Thyroid disease and haemostasis: a relationship with clinical implications?
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Chapter 2

The coagulation system in endocrine disorders
A narrative review

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Abstract

Endocrine disorders can influence the haemostatic balance. Abnormal coagulation test results have been observed in patients with abnormal hormone levels. Also unprovoked bleeding or thrombotic events have been associated with endocrine disease. The aim of the present review is to summarise the available evidence on the influence of common endocrine disorders on the coagulation system, and their possible clinical implications. We focus on thyroid dysfunction, hyper- and hypocortisolism and growth hormone disturbances, while other endocrine disorders are only briefly discussed. In the published literature a clear bleeding diathesis has only been associated with overt hypothyroidism, mainly mediated by an acquired von Willebrand syndrome. A clinically relevant hypercoagulable state may be present in patients with hyperthyroidism, hypercortisolism or abnormal growth hormone levels, but adequate prospective clinical studies are lacking. Also effects of pheochromocytoma, hyperprolactinaemia and hyperaldosteronism on the coagulation system have been described. It is apparent that unprovoked bleeding and thrombotic episodes can be secondary to endocrine disorders.
INTRODUCTION

Haemostasis is a complex biological process that prevents individuals from experiencing excessive bleeding or thrombosis. Many factors are responsible for maintaining the haemostatic balance, and, among them, hormones directly influence both primary and secondary haemostasis[1]. A wide variety of endocrine disorders have been associated with both mild abnormalities in laboratory coagulation tests, and clinical thrombotic or bleeding manifestations. In this overview of the literature, the influence of common endocrine disorders on the coagulation system and their possible clinical effects are discussed. Results will be highlighted for thyroid dysfunction, hyper- and hypocortisolism and growth hormone (GH) abnormalities, while other endocrine disorders are briefly mentioned. The influence of sex hormones, oral contraceptives and hormonal replacement therapy is well known and has been reviewed recently by others[2–5].

THYROID DYSFUNCTION

The link between the haemostatic system and thyroid disease has been investigated since the beginning of the last century. Several mechanisms are involved at different levels[6]. In particular both thyroid dysfunction and autoimmunity may modify physiological processes of primary and secondary haemostasis, and lead to bleeding or thrombosis. Idiopathic thrombocytopenic purpura, secondary antiphospholipid syndrome (APS) and acquired haemophilia are sometimes associated with autoimmune thyroid disorders[7]. The influence on the coagulation system is mainly mediated by the interaction between thyroid hormone and its receptors[8].

