

## REVIEW

# Hemostatic abnormalities in endocrine and metabolic disorders

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## Abstract

The hemostatic balance is a complex system where the delicate equilibrium is regulated by several factors, including hormones. This review summarizes current knowledge of the effects of most frequent endocrine and metabolic diseases (such as hypothyroidism, hyperthyroidism, Cushing's syndrome, GH-related pituitary dysfunctions, pituitary prolactin-producing adenomas, polycystic ovary syndrome, primary hyperparathyroidism, and metabolic syndrome) on coagulation and fibrinolysis. Overt hypothyroidism appears to be associated with a bleeding tendency, whereas all other endocrine diseases appear to be associated with a thrombotic tendency. Globally, the disorders of coagulation and fibrinolysis usually range from mild to moderate, and, rarely, to severe laboratory abnormalities (for example, bleeding diathesis in overt hypothyroidism mainly due to an acquired von Willebrand's disease type 1). Further larger and high-quality studies are needed to provide more definitive information on the effects of endocrine disorders on coagulation and fibrinolysis.

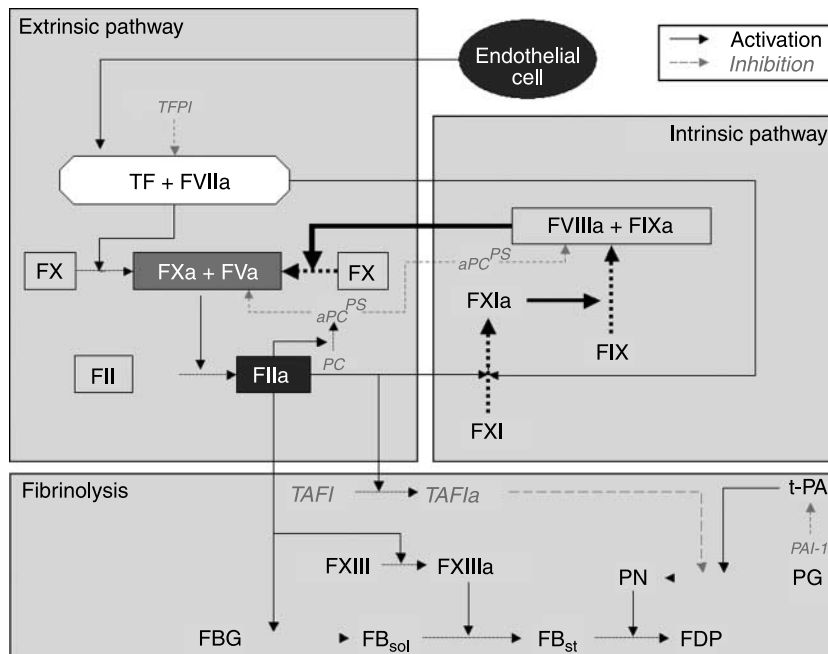
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## Introduction

Endocrine disorders may have a significant influence on the hemostatic balance. Several abnormal coagulation test results have been described in patients with abnormal hormone levels (1). As schematically shown in Fig. 1, two pathways of blood coagulation have been recognized: the so-called extrinsic or tissue factor (TF) pathway and the so-called intrinsic or contact activation pathway (2). These two pathways of activation of the coagulation cascade converge to form a 'common' pathway, which leads to the generation of the pivotal coagulation enzyme thrombin. Thrombin not only catalyzes the conversion of fibrinogen to fibrin, but also exerts a key role in amplifying the cascade by feedback activation of coagulation factors at several sites (the so-called 'thrombin burst') (2). Several physiological antithrombotic mechanisms act in concert to prevent clotting under normal circumstances. Optimal activity of each of the anticoagulant systems depends on the integrity of vascular endothelium. Several of these physiological antithrombotic mechanisms, including antithrombin, the protein C/protein S/thrombomodulin system, and TF pathway inhibitor (TFPI), act at different sites in the coagulation cascade to dampen fibrin accumulation (2). Fibrin that forms despite these anticoagulant defenses is then degraded by the fibrinolytic system. Plasminogen is the inactive zymogen form of plasmin, which represents the major

protease enzyme of the plasma fibrinolytic system, acting to digest fibrin to fibrin degradation products (2). The major physiological plasminogen activators that convert plasminogen to plasmin are tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), although the former is prevailing under physiological circumstances (2). Physiological regulation of plasma fibrinolysis occurs primarily at two levels: i) plasminogen activator inhibitors (PAIs), principally PAI-1, inhibit the physiological plasminogen activators, t-PA and u-PA, in plasma, and ii) alpha 2-antiplasmin inhibits plasmin (2). Further regulation of fibrinolysis occurs by a unique feedback mechanism of thrombin generation via the thrombin-activatable fibrinolysis inhibitor (TAFI) that inhibits fibrinolysis through the removal of carboxy-terminal lysine residues on fibrin monomers, eliminating plasminogen and t-PA-binding sites that normally serve to augment t-PA-mediated conversion of plasminogen to plasmin (2). Table 1 summarizes the main antithrombotic and prothrombotic factors in plasma.

