

## The role of von Willebrand factor alterations in thyroid disorders

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### Abstract

Thyroid hormones are mediators of various metabolic processes including haemostasis. Von Willebrand is a multimeric glycoprotein with a major role in blood coagulation, participating in platelet adhesion to subendothelial collagen. It is also a carrier protein and stabilizer of circulating factor VIII and a marker of endothelial activation. This review aims to summarize the available data with regards to changes of von Willebrand factor in thyroid disorders, possible pathophysiological mechanisms, and their significance in clinical practice. PUBMED database was used for literature search in the English language over the last 20 years. Von Willebrand factor and coagulation factor VIII seem to have a key role in the pathogenesis of bleeding and thrombosis in thyroid disorders. Clinical hypothyroidism is associated with acquired von Willebrand syndrome due to the reduction of von Willebrand factor synthesis and release into the circulation. The implication of the von Willebrand factor in the prothrombotic environment induced by subclinical hypothyroidism is not clear. Hyperthyroidism increases the thromboembolic risk by increasing the levels of procoagulant agents including the von Willebrand factor. However, the available studies are highly heterogeneous in design and most of them investigate the laboratory changes of von Willebrand factor in patients with thyroid disease without any clinical implication. Patients with haemostatic disorders should be screened for underlying thyroid disease. Von Willebrand factor changes are corrected by restoring thyroid function. However, the implementation of early treatment in subclinical thyroid disorders has not been established.

**Keywords:** Haemorrhage, Hyperthyroidism, Hypothyroidism, Thrombosis, von Willebrand factor

### Introduction

Thyroid hormones are potent mediators of various physiological processes, including haemostasis (1). Thyroid disorders can affect various stages of blood coagulation (2). Early years of the past century an episode of cerebral thrombosis was presented in a thyrotoxic patient, raising the suspicion of the relationship between thyroid hormones and haemostatic factors (3). Since then several episodes of cerebral venous sinus thrombosis have been reported in hyperthyroid patients

(4-8). Clinical hypothyroidism is associated with acquired von Willebrand syndrome (AVWS), characterized by reduced levels of von Willebrand factor (VWF) and factor (F) VIII (9). The findings in subclinical disease are unclear with most studies showing the development of prothrombotic phenotype and increased cardiovascular risk (10).

VWF is synthesized in endothelial cells and megakaryocytes and is stored in Weibel-Palade bodies of endothelial cells and platelet alpha granules. It plays a key role in primary haemostasis, mediating the platelet adhesion

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to subendothelium at the site of vascular injury. Besides, it is a carrier protein and stabilizer of FVIII in circulation. In series of patients with thyroid dysfunction, VWF has been assessed either as a marker of bleeding diathesis or as an indicator of endothelial damage and thromboembolic risk (figure 1) (9).

Nevertheless, the effect of the impaired thyroid function on coagulation is often overlooked because the spectrum of haemostatic disorders is wide, ranging from random pathological laboratory findings to rarer major bleeding and fatal thromboembolic events. The relevant research is focused on coagulation abnormalities and their relationship to thyroid function regardless of the clinical picture. In addition, many studies have methodological limitations, such as a small number of patients, absence of control group, heterogeneity of thyroid disease, differences in laboratory assays, and their cut-off values (1). This review examines the alterations of VWF in thyroid disease, the proposed pathophysiological mechanisms, and their clinical significance.

## Methods

PUBMED database was employed for a literature search in the English language over the last 20 years. Haemorrhage, hyperthyroidism, hypothyroidism, thrombosis, thyroxine, von Willebrand factor were used as keywords. The reference list of the retrieved articles was further assessed for relevant studies. VWF parameters in thyroid disorders have been tested in 23 studies, distinguished in 7 case-control studies, 6 interventional studies, assessing coagulation parameters before and after treatment implementation; 7 studies consist of both case-control and interventional arm; 1 experimental study, evaluating the effect of levothyroxine (LT4) in euthyroid subjects and 2 observational studies.