Hypothyroidism

A bleeding tendency is frequently observed in hypothyroid patients. Mild mucocutaneous bleeding (epistaxis, gum bleeding, menorrhagia, bruising), but also, rarely, severe post-traumatic and post-surgical bleeding may occur[9]. Several coagulation abnormalities have been reported in patients with hypothyroidism[9,10]. Case reports describe hypothyroid patients with a bleeding complication who had low levels of von Willebrand factor (VWF), compatible with a diagnosis of acquired von Willebrand’s syndrome type I[11,12]. Franchini and colleagues studied this association in detail[13–15]. First, they screened 131 consecutive subjects with low VWF levels for thyroid hormone levels[13]. Eight of the 131 individuals (6.1%) with low VWF levels had a concomitant subclinical hypothyroidism as documented by normal thyroid hormone levels and raised TSH concentrations. Three of them (37.5%) had bleeding symptoms. Thyroid hormone replacement therapy showed that haemostatic parameters had returned to normal in all patients. Second, they studied 1342 consecutive patients with various thyroid diseases who were candidates for thyroid surgery[13]. A preoperative screening including prothrombin time, activated partial thromboplastin time and platelet function analyser (PFA-100) identified 39 patients (2.9%) with abnormalities. Of these, 35 had von Willebrand’s disease (type 1 in 33 cases and type 2A in 2 cases). However, all these patients were euthyroid at the time of the screening. Other coagulation test abnormalities have been described in hypothyroid patients. Egeberg, and Simone and colleagues, show a significant reduction in coagulation factors
Fluctuations in VIII, IX and XI activity\textsuperscript{16,17}. Other studies report decreased plasma levels of FVII, FX and FXII\textsuperscript{9,18}. These findings are in contrast with the observation that hypothyroid patients who use warfarin require higher dosages to obtain the target International Normalised Ratio (INR) compared to euthyroid anticoagulated patients. In fact, a prolonged half-life of all vitamin K-dependent coagulant factors (FII, FVII, FIX and FX) is reported\textsuperscript{9}. Recent studies suggest that the bleeding tendency is present only in clinically overt hypothyroidism. Muller and colleagues show an increased factor VII activity in subclinical hypothyroid patients, suggesting a possible mild hypercoagulable state\textsuperscript{19}. Chadaverian and colleagues obtain similar results\textsuperscript{20,21}. They demonstrate also that a different pattern of fibrinolytic abnormalities according to the severity of thyroid dysfunction can be distinguished: in overt hypothyroidism, low levels of tissue plasminogen activator (t-PA), low concentrations of plasminogen activator inhibitor (PAI-1) and high D-dimer levels suggest increased fibrinolytic activity. Conversely, in subclinical hypothyroidism, high t-PA, high PAI-1 and low D-dimer indicates decreased fibrinolytic activity. When combined, these results suggest that overt hypothyroidism leads to lower levels of VWF and other coagulation factors, but at the same time an increased half-life of these factors. In addition, fibrinolytic activity may be increased, altogether leading to a bleeding tendency. Unfortunately, most published studies on the relation between the coagulation system and thyroid hormones have important methodological drawbacks. Lack of a control group, small study size, heterogeneity of cause and of severity of thyroid dysfunction, and different laboratory assays hamper definitive conclusions. In summary, hypothyroidism may lead to acquired von Willebrand syndrome type I and to hypocoagulability, with sometimes unexplained bleeding in these patients.

**Hyperthyroidism**

As in hypothyroidism, the heterogeneity of the published studies obscures the real in vivo effects of elevated thyroid hormones on the haemostatic system. However, several coagulation perturbations suggest a hypercoagulable state\textsuperscript{26}. An increased activity of plasma FVIII and FIX, and a reduced fibrinolytic activity (low t-PA levels) potentially increase the risk of thromboembolic events\textsuperscript{22,23}. Conversely to hypothyroid patients, an increased turnover of FII, FVII and FX increase the effect of vitamin K antagonists, reducing the mean warfarin dosage required to reach the target INR\textsuperscript{24}. Rogers and Shane conducted a small but important study\textsuperscript{25}. They administered oral levothyroxine, 0.6 mg daily for 14 days, to 14 volunteers; nine of them continued levothyroxine for an additional 3 days along with oral propanolol, 20 mg four times a day. Moreover, they administered oral L-triiodothyronine, 50 μg three times daily for 7 days, to nine healthy male volunteers; subsequently, the same volunteers received both L-triiodothyronine and oral propanolol; four volunteers received dextrothyroxine, 2 mg daily for 16 days. A significant increase in resting pulse and factor VIII-related activities (FVIII activity, FVIII-related antigen and ristocetin co-factor activity) was detected in patients who received levothyroxine and L-triiodothyronine. No significant effect was seen during oral dextrothyroxine administration. The addition of oral beta-adrenergic blockade significantly reduced or prevented the elevation in resting pulse but not the increase in factor VIII-related properties. Published case reports support the hypothesis that hyperthyroidism is associated with a hypercoagulable state. Sinus and cerebral vein thrombosis have been reported in clinically overt hyperthyroidism, in particular during thyroid storm\textsuperscript{26}. This association is
more than expected, as sinus and cerebral vein thrombosis are rare diseases (4 per million inhabitants per year)\textsuperscript{[27]}. Several inherited and acquired thrombotic risk factors are also present in these patients. Thus far, no studies with clinical outcomes have been published. Prospective studies are therefore necessary before routinely checking the thyroid function status in patients with thromboembolic disorders. Nevertheless, long-standing hyperthyroidism is, besides the increased factor VIII levels, associated with, sometimes, severe cardiomyopathy with or without atrial fibrillation, which is a risk situation for systemic emboli.