This review critically appraises studies examining the effects of the most common endocrine and metabolic disorders – such as hypothyroidism, hyperthyroidism, Cushing's syndrome, GH-related pituitary dysfunction, pituitary prolactin (PRL)-producing adenomas, polycystic ovary syndrome (PCOS), primary hyperparathyroidism (PHPT), and metabolic syndrome – on coagulation and fibrinolysis.



**Figure 1** Schematic representation of the coagulation and fibrinolytic systems. F, factor; FBG, fibrinogen; FDP, fibrin/fibrinogen degradation products; FB sol, soluble fibrin; FB st, stabilized fibrin; PAI-1, plasminogen activator inhibitor-1; PC, protein C; PS, protein S; PG, plasminogen; PN, plasmin; TAFI, thrombin-activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; t-PA, tissue-plasminogen activator.

## Thyroid disorders

The strong relationship between thyroid hormones and the coagulation system has been appreciated since the beginning of the past century (3). Several biological mechanisms were proposed to explain this intriguing association, including effects of thyroid hormones on synthesis of coagulation factors as well as thyroid-related autoimmune processes, involving the hemostatic system (4–6).

As reported in more detail below, the disorders of coagulation and fibrinolysis in patients affected by overt hyperthyroidism or hypothyroidism usually range from mild to moderate, and, rarely, to potentially severe laboratory abnormalities (e.g. bleeding diathesis in overt hypothyroidism mainly due to an acquired von Willebrand's disease (aVWD) type 1), are rapidly reversible after pharmacologic treatment of the hormonal dysfunction, and are usually of limited consequence in clinical practice. Although future clinical trials on larger series of patients are undoubtedly required to better clarify the hemostatic abnormalities in patients with thyroid dysfunctions, a number of small case-control studies have suggested that the influence of thyroid dysfunction on coagulation and fibrinolysis mainly depends on the type of thyroid disorder. In general, patients with clinically overt hypothyroidism appear to have an increased risk of bleeding, whereas those with overt hyperthyroidism are more likely to be prone to thrombosis. At present, very little information is available on hemostatic abnormalities in patients with subclinical hypothyroidism or hyperthyroidism.

## Hypothyroidism

A number of small case-control studies have shown various abnormalities of coagulation and fibrinolysis in patients with overt hypothyroidism (7–10). aVWD is the most relevant coagulation disorder clinically observed in overt hypothyroidism (11–21), and it is mainly characterized by decreased factor VIII activity (FVIII:C), von Willebrand factor antigen (VWF:Ag), and ristocetin cofactor (VWF:RCO) levels. The presenting symptoms

**Table 1** Summary of main antithrombotic and prothrombotic factors in plasma.

Anticoagulant	Procoagulant
Antithrombin	Tissue factor (TF)
Protein C/protein S/thrombomodulin system	Tissue factor-bearing microparticles
Tissue factor pathway inhibitor (TFPI)	Clotting factors
	von Willebrand factor (VWF)
Profibrinolytic	Antifibrinolytic
Tissue-type plasminogen activator (t-PA)	Plasminogen activator inhibitor-1 (PAI-1)
Urokinase-type plasminogen activator (u-PA)	Alpha 2-antiplasmin
	Thrombin-fibrinolysis activatable inhibitor (TAFI)
Platelet inhibitory	Platelet activating
Prostacyclin (PGI <sub>2</sub> )	Platelet-activating factor (PAF)
Nitric oxide (NO)	Endothelin-1
Carbon monoxide (CO)	Thromboxane A <sub>2</sub> (TXA <sub>2</sub> )

are easy bruising, epistaxis, or mucosal bleeding. However, the diagnosis of this coagulopathy is difficult since it is usually not detected by routine laboratory tests, and often hypothyroidism may have an insidious onset with subtle clinical signs and symptoms. Therefore, the correct diagnosis is frequently not established until bleeding tendency is revealed by major hemorrhages following trauma or surgery. We studied 1342 consecutive patients with various thyroid diseases undergoing thyroid surgery (20); a pre-operative coagulation screening, including prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet function (using the PFA-100 analyzer), identified 39 patients (~3% of the whole sample) with coagulation abnormalities, 35 of which had aVWD (20). On the other hand, aVWD could also represent the first sign of an undiagnosed hypothyroidism, and thereby individuals presenting with low plasma VWF levels should also be screened for their thyroid hormonal status (21). The pathogenesis of hypothyroidism-associated aVWD is still unclear. A decrease in VWF protein synthesis or a decreased response to adrenergic stimulation (enhancing the VWF release from endothelial cells) due to hormone deficiency is the most plausible mechanisms involved, as also supported by the finding of a reversal of the hypothyroidism-associated aVWD following thyroid hormone replacement (5, 22).

