherosclerosis and arterial thrombosis remains a controversial subject.

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References

1. A. Squizzato, V.E. Gerdes, D.P. Brandjes, H.R. Büller, J. Stam, Thyroid diseases and cerebrovascular disease. Stroke **36**, 2302–2310 (2005)
2. A. Squizzato, E. Romualdi, H.R. Büller, V.E. Gerdes, Thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. J. Clin. Endocrinol. Metab. **92**, 2415–2420 (2007)
3. L.C. Hofbauer, A.E. Heufelder, Coagulation disorders in thyroid diseases. Eur. J. Endocrinol. **136**, 1–7 (1997)
4. M. Franchini, Hemostatic changes in thyroid diseases. Hematology **11**, 203–208 (2006)
5. C. Erem, H. Kavgacı, H.Ö. Ersoz, A. Hacıhasanoğlu, K. Ukinç, S.S. Kartı, O. Değer, M. Telatar, Blood coagulation and fibrinolytic activity in hypothyroidism. Int. J. Clin. Pract. **57**, 78–81 (2003)
6. L. Porter, S.J. Mandel, The blood in thyrotoxicosis, in *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text*, 8th edn., ed. by L.E. Braverman, R.D. Utiger (Lippincott Williams & Wilkins, Philadelphia, 2000), pp. 627–631
7. Y. Kurata, Y. Nishioeda, T. Tsubakio, Thrombocytopenia in Graves' disease: effect of T_3 on platelet kinetics. Acta Haematol **63**, 185–190 (1980)
8. S. Panzer, A. Haubenstock, E. Minar, Platelets in hyperthyroidism: studies on platelet counts, mean platelet volume, indium-labeled platelet kinetics, and platelet-associated immunoglobulins G and M. J. Clin. Endocrinol. Metab. **70**, 491–496 (1990)
9. K. Hymes, M. Blum, H. Lackner, S. Karpatkin, Easy bruising, thrombocytopenia, and elevated platelet immunoglobulin G in Graves' disease and Hashimoto's thyroiditis. Ann. Intern. Med. **94**, 27–30 (1981)
10. N. Bizzaro, Familial association of autoimmune thrombocytopenia and hyperthyroidism. Am. J. Hematol. **39**, 294–298 (1992)
11. K. Yamaguchi, Y. Ookubo, H. Matsuda, K. Suzaki, H. Fukushima, H. Uzawa, Idiopathic thrombocytopenic purpura subsequent to Graves' disease and insulin-dependent diabetes mellitus. Diabetes Res. Clin. Pract. **3**, 233–237 (1987)
12. S.L. Ho, M. Shah, A.C. Williams, Idiopathic thrombocytopenic purpura and autoimmune thyroiditis in a patient with myasthenia gravis. Muscle Nerve **15**, 966–967 (1992)
13. I. Cordiano, C. Betterle, C.A. Spadaccino, B. Soini, A. Girolami, F. Fabris, Autoimmune thrombocytopenia (AITP) and thyroid autoimmune disease (TAD): overlapping syndromes? Clin. Exp. Immunol. **113**, 373–378 (1998)
14. J.S. Marshall, A.S. Weisberger, R.P. Levy, Coexistent idiopathic thrombocytopenic purpura and hyperthyroidism. Ann. Intern. Med. **67**, 411–414 (1967)
15. A. Adrouny, R.M. Sandler, R. Carmel, Variable presentation of thrombocytopenia in Graves' disease. Arch. Intern. Med. **142**, 1460–1464 (1982)
16. F. Marongiu, M. Conti, M.L. Murtas, G.G. Sorano, G. Mameli, G. Salis, A. Mathieu, E. Martino, Anticardiolipin antibodies in Graves' disease: relationship with thrombin activity in vivo. Thromb. Res. **64**, 745–749 (1991)
17. L.C. Hofbauer, C. Spitzweg, A.E. Heufelder, Graves' disease associated with the primary antiphospholipid syndrome. J. Rheumatol. **23**, 1435–1437 (1996)
18. P. Dagenais, M.B. Urowitz, D.D. Gladman, C.S. Norman, A family study of the antiphospholipid syndrome associated with other autoimmune diseases. J. Rheumatol. **19**, 1393–1396 (1992)
19. C. Erem, H.Ö. Ersoz, S.S. Kartı, K. Ukinç, A. Hacıhasanoğlu, O. Değer, M. Telatar, Blood coagulation and fibrinolysis in patients with hyperthyroidism. J. Endocrinol. Invest. **25**, 345–350 (2002)