**Hyper- and hypocortisolism**

Endogenous hypercortisolism Cushing’s syndrome is uncommon. The estimated annual incidence of pituitary-dependent Cushing’s disease is 0.1–1 per 100 000 inhabitants per year\textsuperscript{[28]}. The estimation of the true incidence and risk of haemostatic disorders is therefore difficult. Nevertheless several venous thromboembolic events, including cerebral sinus thrombosis, have been described in association with endogenous hypercortisolism, suggesting a prothrombotic state in Cushing’s syndrome\textsuperscript{[29–31]}. To test this hypothesis, some published studies explore the in vivo abnormalities of the coagulation and fibrinolytic systems. Obviously, the small number of enrolled patients limits the strength of the evidence. Several coagulation factors (FIX, FXI, FXII) have been found to be increased, but mainly the increase of FVIII and von Willebrand antigen (VWF-Ag) was marked\textsuperscript{[32]}. High levels of plasma thrombin–antithrombin complexes and of plasmin-antiplasmin complexes further support the hypothesis of coagulation cascade activation\textsuperscript{[33]}. A reduced fibrinolytic capacity as a result of increase in plasma PAI-1 activity has been observed in one study\textsuperscript{[34]}, but not confirmed in another\textsuperscript{[35]}. Recently, a retrospective observational study analysed the incidence of postoperative thromboembolic events in a large group of patients with Cushing’s syndrome not receiving (group 1: 75 patients) or receiving (group 2: 232 patients) prophylactic heparin and warfarin, evaluated in the periods 1972–1981 and 1982–2000, respectively\textsuperscript{[36]}. Patients of the group 1 underwent routine haemostatic function testing, i.e., prothrombin time and activated partial thromboplastin time. Patients of the group 2 underwent a thorough investigation as to haemostatic parameters. Patients with Cushing syndrome showed various abnormalities of haemostatic parameters (e.g., VWF antigen and activity, PAI-1 activity, fibrinogen). A significant correlation between activated partial thromboplastin time and urinary free cortisol was observed. During follow-up, 15 patients (20%; mean follow-up, 9.4 ± 6.4 years) from the group 1 and 14 (6.0%; mean follow-up, 6.6 ± 4.2 years) from group 2 had thromboembolic complications. Of these patients, eight in the group 1 and one in the group 2 died. Survival analysis demonstrates a significantly higher morbidity and mortality due to thromboembolic events in patients in the group 1 than in the group 2, who were treated with anticoagulants in the perioperative period until cure of the disease and normalisation of clotting parameters.

In conclusion, even if based on modestly strong evidence, in Cushing’s syndrome whenever a condition of increased risk of venous thromboembolism (VTE) occurs, an adequate thromboembolic risk assessment should be performed to prescribe the best prophylaxis strategy. Conversely, physicians who treat thromboembolic disorder should not be surprised to find typical Cushing’s stigmata (hypokalaemic hypertension, round facies, central obesity and depression) in a patient with VTE.
Exogenous hypercortisolism