## VWF biology and laboratory testing

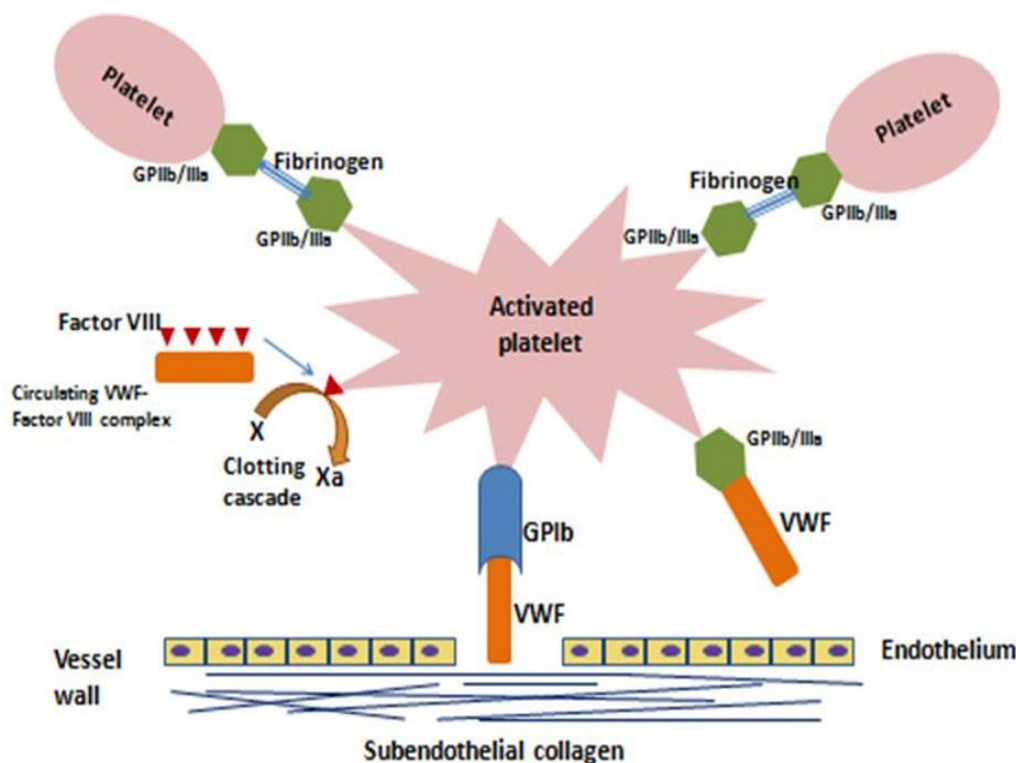
VWF is a glycoprotein synthesized in endothelial cells and megakaryocytes as a single prepolypeptide. VWF monomers are glycosylated and processed into dimers in the endoplasmic reticulum. Multimerization of VWF occurs in the Golgi apparatus and it enters the circulation as a large multimeric molecule of 15-20 million daltons. VWF is either secreted or stored in Weibel-Palade bodies of endothelial cells or alpha granules of megakaryocytes and platelets (9, 10). VWF catabolism is mediated by ADAMTS 13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13) cleaving the polymers in the A2 domain. Haemostatic function of VWF includes platelet adhesion to the injured endothelium through the collagen-binding sites and glycoprotein (GP)Ib $\alpha$ ; and binding FVIII in blood circulation, ensuring its stability (Figure 1) (11).

Von Willebrand disease (VWD) is the commonest hereditary bleeding disorder affecting 1% of the general population. VWF gene mutations lead to VWF quantitative and qualitative changes with heterogeneous clinical presentation (12). Quantitative changes may be mild to moderate (type 1) or severe with undetectable factor (type 3). Qualitative changes constitute type 2 of VWD which is further distinguished in subtypes depending on the affected position in the VWF molecule. Both types 2A and 2B lack the high molecular weight VWF multimers. Type 2B also presents enhanced VWF activity on platelet GPIb binding sites with the subsequent clearance of VWF-platelets complexes from circulation and induction of thrombocytopenia. Defects on platelet and collagen binding sites characterize type 2M, while impaired binding with FVIII is seen in type 2N (12, 13).

The laboratory investigation of VWF changes requires a combination of assays. Screening tests include the quantitative

assessment of VWF antigen (VWF:Ag), VWF ristocetin cofactor activity (VWF:RCo), assessing the ability of VWF to bind GPIIb $\alpha$  on platelets; and FVIII coagulant activity (FVIII:C). Normal levels of VWF vary widely, with the lower limit to extend

down to 50 IU/dL. However, some study groups suggest a cut-off value of 30 IU/dL or even 20 IU/dL. VWF:RCo/VWF:Ag ratio less than 0.6 indicates the need for further testing for type 2 VWD (2A, 2B, 2M) with second-line tests (13).