In addition to decreased plasma VWF levels, patients with overt hypothyroidism may have, in some cases, a megakaryocytopoiesis that is severely inhibited by bone marrow myxedema (7).

Qualitative platelet abnormalities have also been reported in patients with hypothyroidism (23–25). Palareti *et al.* (26) studied 21 patients with acquired hypothyroidism after thyroidectomy, and observed an impaired platelet reactivity not only to ristocetin but also to collagen and adrenalin, which was rapidly normalized after thyroid hormone replacement therapy. Myrup *et al.* (23) reported a significant prolongation of bleeding time, an impaired agglutination response to ristocetin, and an increased platelet aggregation in response to ADP in 19 hypothyroid patients as compared to euthyroid controls. Notably, these hemostatic abnormalities normalized after L-thyroxine (L-T<sub>4</sub>) therapy, suggesting that the prolonged primary hemostasis seen in overt hypothyroidism may be a direct consequence of the hormonal dysfunction (23).

As regards the coagulation–fibrinolytic abnormalities in overt hypothyroidism, Egeberg (27) and Simone *et al.* (28) also documented a significant reduction in coagulation factors VIII, IX, and XI activities in hypothyroid patients. Further small case–control studies (29–31), although not all (32, 33), confirmed these findings and also reported lower levels of plasma coagulation factors VII, X, and XII in hypothyroid patients. Auto-antibodies against factor VIII (aHA, acquired hemophilia A) may also occasionally develop in hypothyroidism caused by chronic autoimmune

thyroiditis (34). Chadarevian *et al.* (35) studied the fibrinolytic system in hypothyroid patients and documented a different plasma fibrinolytic pattern according to the severity of hypothyroidism: an increased plasma fibrinolytic activity (i.e. lower levels of alpha 2-antiplasmin, t-PA, and PAI-1 and higher D-dimer) was observed in overt hypothyroidism, whereas a hypofibrinolytic tendency (i.e. higher levels of alpha 2-antiplasmin, t-PA, and PAI-1 and lower D-dimer) was found in subclinical hypothyroidism. Other small case–control studies confirmed the presence of hypofibrinolysis in patients with subclinical hypothyroidism (8, 36, 37), further supporting the possibility that this condition might be associated with increased risk of cardiovascular disease (38).

### Hyperthyroidism

Platelet abnormalities have been observed in patients with overt primary hyperthyroidism (39–41). Indeed, a number of small case–control studies documented an association between hyperthyroidism and autoimmune thrombocytopenic purpura (AITP) (42–47). Cordiano *et al.* found that ~80% of patients with hyperthyroidism and thrombocytopenia had platelet autoantibodies (48). Conversely, Marshall *et al.* reported that 6 of 42 patients (14% of total) with diagnosed AITP developed hyperthyroidism during the follow-up of the study (43).

However, several other mild to moderate abnormalities of the coagulation–fibrinolytic systems have been reported in patients with overt hyperthyroidism, predisposing these patients to a hypercoagulable state rather than to a bleeding tendency (5). For example, it is known that there is a biological link between anti-phospholipid antibodies and Graves' disease (49–53). Moreover, Homoncik *et al.* found increased plasma VWF levels and enhanced platelet function (as measured with PFA-100 analyzer) in patients with hyperthyroidism compared with euthyroid controls (54). Loeliger *et al.* found that overt hyperthyroidism may increase the turnover rates of coagulation factors II, VII, and X (55). Rogers *et al.* (29) reported that 21 of 22 untreated hyperthyroid patients had increased plasma FVIII:C, VWF:Ag, and VWF:Rco levels, which normalized after treatment with methimazole. The same authors documented a significant increase in plasma VWF:RCO and factor VIII coagulant activity and related antigen in 14 healthy volunteers after receiving a short-term L-T<sub>4</sub> therapy (56). We have recently shown that in a sample of 1329 unselected adult outpatients, 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 overt hyperthyroidism is associated with mild to moderate hypercoagulability (57). Finally, increased plasma factor X activity levels, another marker of a hypercoagulable state, were

recently described by Erem *et al.* in patients with subclinical hyperthyroidism (58). The same authors studied the blood coagulation and fibrinolysis in 41 patients with overt hyperthyroidism (41); they found that patients with hyperthyroidism had increased levels of plasma fibrinogen, factor IX, VWF, antithrombin, and PAI-1 and decreased levels of t-PA compared with euthyroid controls, confirming a reduced plasma fibrinolytic activity. Other small case-control studies showed an impaired fibrinolytic activity in hyperthyroid patients (59, 60).