Glucocorticoid therapy is extremely common for a wide range of inflammatory, autoimmune and neoplastic disorders. It is therefore important to correctly assess the risk-benefit of steroids. Clinical experience suggests that, considering the wide utilisation of glucocorticoids, the risk of venous thromboembolic events during steroid therapy is marginal\textsuperscript{[37]}. The effects of iatrogenic hypercortisolism on the haemostatic balance are probably often unappreciated. In fact, similar to endogenous hypercortisolism, administration of glucocorticoids modifies the coagulation balance towards a hypercoagulable state, increasing plasma FVIII and VWF levels\textsuperscript{[38-40]}. This prothrombotic state is probably counterbalanced by other mechanisms, such as the inhibition of platelet aggregation or the reduced tissue factor-mediated leucocyte procoagulant activity\textsuperscript{[41;42]}. Nonetheless, different types of venous thrombotic events have been observed in patients on steroid therapy: deep venous thrombosis, superficial vein thrombosis, pulmonary embolism, cerebral sinus thrombosis and also kidney intragraft thrombosis\textsuperscript{[43–45]}. Recently, Brotman and colleagues performed an \textit{in vivo} controlled study to explore the effect of glucocorticoid on the coagulation system\textsuperscript{[46;47]}. They randomised 24 healthy men to receive either dexamethasone 3 mg twice daily vs. placebo for 5 days. Subjects were advised to maintain their usual sleep–wake schedule, exercise and dietary habits during the study. The mean ages were 23.3 years in the dexamethasone group and 24.9 in the placebo group. Fasting morning blood samples were drawn before and after the intervention for the following parameters: clotting factors VII, VIII and XI, VWF, D-dimer, PAI-1, soluble CD40-ligand and fibrinogen. Treatment with dexamethasone modestly increased clotting factors levels and fibrinogen without significantly affecting PAI-1, D-dimer or sCD40-ligand. Factor VII increased by a mean of 13% (P=0.04), factor VIII by 27% (P<0.01), factor XI by 6% (P=0.01) and fibrinogen by 13% (P=0.05).

Hypocortisolism

Adrenal insufficiency is not commonly complicated by bleeding or thrombotic episodes. Although a possible bleeding diathesis has been suggested in a patient who developed a spontaneous intracerebral haemorrhage, an extensive search of the literature reveals that no relevant \textit{in vitro} or \textit{in vivo} studies have been published\textsuperscript{[48]}. Nevertheless, an association with the APS has been described\textsuperscript{[49;50]}. Acute adrenal failure may be the first clinical manifestation of APS, whereas a few patients may have a history of Addison’s disease. Adrenal failure is present in 10%–26% of patients with catastrophic APS\textsuperscript{[51]}. The pathophysiologic mechanism is not clearly understood, but an adrenal vein thrombosis could provoke an adrenal haemorrhagic infarction\textsuperscript{[50]}. APS should be considered as a possible cause of Addison’s disease when the aetiology is unclear.

Growth hormone (GH) excess and deficiency in adults

GH is produced by the anterior pituitary, and acts by binding to receptors on liver and other cells leading to the initiation of a cascade of events that results in the secretion of insulin-like growth factor I (IGF-I), which mediates many of the biologic actions of GH\textsuperscript{[52]}. Abnormal GH levels are relatively rare (e.g., the incidence of GH-secreting adenomas is 3–4 cases per million each year)\textsuperscript{[53]}. 
For this reason few small studies are available on the possible interaction between abnormal GH, IGF-1 and the coagulation system. They mainly explore the fibrinolytic system, as an increased cardiovascular and cerebrovascular mortality risk has been associated with both GH-related pituitary dysfunctions\(^54\). Twenty-three patients with active acromegaly (14 women and 9 men, mean age 49.8 years) were compared to a sex-, body mass index- and age-matched control group. An increased PAI-1 activity and t-PA concentration was reported in 30% and 66% of patients, respectively\(^56\). There was a correlation between human GH and PAI-1 \((r=-0.59)\) and between IGF-1 and t-PA activity \((r=-0.44)\). High fibrinogen levels (4.0 g/dl) were decreased to 3.2 g/dl following treatment of acromegaly\(^57\). GH-deficient patients seem to also have increased fibrinogen levels and PAI-1 activity. Seventeen patients with adult-onset GH deficiency were studied during two years of treatment with recombinant human GH (12 μg/kg body weight/day)\(^58\). PAI-1 antigen and activity, t-PA antigen levels and α\(_2\)-antiplasmin decreased during replacement therapy \((p<0.05)\). In contrast, FVII, FVIII and antithrombin were not modified\(^58\). Even though apparently unprovoked thromboses have been described, the relation between GH, IGF-I and the coagulation system remains to be clarified\(^59, 60\).