**Figure 1.** The role of von Willebrand factor (VWF) in haemostasis. Following vessel wall disruption VWF mediates platelet adhesion by binding to subendothelial collagen and platelet glycoprotein (GP) Ib. This induces a conformational change of glycoprotein (GP)IIb/IIIa which interacts with VWF and collagen promoting further platelet adhesion and aggregation. VWF is also a carrier protein and stabilizer of factor VIII in circulation.

Confirmatory tests include VWF multimer distribution, VWF collagen binding (VWF:CB), VWF-platelet binding (VWF:PB), VWF-FVIII binding (VWF:FVIII) and low dose ristocetin-induced platelet aggregation (LD-RIPA) (13). VWF propeptide (VWFpp) can be used to assess VWF biosynthesis and clearance. Reduced VWFpp levels are observed in type 1 and 3 VWD, whereas increased VWFpp/VWF:Ag ratio is expected in case of rapid VWF clearance from plasma (14). VWF gene sequencing has limited value in VWD diagnosis. VWF gene is large with frequent physiological variants, while no

mutations are found in a significant number of patients with congenital VWD. Genetic testing of the VWF gene is not useful in AVWS, as normal findings are expected (13, 15).

#### VWF alterations in hypothyroidism

Hypothyroidism is characterized by low thyroid hormone levels and its prevalence in the United States is estimated at 0.3-0.4%. Subclinical hypothyroidism is characterized by normal levels of free thyroxine (FT4) and high levels of thyroid-stimulating hormone (TSH) and is observed in 4.5-8.5% of the

United States population. The disease is more common in women (16).

The effect of hypothyroidism on haemostasis is controversial, since both haemorrhagic and thrombotic predisposition has been reported. AVWS is the commonest bleeding disorder in hypothyroidism (17, 18). However, some studies implicate the underactive thyroid gland and mainly the subclinical disease in the pathogenesis of hypercoagulable state.

### Hypothyroidism and AVWS

AVWS is a rare bleeding syndrome in patients without a personal or family history of haemostatic disorder. The incidence is approximately 0.04%, although it is underestimated. It usually affects adult patients, presenting with mild to moderate mucocutaneous bleeding events, similar to those in congenital VWD. The diagnosis requires the laboratory demonstration of VWF disorder with the simultaneous presence of an underlying disease. The pathophysiology is multifactorial and depends on the underlying disorder (19). AVWS is often diagnosed in the setting of lymphomas, monoclonal gammopathies, myeloproliferative syndromes, solid tumors, autoimmune disorders, cardiac diseases, and pharmaceutical agents. According to International Society on Thrombosis and Haemostasis (ISTH) registry, lymphoproliferative disorders (48%), myeloproliferative syndromes (15%), cardiovascular disease (21%), congestive heart failure, solid tumors (5%) and autoimmune disorders (2%) are the commonest associated entities (20).

Approximately 8% of AVWS cases are attributable to hypothyroidism (2). A prospective study of 90 newly diagnosed patients with overt hypothyroidism showed a high incidence of AVWS (33%) using levels less than 50% as cut-off values for VWF:Ag and VWF:RCo (21). Thyroid hormone deficiency down-regulates VWF synthesis in

endothelial cells and release into circulation (18, 21-23). The interaction between thyroid hormones and beta-adrenergic receptors induces the release of VWF from endothelial cells. Consequently, the hypothyroid state reduces the endothelial response to adrenergic stimuli (24). Interactions between thyroid hormones and nuclear receptors in hepatocytes influence the synthesis of coagulation factors (25). High TSH with normal free thyroid hormone levels does not affect the haemostatic parameters (26). Even in overt hypothyroidism TSH levels are not significantly correlated with VWF levels (21).

Hemorrhagic complications include mild mucocutaneous bleeding, epistaxis, menorrhagia, postsurgical and postpartum bleeding. Mild and moderate haemorrhagic events were recorded in 9% and 23% of hypothyroid patients respectively. Bleeding score was negatively correlated with VWF:Ag ( $\beta$  -0.32,  $p=0.03$ ) and VWF:RCo ( $\beta$  -0.32,  $p=0.02$ ), while there is no significant correlation with thyroid hormone levels (21). The insidious onset of hypothyroidism along with the mild bleeding diathesis makes the diagnosis of AVWS difficult. Furthermore the conventional coagulation assays applied in clinical practice cannot establish the diagnosis of AVWS (17). Haemorrhagic predisposition may be overlooked and further investigation may be initiated only after surgery or major injury (27).