## Cushing's syndrome

Several small reports have reported an increased incidence of both venous and arterial thrombotic events in patients with active Cushing's syndrome (61–68), underlining the existence of a prothrombotic state in this condition. To date, a number of studies have experimentally explored the effects of acute hypercortisolism on the coagulation and fibrinolytic systems (1). *In vitro* studies have shown a lower fibrinolytic activity induced by corticosteroids, mainly due to a stimulated synthesis/secretion of PAI-1 (69–71). Increased levels of thrombin-antithrombin complex (caused by elevated procoagulant factors and decreased antithrombin) have been documented by Jacoby *et al.* in a canine model (72). The activation of the coagulation system and a reduction of plasma fibrinolytic activity have also been confirmed in small clinical studies conducted in patients with chronic hypercortisolism (73–76). Several investigators have shown higher levels of plasma VWF, factor VIII, factor IX, factor XI, and factor XII in patients with active Cushing's syndrome than in healthy controls (75–78). Conversely, a recent case-control study did not find any significant difference in plasma PAI-1, t-PA, and VWF levels between patients with Cushing's syndrome and control subjects (79).

In a retrospective observational study, Boscaro *et al.* (80) assessed the incidence of postoperative venous thromboembolic events in 307 patients with active Cushing's syndrome, including 75 patients (group 1) not receiving anticoagulants and undergoing routine hemostatic function testing (i.e. PT and APTT), and 232 patients (group 2) receiving anticoagulation therapy with heparin or warfarin and undergoing a thorough investigation as to hemostatic parameters. Compared with control subjects, those with active Cushing's syndrome showed various abnormalities of plasma hemostatic parameters (increased levels of VWF:Ag and VWF:RCo, FVIII:C, PAI-1, and fibrinogen). An inverse, significant correlation was also observed between APTT and 24-h urinary free cortisol excretion. Interestingly, during the follow-up, 15 patients (20%) from group 1 and 14 patients (6%) from group 2 developed venous thromboembolic complications (80). Eight of these patients in group 1 and one in

group 2 died. Overall, survival analysis demonstrated a significantly lower mortality and morbidity for venous thromboembolism in patients in group 2, who were treated with anticoagulants in the perioperative period until cure of the endocrine disease (80). To further explore the acute effects of glucocorticoids on the coagulation system, Brotman *et al.* performed a small controlled clinical study (81). They randomized 24 healthy men to receive either dexamethasone 3 mg twice daily or placebo for 5 days, and then controlled several plasma hemostatic factors (clotting factors VII, VIII, and XI, VWF, D-dimer, PAI-1, and fibrinogen) before and after drug intervention; dexamethasone significantly increased plasma factor VII, factor VIII, factor XI, and fibrinogen levels (81).

Recently, Van Zaane *et al.* (82) performed a systematic review on the chronic effects of active Cushing's syndrome on coagulation and fibrinolysis. The authors confirmed that there is an increased risk of unprovoked and post-operative venous thromboembolism in patients with Cushing's syndrome (82). Glucocorticoid-induced hypercoagulability as well as surgery and obesity, conditions that are commonplace in patients with Cushing's syndrome, almost certainly contributes to this prothrombotic tendency. In this review, it was also reported that no univocal statistical differences in plasma hemostatic markers can be found between patients with active Cushing's syndrome and those in remission. Likewise, no clear difference was observed for subclinical Cushing's syndrome due to adrenal adenomas (82). In the absence of prospective randomized clinical trials, there is currently a general agreement that thromboprophylaxis should be routinely used in patients with active Cushing's syndrome undergoing transsphenoidal or adrenal surgery. However, future large prospective trials are needed to evaluate the type, intensity, and duration of thromboprophylaxis.

## GH-related pituitary dysfunctions

There are some data in the current scientific literature based on small case-control and intervention studies suggesting the presence of a prothrombotic state in patients with GH-related pituitary dysfunctions – as reported in detail below. However, further information from larger case-control and intervention studies is needed to better clarify the effects of GH-related pituitary dysfunctions on the coagulation-fibrinolytic system.

### Acromegaly

Acromegaly is associated with an increased risk of cardiovascular morbidity and mortality (83). Indeed, GH hypersecretion may adversely affect carbohydrate and lipid metabolism, thus contributing to the high thrombotic risk profile of such patients. Some small

case-control studies suggested the presence of a prothrombotic tendency in acromegalic patients that might partially contribute to the development of cardiovascular complications (1). For example, in a small case-control study, Wildbrett *et al.* (84) reported higher levels of plasma PAI-1 and t-PA in 23 patients with active acromegaly than in healthy controls. Moreover, a positive, significant association was observed between plasma insulin-like growth factor 1 (IGF1), GH, and PAI-1 levels among these patients (84). Recently, Erem *et al.* (6) reported higher plasma fibrinogen, antithrombin, and PAI-1 levels, and lower protein S activity and TFPI levels in 22 patients with active acromegaly than those in 22 age-matched healthy controls. Serum GH levels were inversely correlated to plasma TFPI levels, and there was also a negative correlation between IGF1 and PAI-1 (6). A significant increase in plasma fibrinogen and t-PA levels was also reported by Sartorio *et al.* in ten acromegalic patients (85). Interestingly, Landin-Wilhelmsen *et al.* showed significantly higher plasma fibrinogen concentrations, but similar values of PAI-1 activity, in 20 patients with active acromegaly compared with 20 age-, sex-, and body weight-matched control subjects (86). Plasma fibrinogen was positively associated with IGF1 levels, and decreased following pharmacological treatment of acromegaly (86). A beneficial effect of a short-term treatment with somatostatin analogs on plasma fibrinogen and PAI-1 was also reported by Delaroudis *et al.* in 18 acromegalic patients (87).

