# The Spectrum of Coagulation Abnormalities in Thyroid Disorders

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## ABSTRACT

The hemostatic balance is a complex system where the delicate equilibrium is regulated by several factors including hormones. A variety of endocrine disorders have been reported to be associated with coagulation abnormalities, ranging from mild laboratory changes to clinically relevant thrombotic or bleeding manifestations. In this review, we summarize the current knowledge on the main abnormalities of the coagulation and fibrinolytic systems associated with thyroid dysfunctions. Overall, although mostly based on uncontrolled studies, data in the literature suggest that patients with hyperthyroidism or subclinical hypothyroidism have a hypercoagulative state, whereas patients with overt hypothyroidism have a bleeding tendency.

**KEYWORDS:** Bleeding, thrombosis, hyperthyroidism, hypothyroidism

Various hemostatic abnormalities, involving both primary hemostasis and the coagulation/fibrinolytic system, have been reported in patients affected by a wide variety of endocrine disorders.[1–6] These modifications may range from subclinical laboratory abnormalities to clinically relevant hemorrhagic or thrombotic events. In particular, several thyroid disorders have been found to be associated with hemostatic changes, and several pathogenic mechanisms have been suggested to explain this relationship including the effects of thyroid hormones on the synthesis of coagulation factors or thyroid-related autoimmune processes that also involve the hemostatic system.

In this review, we summarize the studies examining the effects of thyroid disorders on coagulation and fibrinolysis. These topics are also more extensively addressed in two other articles from this issue of *Seminar in Thrombosis and Hemostasis*.[7,8]

## HYPOTHYROIDISM

Several studies have shown various coagulation abnormalities in patients with primary hypothyroidism.[9–13] Acquired von Willebrand syndrome (aVWS) is the most frequent coagulation disorder clinically observed in overt hypothyroidism, characterized by decreased factor VIII

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Hormones, Endocrine Disorders, and Hemostasis; Guest Editors, Massimo Franchini, M.D., Pier Paolo. Vescovi, M.D., Franco Manzato, M.D., and Emmanuel J. Favaloro, Ph.D., M.A.I.M.S.

Semin Thromb Hemost 2011;37:7–10. 
DOI: http://dx.doi.org/10.1055/s-0030-1270065.
ISSN 0094-6176.

activity (FVIII:C), von Willebrand factor antigen (VWF:Ag), and ristocetin cofactor (VWF:RCo) levels.[14–22] The presenting symptoms are easy bruising, epistaxis, or mucosal bleeding. However, the diagnosis of this associated coagulopathy is very difficult because it is usually not detected by routine laboratory tests, and often hypothyroidism may have an insidious onset with subtle clinical signs and symptoms. Thus the correct diagnosis is frequently not established until the bleeding tendency is revealed by major hemorrhages following trauma or surgery. We previously studied 1342 consecutive patients with various thyroid diseases undergoing thyroid surgery.[23] A preoperative coagulation screening including prothrombin time, activated partial thromboplastin time (aPTT), and platelet function (using the PFA-100 analyzer) identified 39 patients (~3% of total) with coagulation abnormalities, 35 of them having an aVWS. The pathogenesis of hypothyroidism-associated aVWS is still unclear. A decrease in von Willebrand factor (VWF) protein synthesis or a decreased response to adrenergic stimulation (otherwise enhancing the VWF release from endothelial cells) due to the hormone deficiency are the most plausible mechanisms involved, as also supported by the finding of a reversal of the hypothyroidism-associated aVWS following thyroid hormone replacement.[18]

Patients with hypothyroidism may have also qualitative platelet abnormalities.[5] Palareti and colleagues[24] studied 21 patients with acquired hypothyroidism after total thyroidectomy, and they found impaired platelet reactivity not only to ristocetin but also to collagen and adrenalin, which was rapidly normalized after thyroid hormone replacement. Similarly, the platelet dysfunction (impaired agglutination response to ristocetin) observed by Myrup and colleagues[25] in nine hypothyroid patients disappeared after thyroid hormone replacement.

Regarding the coagulation-fibrinolytic abnormalities in overt hypothyroidism, the finding by Egeberg[26] in 1963 of a significant reduction in coagulation FVIII, factor IX (FIX), and factor XI (FIX) levels in hypothyroid patients was confirmed by subsequent small case-control studies.[27,28] Autoantibodies against FVIII (acquired hemophilia A [aHA]) may also be rarely associated with autoimmune hypothyroidism.[29] Chadarevian and colleagues[30] studied the fibrinolytic system in hypothyroid patients and documented a different fibrinolytic pattern according to the severity of hypothyroidism: An increased fibrinolytic activity (i.e., low levels of $\alpha_2$-antiplasmin, tissue plasminogen activator [tPA] and plasminogen activator inhibitor [PAI-1], and high D-dimer levels) was observed in overt hypothyroidism, whereas a decreased fibrinolytic activity (high levels of $\alpha_2$-antiplasmin, tPA and PAI-1, and low D-dimer levels) was found in subclinical hypothyroidism. Other small case-control studies confirmed the presence of hypofibrinolysis in subclinical hypothyrodism,[31,32] thus further supporting the clinical evidence that this condition may be associated with an increased risk of cardiovascular disease.[33] Duntas and Biondi[34] expand this latter topic in this issue of *Seminars in Thrombosis and Hemostasis*.