**Other endocrine disorders**

The aetiology of pathological hyperprolactinaemia is diverse: any process interfering with dopamine synthesis, its transport to the pituitary gland or its action on lactotroph dopamine receptors can lead to hyperprolactinaemia\(^53\). Once drugs are excluded, prolactinomas are the most common causes of hyperprolactinaemia. In several conditions such as pregnancy, and oestrogen and antipsychotic therapy, hyperprolactinaemia and an increased risk of VTE co-exist.

A direct effect of prolactin on the coagulation system has not been systematically investigated, but Wallaschofski and colleagues demonstrate that hyperprolactinaemia is a potent co-stimulator of platelet aggregation\(^61\). In a subsequent study the same group shows that patients with VTE have significantly increased plasma prolactin levels in comparison to healthy subjects\(^62\). The mean values of prolactin were 185 ± 60 and 165 ± 50 mU/l in 100 healthy controls and 96 patients with congenital risk for VTE, respectively. In contrast, in 98 patients with VTE but without congenital or acquired risk factors, the mean prolactin value was 285 ± 351 mU/l \((p<0.01)\). Likewise, they found 6 patients with documented VTE in their series of 136 prolactinoma patients\(^62\). The hypothesis that an overactivity of the sympathetic nervous system and increased catecholamine levels may have an influence on haemostasis (platelets, coagulation and fibrinolytic factors, and endogenous anticoagulants) is actually an old topic\(^63\). Since the beginning of the last century investigators observed that parenteral administration of adrenaline hastened blood coagulation in animals and in man\(^64-66\). As recently reviewed, adrenergic infusions increase FV activity, FVIII activity, VWF antigen, t-PA antigen and plasmin-α\(_2\)-antiplasmin complexes, mainly mediated by endothelial β-adrenoceptors (most likely β\(_2\)-receptors), leading to an activation of both the coagulation and fibrinolytic system\(^63; 67\). However, only a few published case reports report an association between pheochromocytoma and venous thrombosis, in which other mechanisms have been claimed, such as paraneoplastic polycythaemia and vascular compression\(^68-70\). These apparently conflicting data could be explained by considering overactivity of the sympathetic nervous system as a physiological mechanism to protect the organism from deleterious bleeding in a ‘fight or flight’ situation\(^63\). Recently, β-receptor blocker propanolol was shown to decrease FVIII:C levels in patients with
venous thrombosis and elevated fVIII:C\textsuperscript{[14]}. Two cohorts of patients with documented deep venous thrombosis and elevated fVIII:C (>175 IU/dl) and healthy volunteers were studied. One of the former and healthy volunteers received propanolol, 40 mg thrice daily, for 14 days. The mean baseline level of FVIII:C was 220 and 102 IU/dl. A significant 23\% reduction of fVIII:C was shown, with a return to initial high levels after propanolol discontinuation. No effect was seen in healthy volunteers. Recent evidence suggests that the renin-angiotensinaldosterone system (RAAS) may participate in the regulation of fibrinolytic activity. Angiotensin II, and probably aldosterone, stimulates PAI-1 expression, whereas angiotensin-converting-enzyme inhibition decreases PAI-1 both in vitro and in vivo\textsuperscript{[72–74]}. Primary aldosteronism is usually secondary to Conn’s adenoma or bilateral adrenal hyperplasia. Prevalence estimates vary from 0.5\% to 2\% of the hypertensive population\textsuperscript{[75]}. Low plasma renin is present, concomitant with elevated aldosterone levels. The effect of primary aldosteronism on the coagulation system has not been systematically investigated. An association with VTE has not been claimed. However, an increased risk of cardiovascular events has recently been shown in patients with primary aldosteronism in comparison to patients with essential hypertension\textsuperscript{[76]}. Overall, there are indications that hyperprolactinaemia, pheochromocytoma and primary aldosteronism may influence elements of the haemostatic balance, however, there is no clear evidence available to suggest that this is clinically relevant.