### GH deficiency

A very small number of case-control studies suggested the presence of a mild to moderate prothrombotic state in adult patients with GH deficiency, which could partly contribute to the increased risk for arterial and venous thrombosis seen in hypopituitarism (88–91). Increased circulating levels of VWF, thrombomodulin, and some endothelial adhesion molecules (such as intercellular adhesion molecule-1 and E-selectin) were observed by Elhadd *et al.* in 52 GH-deficient adults (91). Sartorio *et al.* reported increased plasma levels of PAI-1, fibrinogen, and thrombin-antithrombin complex in 24 patients with adult-onset GH deficiency (85). Similarly, Johansson *et al.* showed a significant increase in plasma fibrinogen and PAI-1 activity levels in 20 GH-deficient adults, and demonstrated reversal of these hemostatic abnormalities after 2 years of recombinant human GH replacement therapy (92, 93). Almost identical results were observed in a small intervention study by Kvasnicka *et al.* (94), who confirmed a favorable effect of a 1-year GH replacement therapy on plasma fibrinogen, PAI-1, intercellular adhesion molecule-1, and E-selectin levels in GH-deficient adults (95). In contrast, no significant changes in plasma fibrinolytic markers were observed by Gomez *et al.* in

ten GH-deficient adults following short-term GH replacement therapy (96), whereas significant increases in PT and APTT values, but not in plasma fibrinogen, were reported by Miljic *et al.* in 21 GH-deficient adults after 12 months of GH replacement treatment (97).

### Prolactinomas

Although several conditions (pregnancy, estrogen, and antipsychotic therapy) increase plasma PRL levels, pituitary PRL-producing adenomas represent the most common endogenous cause of hyperprolactinemia. Currently, there is very little information on the effects of this hormone on the coagulation and fibrinolytic systems. However, Wallaschofski *et al.* have experimentally shown that hyperprolactinemia is a potent platelet co-stimulator due to the potentiation of ADP-induced platelet aggregation (98, 99). The same group of investigators also assessed the potential association between hyperprolactinemia and venous thromboembolism. Plasma PRL levels were significantly higher in 98 patients with unprovoked venous thromboembolism without congenital risk factors than those in healthy controls (100). Finally, according to other two small studies (101, 102), hyperprolactinemia could be implicated in enhanced platelet reactivity seen in patients with ischemic stroke or acute coronary syndromes. Nevertheless, further larger case-control and intervention studies are needed that directly investigate the hemostatic and fibrinolytic disorders in patients with prolactinomas.

### Polycystic ovary syndrome

PCOS is a common endocrine disorder, affecting up to 10% of women of reproductive age, associated with multiple co-morbidities such as type 2 diabetes, dyslipidemia, hypertension, and metabolic syndrome, all of which predispose women with PCOS to early atherosclerosis (103). PCOS women also have a higher prevalence of subclinical atherosclerosis as reflected in dysregulation of endothelial function, increased carotid intima-media thickness and presence of coronary artery calcification (104, 105). The largest retrospective survey of PCOS women in the United Kingdom could not confirm an increased all-cause and cardiovascular mortality (106). However, one explanation might be that the number of deaths was quite small, and longer follow-up might be advisable to show the adverse effect of PCOS on mortality. At present, there are quantitatively limited data on abnormalities in the coagulation-fibrinolytic system in PCOS women. Yildiz *et al.* found that 58 nonobese, nondiabetic PCOS women had a significantly lower global fibrinolytic capacity than age- and weight-matched controls ( $n=23$ ), which was inversely associated with serum testosterone levels

(107). In contrast, no significant differences were found in PT, APTT, antithrombin, D-dimer, plasminogen, fibrinogen, or factor II, V, VII, and X activities between the two groups (107). Kelley *et al.* measured plasma fibrinogen, factor VII, VWF, t-PA antigen, and D-dimer concentrations in 17 young PCOS women and 15 age- and weight-matched controls (108). Of these plasma hemostatic markers, only t-PA concentration was significantly elevated in PCOS women relative to controls (108). A reduced plasma fibrinolytic activity – as measured by PAI-1, TAFI, or euglobulin clot lysis time – in PCOS women was also confirmed in some, but not all, small case–control studies (109–112).