AVWS in hypothyroidism is characterized by decreased levels of VWF:Ag, VWF:RCo and FVIII:C (24). FT4 values correlated positively to VWF:Ag ( $\beta$  0.23,  $p=0.03$ ) and VWF:RCo ( $\beta$  0.23,  $p=0.03$ ) (21). In a prospective study of 22 patients who underwent total thyroidectomy for differentiated thyroid cancer, the levels of VWF:Ag, VWF:CBA, and FVII:C were significantly decreased compared to those after euthyroid restoration (23). In contrast to acquired haemophilia, the presence of VWF

inhibitors is rare (28). However, mixing studies with normal plasma at 37°C for 1-4 hours and subsequent measurement of VWF or enzyme-linked immunosorbent assay (ELISA) should always be performed to identify VWF antibodies as their presence is associated with severe bleeding events and worse prognosis (29).

The treatment of AVWS aims to control or to prevent bleeding in high-risk patients as those undergoing surgery, to treat the underlying disease, and to eradicate the inhibitor (30). In the absence of active bleeding and wherever the postponement of surgery is feasible, the treatment of the underlying disorder is a priority (31). Surgical interventions can be postponed until the recovery of euthyroid function, since hormonal therapy usually improves laboratory findings and bleeding tendency. In a study of 131 patients with VWD, eight patients (6%) were diagnosed with hypothyroidism and their VWF levels resumed to normal after hormonal substitution (32). Patients with overt and subclinical hypothyroidism had significantly lower FVIII and VWF:RCo levels compared to euthyroid controls, however with no clinically apparent hemorrhagic events (18). LT4 in 16 reported cases with hypothyroidism-associated AVWS resolved the bleeding diathesis and the levels of FVIII:C, VWF:Ag and VWF:RCo increased by 47%, 60% and 71%, respectively (33). In a prospective study of 29 patients with overt hypothyroidism and AVWS, restoration of euthyroid function resulted in a significant increase of VWF:Ag, VWF:RCo and FVIII levels by 44%, 36% and 39% respectively (21). VWF:Ag increased after 3 months of thyroxine substitution and this response was sustained after 6 and 12 months (18, 34). After an average 10-month LT4 therapy FVIII:C, and VWF:Ag increase significantly with TSH normalization (35). However, in a paediatric series of 11 hypothyroid children

with AVWS, only 2 children responded to thyroxine treatment after one-year follow-up (36).

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) could be useful in hypothyroid patients with AVWS undergoing thyroidectomy (37). In a study of 1,342 patients with thyroidectomy, 35 patients (3%) found with AVWS and responded to DDAVP presenting minimal or no bleeding complications (17). However, the efficacy of DDAVP in AVWS is difficult to be predicted, especially in the presence of autoantibodies or increased VWF clearance. Therefore, the assessment of VWF:Ag and VWF:RCo levels is required during treatment (30, 38). In cases of thyroid gland biopsy or surgery, prophylaxis with DDAVP or VWF concentrates can be given before the restoration of thyroid function (indication 2c) (38). Other treatment modalities include substitution with FVIII or VWF concentrates, antifibrinolytic agents; and inhibitor eradication with intravenous immunoglobulin, immunosuppression, plasma exchange, and immunoadsorption (15).

#### Hypothyroidism and hypercoagulation

The prothrombotic phenotype in hypothyroidism is attributed to alterations on haemostatic and fibrinolytic factors without a proven causative implication of VWF. The role of VWF in subclinical hypothyroidism is controversial with a limited number of studies (39-42).

A study of 410 patients with acute coronary events showed a high incidence of overt and subclinical hypothyroidism 6-24 months after the episode (11.5%). High VWF levels were observed in male patients with no correlation between hypothyroidism and coronary heart disease (43). In a prospective cohort study of 41 patients with subclinical hypothyroidism baseline VWF levels were lower compared to controls without bleeding