20. J.S. Rogers, S.R. Shane, F.S. Jencks, Factor VIII activity and thyroid function. Ann. Intern. Med. **97**, 713–716 (1982)
21. F. Marongiu, M. Conti, M.L. Murtas, G. Mameli, G.G. Sorano, E. Martino, Activation of blood coagulation and fibrinolysis in Graves' disease. Horm. Metab. Res. **23**, 609–611 (1991)
22. F. Marongiu, M. Conti, G. Mameli, M.L. Murtas, S. Balzano, G. Sorano, A.M. Mamusa, E. Martino, Fibrinogen and fibrinolytic activity in hyperthyroidism before and after antithyroid treatment. J. Endocrinol. Invest. **11**, 723–725 (1988)
23. M. Franchini, Hemostasis and thyroid diseases revisited. J. Endocrinol. Invest. **27**, 886–892 (2004)
24. J. Burggraaf, S. Lalezari, J.J. Emeis, U.M. Vischer, P.H. de Meyer, H. Pijl, A.F. Cohen, Endothelial function in patients with hyperthyroidism before and after treatment with propranolol and thiamazol. Thyroid **11**, 153–160 (2001)
25. M. Soma, Y. Maeda, R. Matsuura, I. Sasaki, S. Kasakura, Y. Saeki, K. Ikekubo, T. Ishihara, H. Kurahachi, S. Sasaki, T. Tagami, K. Nakao, Study of serum thrombomodulin (TM) levels in patients with hyper- or hypo-thyroidism. Rinsho Byori **45**, 77–81 (1997)
26. L. Liu, X. Wang, Z. Lin, H. Wu, Elevated plasma levels of VWF:Ag in hyperthyroidism are mediated through beta-adrenergic receptors. Endocr. Res. **19**, 123–133 (1993)
27. Ö. Üçüncü, C. Erem, M. Yılmaz, H.O. Ersöz, M. Koçak, İ. Nuhoğlu, Hipertiroidili hastalarda hemostatik değişiklikler: artmış trombinle aktive edilebilen fibrinoliz inhibitörü (TAFI) ve azalmış doku faktör yolağı inhibitörü (TFPI). 3. Türkiye Tiroid Hastalıkları Kongresi, 17–20 Nisan 2008, Trabzon, Özet Kitabı, Sayfa 17, P04 (2008)
28. Y. Morikawa, A. Morikawa, I. Makino, Relationship of thyroid states and serum thrombomodulin (TM) levels in patients with Graves' disease: TM, a possible new marker of the peripheral activity of thyroid hormones. J. Clin. Endocrinol. Metab. **76**, 609–614 (1993)
29. M.A. Ozcan, A. Comlekci, F. Demirkan, F. Yuksel, I. Sari, T. Demir, G.H. Ozsan, G. Oruk, S. Yesil, B. Undar, Plasma levels of free tissue factor pathway inhibitor in patients with various thyroid disorders. Thromb. Res. **110**, 243–247 (2003)
30. B. Akinci, A. Comlekci, S. Yener, T. Demir, M.A. Ozcan, F. Bayraktar, S. Yesil, Thrombin activatable fibrinolysis inhibitor antigen levels are inversely correlated with plasminogen activator inhibitor-1 antigen levels in hyperthyroid patients. Endocr. J. **54**, 593–599 (2007)
31. F. Marongiu, C. Cauli, S. Mariotti, Thyroid, hemostasis and thrombosis. J. Endocrinol. Invest. **27**, 1065–1071 (2004)
32. M. Homoncik, A. Gessl, A. Ferlitsch, B. Jilma, H. Vierhapper, Altered platelet plug formation in hyperthyroidism and hypothyroidism. J. Clin. Endocrinol. Metab. **92**, 3006–3033 (2007)
33. N. Jayaprasad, J. Francis, Atrial fibrillation and hyperthyroidism. Indian Pacing Electrophysiol. J. **5**, 305–311 (2005)
34. S. Bar-Sela, M. Ehrenfeld, M. Eliakim, Arterial embolism in thyrotoxicosis with atrial fibrillation. Arch. Intern. Med. **141**, 1191–1192 (1981)
35. European Heart Rhythm Association, Heart Rhythm Society, V. Fuster, L.E. Rydén, D.S. Cannom, H.J. Crijns, A.B. Curtis, K.A. Ellenbogen, J.L. Halperin, J.Y. Le Heuzey, G.N. Kay, J.E. Lowe, S.B. Olsson, E.N. Prystowsky, J.L. Tamargo, S. Wann, S.C. Smith Jr., A.K. Jacobs, C.D. Adams, J.L. Anderson, E.M. Antman, S.A. Hunt, R. Nishimura, J.P. Ornato, R.L. Page, B. Riegel, S.G. Priori, J.J. Blanc, A. Budaj, A.J. Camm, V. Dean, J.W. Deckers, C. Despres, K. Dickstein, J. Lekakis, K. McGregor, M. Metra, J. Morais, A. Osterspey, J.L. Zamorano, American College of Cardiology, American Heart Association Task Force on