## HYPERTHYROIDISM

Although several studies have documented an association between hyperthyroidism and autoimmune thrombocytopenic purpura (AITP),[35–37] overall the hemostatic abnormalities observed in patients with overt hyperthyroidism seem to predispose to a hypercoagulable state rather than to a bleeding tendency.[5] For instance, as reported by Erem in this issue of *Seminars in Thrombosis and Hemostasis*,[8] the association between antiphospholipid antibodies and Graves' disease is well known.[38,39] Furthermore, Homoncik and colleagues[40] found increased plasma VWF levels and enhanced platelet function (as measured with the PFA-100 analyzer) in patients with hyperthyroidism compared with euthyroid controls. Rogers and colleagues[27] reported that 21 of 22 untreated hyperthyroid patients had increased levels of plasma FVIII:C, VWF:Ag, and VWF:RCo that normalized after pharmacological treatment with antithyroid drugs. Similarly, the same authors documented a significant increase in plasma FVIII:C, VWF:Ag, and VWF:RCo in 14 healthy volunteers after receiving L-thyroxine therapy.[41] In addition, we have recently shown that in a large sample of unselected adult outpatients ($n$ = 1329), those with hyperthyroidism had shortened aPTT and higher plasma fibrinogen levels when compared with euthyroid patients, whereas no significant differences were observed between euthyroid patients and those with hypothyroidism, thus confirming that hyperthyroidism is associated with mild to moderate hypercoagulability.[42] This finding could explain the increasing number of venous thromboembolic episodes, mostly involving the venous cerebral district, reported in patients with hyperthyroidism.[43] Erem and colleagues studied the blood coagulation and fibrinolysis in 41 patients with overt hyperthyroidism.[44] Compared with euthyroid controls, patients with hyperthyroidism had increased levels of plasma fibrinogen, FIX, VWF, antithrombin, and PAI-1 and decreased levels of factor X and tPA, suggesting a potential hypercoagulable and hypofibrinolytic state in this condition. Other small case-control studies also confirmed an impaired fibrinolysis in hyperthyroid patients.[45,46]

## CONCLUSIONS

Increasing evidence indicates that several hemostatic abnormalities occur in patients with both hyperthyroidism and hypothyroidism. Although a wide interpatient heterogeneity exists, it can be roughly generalized that

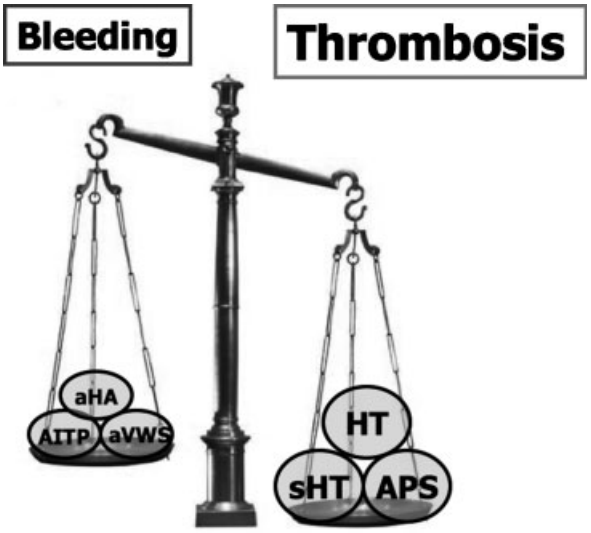


**Figure 1** Hemostatic abnormalities in thyroid disorders. Overall, the hemostatic balance is unbalanced toward a hypercoagulability state. AITP, autoimmune thrombocytopenic purpura (associated with hyperthyroidism); aHA, acquired hemophilia A (rarely associated with autoimmune hypothyroidism); APS, antiphospholipid syndrome (associated with Graves' disease); aVWS, acquired von Willebrand syndrome (associated with overt hypothyroidism); HT, hyperthyroidism; sHT, subclinical hypothyroidism.

overt hypothyroidism is associated with a bleeding tendency, whereas a hypercoagulative tendency has been observed more frequently in patients with subclinical hypothyroidism and overt hyperthyroidism. Thus, with few exceptions (e.g., aVWS, aHA, and AITP), the hemostatic balance in thyroid disorders seems to unbalance toward a hypercoagulative state (Fig. 1). However, several issues are still unclear, first of all the pathogenic mechanisms underlying the interaction between hormones and coagulation-fibrinolytic systems. In addition, large observational and intervention studies are needed to provide more definitive information on the clinical relevance of this association and the possible impact of the pharmacological treatment of the hormonal dysfunction on coagulation-fibrinolytic abnormalities. In this context, with the aim of elucidating the association between hemostatic abnormalities and thyroid disorders, we have recently started a single-center prospective study (the Mantova Investigation on Thyroid and Hemostasis [MITH]). In this trial, all patients with hypothyroidism or hyperthyroidism seen at the Internal Medicine Department of City Hospital of Mantova, Italy, are screened for some coagulation parameters (first-level screening: aPTT, PFA-100, fibrinogen, and D-dimer levels). Patients with laboratory abnormalities will then progress to second-level coagulation tests to identify the underlying hemostatic abnormality. The study includes a follow-up of at least 6 months in which the response of abnormal coagulation parameters to therapy for the thyroid disease will be analyzed. First results will be available in mid to late 2011.

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