events. After a 6-month LT4 therapy there was an increase in VWF levels ( $119.5\pm 16.6\%$  vs  $122.1\pm 10.2\%$ ,  $p=0.04$ ), with no change in FVIII levels. The same study showed increased levels of FVII, plasminogen activator inhibitor-1 (PAI-1), mean platelet volume (MPV), tissue plasminogen activator (t-PA), and low d-dimers before the treatment. Substitution treatment decreased the levels of PAI-1 and t-PA and increased marginally d-dimers levels (41). No significant changes in VWF and FVIII levels found in 42 women with subclinical hypothyroidism compared to controls. Increased FVII:C and FVII:C/FVII:Ag were associated with a potential hypercoagulable state (42). Furthermore, reduced fibrinolytic activity has been reported in patients with TSH between 10-50 mIU/L (40). Increased levels of fibrinogen, PAI-1, and FVII, and decreased levels of antithrombin were found in 35 patients with subclinical hypothyroidism (39). In a study of 15 untreated hypothyroid patients, FVII and VWF were low, whereas increased levels of FVII, thrombomodulin, and thrombin-activatable fibrinolysis inhibitor (TAFI) were associated with a potential endothelial dysfunction and increased cardiovascular risk (44). In paediatric series of hypothyroid children, VWF concentration was not correlated with FT4 levels, whereas potential endothelial dysfunction was associated with high levels of FVII:C, fibrinogen, and leukocyte adhesion molecules, such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) (45, 46).

#### Congenital VWD and hypothyroidism

In a retrospective study of 197 patients with VWD, 32 subjects (16%) were found with hypothyroidism versus 11 (5.6%) in the control group ( $p 0,001$ ). In all cases VWD was type 1 and 87% of them were females. VWD was an independent prognostic factor

for the development of overt hypothyroidism (OR, odds ratio 3.45,  $p < 0.0001$ ). The most common bleeding manifestations were menorrhagia (53%) and postoperative bleeding (26%) in females; epistaxis (48%), postoperative bleeding (20%), and lower gastrointestinal tract haemorrhage (16%) in males (12).

#### VWF in hyperthyroidism

Hyperthyroidism is characterized by high thyroid hormone levels with low TSH, affecting 1.2% of the general population in the United States. The incidence is 2-10 times higher in women. Graves's disease is the cause of hyperthyroidism in 50-80% of cases. Other causes include multinodal goiter, toxic adenoma, and thyroiditis (47). Overt hyperthyroidism is associated with an increased risk of thrombotic complications. Major embolic events account for 18% of deaths in patients with thyrotoxicosis (48). The incidence of arterial thromboembolic events was higher in hyperthyroid patients with atrial fibrillation over euthyroid counterparts (49). High antigenic and functional levels of VWF in hyperthyroid patients have been confirmed in a series of studies (1, 50-54).

The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study included 2,177 patients with venous thrombosis and 2,826 gender and age-matched controls. An increase in FT4 levels was followed by an increase of VWF, FVIII, FIX, and fibrinogen. Levels of  $FT4 > 24.4$  pmol/L and  $T4 > 22.2$  pmol/L were associated with increased risk of deep vein thrombosis (OR 2.5) and pulmonary embolism (OR 2.7) respectively. With the inclusion of 11 cases diagnosed with hyperthyroidism within one year of the thrombotic episodes, the OR for thrombosis increased up to 17.0 (55). A case-control study of 190 patients with venous thromboembolism showed a double risk of

thrombosis at FT4 levels >17 pmol/L (OR 2.2) which increased further (OR 13.0) for FT4 levels above the reference range (56). In a prospective population-based study, the thrombotic risk increased progressively with elevated FT4 levels and was up to 10 times higher in patients with FT4 >17.3 pmol/L 0.5 years after the thrombotic event (57).

High LT4 dose increases coagulation markers and inhibits fibrinolysis. LT4 intoxication (25mg) increased FVIII, FIX, FX, VWF:Ag, VWF:RCo, and PAI-1 (58). The administration of 0.3 mg LT4 in 16 healthy volunteers and 0.45-0.6 mg LT4 in 12 others, depending on body weight for 14 days, resulted in a dose-dependent increase of VWF:Ag, VWF RCo, FVIII, and PAI-1. Partial thromboplastin time (APTT) was 3% shorter in the group receiving higher LT4 doses (59).

Subclinical hyperthyroidism is characterized by low TSH and normal thyroid hormone levels and is caused by disorders encountered in overt hyperthyroidism (60). A meta-analysis revealed that haemostatic balance shifts towards a hypercoagulable and hypofibrinolytic state in both subclinical and overt hyperthyroidism (61). A study of 40 euthyroid subjects showed significantly higher VWF levels in those with subclinical hyperthyroidism (62). LT4 administration in 90 patients underwent thyroidectomy for thyroid cancer resulted in an increase of PAI-1, FVIII, VWF:Ag, fibrinogen and ATIII; and reduction of CEPI-CT and prothrombin fragments 1 + 2 (63).