Practice Guidelines, European Society of Cardiology Committee for Practice Guidelines, Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J. Am. Coll. Cardiol. **48**, 854–906 (2006)

36. E. Marqusee, S.J. Mandel, The blood in hypothyroidism, in *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text*, 8th edn., ed. by L.E. Braverman, R.D. Utiger (Lippincott Williams & Wilkins, Philadelphia, 2000), pp. 800–803
37. D.J. Meiklejohn, H.G. Watson, Acquired haemophilia in association with organ-specific autoimmune disease. Haemophilia **7**, 523–525 (2001)
38. J.V. Simone, C.F. Abildgaard, I. Schulman, Blood coagulation in thyroid dysfunction. N. Engl. J. Med. **273**, 1057–1061 (1965)
39. B.O. Egeberg, Influence of thyroid function on the blood clotting system. Scand. J. Clin. Lab. Invest. **15**, 1–7 (1963)
40. A. Nordoy, H. Vik-Mo, H. Berntsen, Haemostatic and lipid abnormalities in hypothyroidism. Scand. J. Haematol. **16**, 154–160 (1976)
41. R. Chadarevian, E. Bruckert, A. Ankri, I. Beucler, P. Giral, G. Turpin, Relationship between thyroid hormones and plasma D-dimer levels. Thromb. Haemost. **79**, 99–103 (1998)
42. S.G. Thompson, J. Kienast, S.D. Pyke, F. Haverkate, J.C. van de Loo, Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N. Engl. J. Med. **332**, 635–641 (1995)
43. R. Chadarevian, E. Bruckert, L. Leenhardt, P. Giral, A. Ankri, G. Turpin, Components of the fibrinolytic system are differently altered in moderate and severe hypothyroidism. Clin. Endocrinol. Metab. **86**, 732–737 (2001)
44. S. Gullu, H. Sav, N. Kamel, Effects of levothyroxine treatment on biochemical and hemostasis parameters in patients with hypothyroidism. Eur. J. Endocrinol. **152**, 355–361 (2005)
45. B. Akinci, A. Comlekci, M. Ali Ozcan, T. Demir, S. Yener, F. Demirkan, F. Yuksel, S. Yesil, Elevated thrombin activatable fibrinolysis inhibitor (TAFI) antigen levels in overt and subclinical hypothyroid patients were reduced by levothyroxine replacement. Endocr. J. **54**, 45–52 (2007)
46. C. Erem, O. Ucuncu, M. Yilmaz, M. Kocak, I. Nuhoglu, H.O. Ersoz, Increased thrombin-activatable fibrinolysis inhibitor and decreased tissue factor pathway inhibitor in patients with hypothyroidism. Endocrine **35**, 75–80 (2009)
47. M.P. Vanderpump, W.M. Tunbridge, J.M. French, D. Appleton, D. Bates, F. Clark, J. Grimley Evans, D.M. Hasan, H. Rodgers, F. Tunbridge, E.T. Young, The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham survey. Clin. Endocrinol. **43**, 55–68 (1995)
48. C. Erem, Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. Clin. Endocrinol. **64**, 323–329 (2006)
49. B. Muller, D.A. Tsakiris, C.B. Roth, M. Guglielmetti, J.J. Staub, G.A. Marbet, Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. Eur. J. Clin. Invest. **31**, 131–137 (2001)
50. Z. Cantürk, B. Cetinarslan, I. Tarkun, N.Z. Cantürk, M. Ozden, C. Duman, Hemostatic system as a risk factor for cardiovascular disease in women with subclinical hypothyroidism. Thyroid **13**, 971–977 (2003)
51. S. Guldiken, M. Demir, B. Turgut, B.U. Altun, E. Arikan, M. Kara, Global fibrinolytic capacity in patients with subclinical hypothyroidism. Endocr. J. **52**, 363–367 (2005)
52. P.C. Kek, S.C. Ho, D.H. Khoo, Subclinical thyroid disease. Singapore Med. J. **44**, 595–600 (2003)
53. C.H. Shih, S.L. Chen, C.C. Yen, Y.H. Huang, C.D. Chen, Y.S. Lee, K.H. Lin, Thyroid hormone receptor dependent transcriptional regulation of fibrinogen and coagulation proteins. Endocrinology **145**, 2804–2814 (2004)