### Primary hyperparathyroidism

Patients with PHPT have a higher prevalence of hypertension, glucose intolerance, altered vascular tone, presence of coronary artery calcification, and are at increased risk for future cardiovascular events; this risk appears to decrease with time after parathyroidectomy (113–115).

Abnormalities in coagulation and fibrinolysis pathways have been detected in PHPT, although the evidence is still conflicting and mostly supported by a small number of case–control studies. Erem *et al.* reported that 24 patients with symptomatic PHPT had significantly higher plasma levels of t-PA and PAI-1, and lower TFPI levels than those in 20 age-, sex- and body weight-matched controls (116). Moreover, serum parathyroid hormone (PTH) levels were positively associated with plasma PAI-1 levels in PHPT patients (116). In a previous article, the same authors found increased platelet count, higher activities of factor VII and IX, and increased levels of D-dimer in 23 PHPT patients compared with healthy controls, whereas no significant differences were found in plasma fibrinogen, VWF, factor V, factor IX, antithrombin, protein C, protein S, t-PA, and PAI-1 between the two groups (117). Chertok-Shacham *et al.* reported a positive, graded, relationship between plasma PTH and PAI-1 levels in 35 patients with symptomatic PHPT without clinically manifest cardiovascular disease (118). However, further larger case–control and intervention studies are needed that directly investigate the hemostatic and fibrinolytic disorders in PHPT patients.

### Metabolic syndrome

The metabolic syndrome represents a public health concern because its prevalence is steadily increasing worldwide – affecting up to one-third of the general adult population in various countries – and it is strongly associated with an increased risk of future cardiovascular events (119, 120). The metabolic syndrome is a cluster of inter-related metabolic abnormalities, which includes abdominal overweight/obesity, glucose

intolerance (i.e. impaired fasting glycemia, impaired glucose tolerance or type 2 diabetes), insulin resistance, atherogenic dyslipidemia (i.e. high triglycerides and low high-density lipoprotein (HDL)-cholesterol) and hypertension, all established risk factors for cardiovascular disease (119).

As recently reviewed by several investigators including our group (120–125), the metabolic syndrome is frequently associated with a hypercoagulable condition, in that the coagulation system is switched toward a prothrombotic state, involving increased plasmatic coagulation, reduced fibrinolysis, decreased endothelial thromboresistance, and predominantly platelet hyperactivity. All of these abnormalities in the coagulation and fibrinolytic systems may contribute to the development of cardiovascular complications in patients with the metabolic syndrome.

### Circulatory endothelium dysfunction

Endothelial dysfunction is defined as an alteration of vascular relaxation induced by reduction of endothelium-derived relaxing factors, mainly nitric oxide (NO), causing a relative predominance of the vasoconstrictive stimuli and a prothrombotic tendency in the vasculature (126–128). Insulin resistance, a pathogenic factor of the metabolic syndrome, is thought to be a key determinant of this process, by suppressing the synthesis and release of both NO and prostacyclin (PGI<sub>2</sub>) by endothelium, and by increasing the synthesis and bioavailability of endothelin-1 (126–128). Impaired endothelial NO synthesis plays a central role in the pathophysiology of vascular disease. In addition to its vasodilatory activity, NO inhibits platelet aggregation and adhesiveness, reduces vascular permeability, and inhibits vascular smooth muscle cell proliferation (126–128). Glucotoxicity, lipotoxicity, and chronic inflammation play a pathogenetic role in the development of circulatory endothelial dysfunction – through mechanisms possibly mediated by the activation of nuclear factor K- $\beta$  and other transcription factors – and may further aggravate insulin resistance, thereby promoting the development of other metabolic abnormalities (128, 129). The adipose tissue, especially visceral adipose tissue, is an endocrine organ that secretes several pro-inflammatory and pro-atherogenic mediators, including free fatty acids, leptin, resistin, visfatin, tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6 and PAI-1 and (decreased) adiponectin (119, 123, 125, 130). Particularly, in the presence of abdominal obesity, the ‘dysfunctional’ adipocyte, as also specifically reflected by lower adiponectin and higher IL-6 and TNF- $\alpha$  levels, may exert its adverse systemic effects contributing to endothelial dysfunction, chronic inflammation, insulin resistance, and accelerated atherogenesis (125–130). TNF- $\alpha$  inhibits lipoprotein-lipase action and increases oxidative stress and acute phase-proteins synthesis (125, 128–131). Similarly, IL-6

inhibits insulin signaling/action and activates endothelial cells, thus modulating the systemic inflammatory response; it also participates in the systemic immune response and the increased monocyte expression of TF (125, 128–131).