The role of thyroxine in haemostatic mechanism seems to be associated with a direct effect on either gene replication in the liver and endothelial cells or on adrenergic activity (64). In vitro studies showed a direct effect of T3 on hepatocytes and endothelium with increased expression of fibrinogen, prothrombin, FX, VWF, and plasminogen (25, 63, 65). Changes in clotting factors are mediated through thyroid hormone receptors

beta (TR beta). Patients with defective TR beta exhibit thyroid hormone resistance (THR) and elevated thyroid hormone levels in circulation. In a study involving 18 patients with defective TR beta, 16 hyperthyroid patients, and 18 euthyroid controls, the clotting factors were increased in hyperthyroid subjects, while there was no difference between those with THR and the control group (66).

The incubation of umbilical vein endothelial cells with T3 led to an increase of VWF, endothelin, and fibronectin levels, mediated by protein kinase C (PKC) (65). However, Deikman et al. failed to induce VWF secretion after incubation of ECRF24 immortalized human umbilical vein endothelial cells with T3, probably due to decreased expression of thyroid receptors in these cells (67). The autoimmune process and the induced inflammatory response are associated with increased thrombotic risk. Endothelial function markers, namely interleukin (IL)-6, IL-12, IL-18, fibrinogen, PAI-1, VCAM-1, and VWF, in 52 hyperthyroid patients with Grave's thyroiditis, were significantly high in those with hyperthyroidism in comparison to controls (68). In addition, the increase of VWF in hyperthyroidism appears to be related to enhanced platelet activity, resulting in shortened collagen-epinephrine induced closure time (CEPI-CT) and increased cardiovascular risk. Platelet clot formation decreases during thiamazole treatment (53, 63). The assessment of thyroxine effect on fibrin formation showed denser and resistant to fibrinolysis clots in hyperthyroid patients, partially due to inflammatory response. However, no alteration in the clot structure observed in healthy volunteers with exogenous hyperthyroidism post-LT4 administration (69).

Thyroid function restoration leads to normalization of endothelial damage markers, including VWF parameters (50, 64,

70). In hyperthyroid patients undergoing antithyroid treatment, VWF levels return to normal range after thyroid function normalization. Treatment with beta-adrenergic receptor blocker (propranolol 160 mg daily) for 28 days reduced VWF:Ag to normal, despite the persistence of high T3 and T4 levels, indicating the role of beta-adrenergic receptors in the pathophysiology of VWF alterations (70). Fourteen hyperthyroid patients were tested one week after propranolol treatment (40 mg, 4 times daily) and after treatment with thiamazole. Propranolol significantly reduced VWFpp, whereas thiamazole reduced both VWFpp and VWF:Ag. Longer VWF:Ag half-life (12 hours) compared to VWFpp half-life (3 hours) may explain the delay of VWF:Ag normalization with propranolol treatment (50).

## Discussion

VWF is a multimeric glycoprotein synthesized in megakaryocytes and endothelial cells and has a key role in haemostasis, contributing to platelet adhesion to subendothelial collagen and stabilization of FVIII. Thyroid hormones influence the synthesis and release of VWF in circulation through the direct effect on gene expression in endothelial cells and the response of vascular endothelium to adrenergic stimuli. Hypothyroidism has been associated with both hypocoagulability and hypercoagulability, depending on disease severity. Clinically overt hypothyroidism is accompanied by bleeding diathesis, while subclinical disease by the development of prothrombotic phenotype (24).

The most common haemostatic disorder in overt hypothyroidism is AVWS, accounting for approximately 8% of AVWS cases. Conversely, AVWS disease may be the first manifestation of hypothyroidism, so thyroid hormone testing is recommended in those with low VWF levels (42). The clinical

manifestation of the syndrome is characterized by asymptomatic deranged coagulation assays or mild to moderate mucocutaneous haemorrhages. In some cases bleeding diathesis becomes prominent only during invasive procedures. The laboratory findings include normal or prolonged APTT, low antigenic and functional levels of VWF such as in type 1 of congenital disease. However in relevant studies the degree of VWF reduction did not always establish the diagnosis of AVWS, possibly due to the short duration of the hypothyroid phase (23).