**Conclusions**

The main findings on the relationship between endocrine disorders and the coagulation system are summarised in Table 1. As we state in the table, the only demonstrated clinically relevant effect of endocrine disorders on the coagulation system is the acquired von Willebrand’s syndrome type I in overt hypothyroidism. Laboratory studies confirm that low levels of VWF are responsible for bleeding episodes that frequently occur in these patients. In Table 2, we summarise the main published study for each endocrine disorder. As it is not a systematic review of the literature, we report the best available evidence.

**Table I. Overall effect on the coagulation system in common endocrine disorders**

<table>
<thead>
<tr>
<th>Endocrine disorder</th>
<th>Coagulation imbalance</th>
<th>Certain clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overt</td>
<td>Probable mild hypercoagulable state</td>
<td></td>
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<tr>
<td>- Subclinical</td>
<td>Possible mild hypercoagulable state</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overt</td>
<td>Certain mild/moderate bleeding diathesis</td>
<td>Acquired von Willebrand syndrome type I</td>
</tr>
<tr>
<td>- Subclinical</td>
<td>Possible mild hypercoagulable state</td>
<td></td>
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<tr>
<td>Hypercortisolim</td>
<td></td>
<td></td>
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<tr>
<td>- Endogenous</td>
<td>Possible moderate hypercoagulable state</td>
<td></td>
</tr>
<tr>
<td>- Exogenous</td>
<td>Probable mild hypercoagulable state</td>
<td></td>
</tr>
<tr>
<td>Abnormal GH levels</td>
<td>Possible mild hypercoagulable state</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorder</td>
<td>Type</td>
<td>Population</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Observational</td>
<td>131 consecutive individuals with low VWF</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Drug interventional</td>
<td>14 and 9 healthy volunteers</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>Endogenous, retrospective</td>
<td>Cushing’s syndrome not (group 1) or receiving (group 2) prophylactic perioperative heparin and/or warfarin</td>
</tr>
<tr>
<td></td>
<td>Exogenous RCT</td>
<td>Healthy man volunteers</td>
</tr>
<tr>
<td>Abnormal GH levels</td>
<td>Acromegaly Case-control</td>
<td>23 patients with active acromegaly compared to sex, BMI, age-matched control group</td>
</tr>
<tr>
<td></td>
<td>GH deficiency in adults</td>
<td>Drug interventional (recombinant human GH 12 μg/Kg body weight/day)</td>
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<tr>
<td></td>
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<tr>
<td>Hyperprolactinaemia</td>
<td>Case-control</td>
<td>Patients with VTE (96 with congenital risk factor; 98 without risk factor) and 100 healthy subjects</td>
</tr>
</tbody>
</table>
Based on these data and the briefly described others, we can undoubtedly conclude that hormones influence the haemostatic system, as each described hormone modifies several plasma coagulation and fibrinolysis markers. Several papers on the relation between the haemostatic system and endocrine dysfunction have important methodological drawbacks that do not allow definitive conclusions. Well-designed clinical studies are therefore necessary for a better definition of the interaction between hormones and the haemostatic system, and, in particular, to assess the clinical relevance of coagulation abnormalities. Therefore future studies should prospectively evaluate both in vivo and in vitro effects, exploring the molecular mechanism of interaction between each hormone and the synthesis, secretion and clearance of coagulation and fibrinolytic factors. In particular, in vitro studies will allow the definition of the level at which the hormones physiologically regulate the coagulation cascade. Moreover, clinical studies should prospectively evaluate the effect of a well-conducted treatment of each endocrine disorder on individual thromboembolic or bleeding risk, and evaluate the clinical relevance of introducing hormone screening tests in patients with a venous thromboembolic episode. Nowadays, VTE is best understood as a ‘multi-causal’ disease in which more than one genetic or environmental condition coincide to produce clinically apparent thrombosis[77]. For this reason, also combinations of weak thromboembolic risk factors could imbalance the coagulation system and provoke thrombotic episodes. Endocrine disorders could be clinically relevant for this reason. If further evidence becomes available, some endocrine disorders will need to be included in the checklist of venous thromboembolic risk factors. In conclusion, endocrine disorders are involved in the pathogenesis of apparently unprovoked bleeding or thrombotic episodes.
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