### **Platelet hyperactivity**

In general, platelets from patients with the metabolic syndrome – especially those with glucose intolerance and abdominal obesity – show increased adhesiveness and hyperaggregability, both spontaneous and in response to stimulating agents (120, 123, 124, 132–134). The possible causes for this activation are multifold: altered exposure and/or abundance of glycoprotein receptors for agonists and adhesive proteins on the platelet surface, increased binding of fibrinogen, decreased membrane fluidity, altered platelet metabolism, and changes in intra-platelet signaling pathways (120, 123, 124, 132–134). The altered biophysical state of platelet membrane components in the metabolic syndrome may be one of the major determinants of platelet hypersensitivity and hyperfunction, and may contribute to impairments in various metabolic pathways, like intensified calcium mobilization and accentuated thromboxane synthesis and release (132–134). Simultaneously, the presence of endothelial dysfunction and atherogenic dyslipidemia, mainly hypertriglyceridemia, may trigger platelet aggregation, thus further increasing the risk of thrombotic events (120, 123, 124, 132, 133). A disorder of triglyceride metabolism is a key feature in the metabolic syndrome, and there is now ample evidence supporting a strong association between hypertriglyceridemia and hypercoagulability (120–125, 135). In particular, the concentrations of very-low density lipoprotein (VLDL) and remnant lipoproteins are often increased in the metabolic syndrome, and they can trigger platelet activation and activate the coagulation pathway, supporting the assembly of the prothrombinase complex (120–125, 135). VLDL can also up-regulate PAI-1 gene expression, thus increasing the PAI-1 concentration and activity in plasma – a process that is strongly associated with increased platelet aggregation and clot formation (120–125, 136). Finally, it has also been shown that the amount of platelet microparticles, small membrane vesicles that support the coagulation by exposure of anionic phospholipids and TF, is closely associated with the increasing number of the components of the metabolic syndrome (137).

### **Hypercoagulability and hypofibrinolysis**

Several epidemiological and experimental studies have shown that patients with the metabolic syndrome have higher plasma concentrations of fibrinogen, VWF, factor VIII, and factor VII than those without the syndrome (119–125). Moreover, many large cross-sectional

studies conducted in different populations have consistently demonstrated that the fibrinolytic parameters PAI-1 and t-PA antigen (which represents t-PA/PAI-1 complexes) are strongly correlated to the components of the metabolic syndrome (especially abdominal obesity, insulin resistance, and hypertriglyceridemia), and that the improvement of insulin resistance may improve the concentration of the fibrinolytic parameters (119–125).

Currently, there is growing evidence that non-alcoholic fatty liver disease (NAFLD), which is now regarded as the hepatic manifestation of the metabolic syndrome (138, 139), is strongly associated with a systemic pro-inflammatory/procoagulant state, independently of shared cardiometabolic risk factors. As recently reviewed in detail by our group (140), a number of case-control studies using liver biopsies for diagnosing NAFLD have shown that circulating levels of several proinflammatory (e.g. C-reactive protein, IL-6, IL-8, and TNF- $\alpha$ ) and prothrombotic (e.g. PAI-1, fibrinogen, VWF, and intercellular adhesion molecule-1) factors are highest in patients with nonalcoholic steatohepatitis (NASH), intermediate in those with simple steatosis and lowest in nonsteatotic healthy controls, independently of underlying metabolic abnormalities. Notably, some of these studies have reported a strong, graded, relationship between intra-hepatic mRNA expression of C-reactive protein, IL-6, or PAI-1 and the histological severity of NASH (140). Recently, we have shown that NASH patients are more insulin resistant and have higher plasma levels of C-reactive protein, fibrinogen, and PAI-1 activity, and lower plasma adiponectin concentrations than overweight, nonsteatotic controls with comparable values of visceral adiposity, thus suggesting that NASH predicts a prothrombotic/procoagulant risk profile in a manner that is partly independent from the contribution of visceral adiposity (141). This finding was further supported by the strong, graded relationships of these plasma inflammatory/hemostatic markers with the histological severity of NASH, independently of visceral adiposity, insulin resistance, plasma triglycerides, and smoking (141). Overall, therefore, the evidence from this and other studies suggests that NASH is not simply a marker of the prothrombotic state in the metabolic syndrome but is directly involved in its pathogenesis, possibly through the systemic release of proinflammatory and procoagulant factors from the steatotic/inflamed liver (138–140).

Although the available data are still controversial and less conclusive, patients with the metabolic syndrome also exhibit higher plasma levels of TAFI, TF, factor XIII, and endothelial adhesion molecules (e.g. intercellular adhesion molecule-1, P-selectin, and E-selectin) than those without the syndrome (142–145). Moreover, increased endothelial cell microparticles (EMP) release, platelet and leukocyte hyperactivation, increased binding of both EMPs and platelets to leukocytes are also shown in patients with the metabolic syndrome

**Table 2** Summary of main abnormalities of the coagulation and fibrinolytic systems observed in patients with various endocrine and metabolic diseases.