However, the haemorrhagic tendency in hypothyroidism is multifactorial. Functional disorders of platelet and reduced activity of FVIII, FIX, and FXI have been reported. Menorrhagia is attributed to oestrogen breakthrough bleeding secondary to anovulation and to direct effect of thyroid hormones on muscle contractility and connective tissue in hypothyroid women (71, 72). Myxoedematous changes around the superficial vessels are responsible for the cutaneous bleeding manifestations in these patients (72). It is estimated that 3% of patients undergoing thyroid surgery have acquired haemostatic disorders and given the increased thyroid gland vascularity, preoperative clotting tests are recommended (17). The variety of haemorrhagic mechanisms often delay further investigation and make difficult the diagnosis of AVWS leading to underestimation of its prevalence. The hypercoagulable state in hypothyroidism does not seem to relate to VWF or FVIII. In some studies decreased VWF and FVIII levels are observed, while in others there is no significant difference between subclinical hypothyroid patients and controls (70, 73). Changes of other clotting and fibrinolytic factors, such as an increase of FVII, thrombomodulin, fibrinogen, thrombin activatable fibrinolysis inhibitor (TAFI), and decrease of antithrombin, protein C and protein S are implicated in the pathogenesis



of prothrombotic state. Moreover, hypothyroid patients have other thrombosis-associated factors, such as increased body weight, hypertension, and dyslipidaemia (71).

Hyperthyroidism shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state. In MEGA study, elevated thyroxine levels were associated with an increased thrombotic risk (55). In several studies treatment with LT4 increased significantly VWF and FVIII activity (53, 54). The pathophysiology of thrombotic phenotype involves the direct effect of thyroid hormones on clotting and fibrinolytic factors synthesis in liver and vascular endothelium. Thyroid hyperactivity induces fibrinolytic abnormalities, such as high levels of fibrinogen and PAI-1 and low levels of t-PA (63, 68,74). Autoimmune thyroid disorders affect the cardiovascular risk due to alteration in fibrinogen and fibrinopeptide A and B levels; and due to the presence of antiphospholipid antibodies and enhanced thrombin activity (73, 75). However, the evaluation of haemostatic and fibrinolytic parameters during the acute phase of thrombosis exhibits several limitations. The most common and early change is the inhibition of T4 conversion to T3, resulting in higher T4 levels. Furthermore, FVIII levels are not representative of those before the thrombotic event. Both reduction of FVIII due to increased consumption; and increase of FVIII as an acute phase response have been observed during the acute phase of a thrombotic event (56).

Coagulation and fibrinolysis disorders in thyroid disease are usually of mild to moderate severity and subside with the improvement of thyroid function (24). Restoration of VWF levels post thyroxine or thiamazole treatment in hypothyroidism and hyperthyroidism respectively indicates the effect of thyroid hormones on the transcriptional process of haemostatic factors

and the endothelial release of VWF (18, 33, 61). Hyperthyroidism as a thrombotic risk factor can affect the treatment as a shorter duration of anticoagulation may be required. It may also lead to increased vigilance for signs of thrombosis in hyperthyroid patients and initiation of prophylactic measures for those undergoing high risk surgical interventions. Thromboembolic disease is multicausal, thus the presence of thyroid disease is of particular relevance in those with additional risk factors (56, 61, 71). Based on the criteria of the Scientific and Standardization Committee of the ISTH, hyperthyroidism is considered as a minor transient thrombotic risk factor (56, 71). Moreover, screening for thyroid function in patients with thrombotic episode or new diagnosis of VWD could contribute to early diagnosis of thyroid defects, especially the subclinical ones that may remain undiagnosed for years due to absence of symptoms.

Several case reports and studies of low to medium quality are available in the literature with regards to the effect of thyroid hormones on haemostasis. However, they exhibit remarkable heterogeneity in design and methodology, leading to contradicting results. They often investigate laboratory changes of haemostatic parameters in a small number of patients with thyroid disease without overt haemostatic disorder. These limitations reduce the clinical relevance and strength of evidence. Ideally, prospective studies including patients with a defined degree of thyroid disease and with proven haemostatic disorder are needed. Only then the clinical significance of the outcomes could influence the therapeutic decision and prevention of coagulation disturbances in thyroid disease.

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### Conflict of Interest

There is no conflict of interest to declare.

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