Endocrine disease(s)	Coagulation–fibrinolytic abnormality
Thyroid dysfunctions	
Overt hypothyroidism	aVWD, ↓ coagulation factor levels, aHA, ↑ fibrinolysis (↓ fibrinolysis in subclinical hypothyroidism)
Overt hyperthyroidism	AITP, APS, ↑ VWF levels, ↑ coagulation factor levels, ↓ fibrinolysis
Cushing's syndrome	↑ VWF levels, ↑ coagulation factor levels, ↓ fibrinolysis
GH-related pituitary dysfunctions	
Acromegaly	↑ Fibrinogen, ↓ fibrinolysis
GH deficiency	↑ Fibrinogen, ↓ fibrinolysis, endothelial dysfunction
Prolactinoma	↑ Platelet aggregation
Metabolic syndrome	Endothelial dysfunction, ↑ platelet aggregation, ↑ VWF levels, ↑ coagulation factor levels, ↓ fibrinolysis
Polycystic ovary syndrome	↓ Fibrinolysis
Primary hyperparathyroidism	↓ Fibrinolysis

aVWD, acquired von Willebrand disease; aHA, acquired hemophilia A; AITP, autoimmune thrombocytopenic purpura; APS, anti-phospholipid syndrome; VWF, von Willebrand factor.

(133, 146). Conversely, plasma levels of anticoagulant protein C, protein S, and antithrombin appear to be decreased in these patients (122–124). In addition, plasma TFPI levels are also shown to be reduced in the metabolic syndrome, and correlate significantly with plasma lipid parameters and obesity (122–124, 147).

## Conclusions

There is growing evidence that several abnormalities of the coagulation and fibrinolytic systems can be observed in patients affected by hyperthyroidism, hypothyroidism, GH-related pituitary dysfunctions, pituitary PRL-producing adenomas, Cushing's syndrome, PCOS, PHPT, and metabolic syndrome.

As schematically summarized in Table 2, clinically overt hypothyroidism appears to be associated with a bleeding tendency, whereas all other endocrine and metabolic disorders appear to be associated with a thrombotic tendency. From a clinical standpoint, it is important to note that these coagulation–fibrinolytic disorders usually range from mild to moderate, and, rarely, to severe laboratory abnormalities. In addition, as they are rapidly reversible after pharmacologic treatment of the hormonal dysfunction, they would appear to be usually of limited importance in clinical practice, providing the underlying disorder is recognized quickly and treated appropriately. On the other hand, the prompt recognition of potentially severe disorders of blood coagulation – for example, bleeding diathesis in some cases of overt hypothyroidism mainly due to an aVWD type 1 – is mandatory for the correct management of these patients. However, it should also be noted that, except for the metabolic syndrome, the number of case–control and intervention studies performed in patients with the above-mentioned endocrine diseases is quantitatively limited, and the sample size of most of

these studies is very small. Moreover, the selection of the control group is not always appropriate, and the strength of the few medium-quality studies is tempered by the limited number of coagulation tests performed. Thus, future larger clinical and intervention studies are required to provide more definitive information on the clinical relevance and the effects of the pharmacologic treatment of the hormonal dysfunction on the abnormalities of coagulation and fibrinolysis in these endocrine disorders. At present, there is a general agreement that a high risk of venous thromboembolism is present in patients with active Cushing's syndrome, and that thromboprophylaxis with low-molecular-weight heparin should be (routinely) considered in patients with this disorder undergoing surgery (82). Although the available data are controversial and more extensive studies are necessary, prophylactic anticoagulation might be also recommended in older patients with hyperthyroidism and atrial fibrillation in the presence of other heart disease, hypertension, or other important risk factors for embolization (148). On the contrary, in younger patients with hyperthyroidism and new-onset atrial fibrillation who do not have other heart disease or other risk factors for embolization, the risk of anticoagulant therapy probably outweighs the benefits. Aspirin provides an alternative for lowering risk for embolic events in young people and can be used safely (148). Although low-dose aspirin prophylaxis is frequently recommended also to patients with the metabolic syndrome (119, 123, 124), there are no specific studies of the use of aspirin or other anti-platelet agents for the primary prevention of cardiovascular disease in individuals with the metabolic syndrome. Long-term use of aspirin therapy has been advocated in the secondary prevention of cardiovascular disease (149), and some important scientific associations have strongly recommended low-dose aspirin in high-risk patients with the metabolic syndrome, especially in

those with established atherosclerotic cardiovascular disease or type 2 diabetes (150). Until more data are available, however, the prophylactic use of low-dose aspirin in the primary prevention of cardiovascular disease in nondiabetic patients with the metabolic syndrome as well as in those with endocrine diseases included in this review is an attractive therapeutic option to lower cardiovascular events, but it should remain as an 'individual clinical judgment'.

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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## Author contribution statement

M Franchini, G Lippi, and G Targher wrote the manuscript; F Manzato and P P Vescovi revised and approved the final version of the manuscript.

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