Hormones, haemostasis, and the risk of thrombosis

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Chapter 2

The influence of pituitary, adrenal, and parathyroid hormones on haemostasis and thrombosis

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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. The aim of the present review is to update the available evidence on the influence of pituitary, adrenal, and parathyroid hormones on the coagulation and the fibrinolytic system, and their possible clinical implications. The literature supports a possible relevant clinical effect of the imbalance between coagulation and fibrinolysis on thrombotic events in endogenous Cushing’s syndrome. An effect on markers of coagulation and fibrinolysis has been shown for hyperprolactinaemia, growth hormone excess or deficiency, exogenous hypercortisolism, pheochromocytoma, primary hyperaldosteronism, and hyperparathyroidism. However, the clinical relevance is still unproven. Until definitive evidence is available, clinicians should be aware of the possibility that endocrine disorders may be risk factors for thrombotic events.

**Introduction**

Haemostasis is a complex biological process that prevents individuals from bleeding and which also should prevent thrombosis. Many factors are responsible for maintaining the haemostatic balance, among which, hormones may directly influence both primary and secondary haemostasis. A wide variety of endocrine disorders have been associated with both mild abnormalities in laboratory coagulation tests and clinical thrombotic or bleeding manifestations. In 2007, we summarised the published evidence on this topic in a narrative review. In the present manuscript, we discuss the influence of common endocrine disorders of the pituitary, adrenal, and parathyroid gland on the coagulation system and their possible clinical effects, providing supplementary data to that we had already reviewed. Thyroid dysfunction and diabetes mellitus have been previously discussed in detail and are outside the scope of this review.

**Literature search**

**Search strategy**

We attempted to identify all recent publications that evaluated the effects of anterior pituitary, adrenal, and parathyroid gland dysfunction on laboratory coagulation and fibrinolytic markers and on clinical thrombotic risk in order to provide supplementary data to that we had already reviewed in 2007. We used the PubMed (2006 to November, Week 2, 2009) electronic database. The following search terms (textwords) were used: Haemostasis, Thrombosis, Bleeding, Prolactin, Hyperprolactinaemia, Growth Hormone, Hypercortisolism, Hypocortisolism, Pheochromocytoma, Aldosterone, Renin, Hyperparathyroidism. The search strategy was developed without any language restriction.

**Study selection**

One author (AS) independently reviewed all selected titles and abstracts. Studies were excluded if the title and abstract were not appropriate for the aim of our review. Selected studies were eligible if they included the following endocrine dysfunctions in adult patients: hyperprolactinaemia, growth hormone (GH) excess or deficiency, endogenous and exogenous hypercortisolism, hypocortisolism, pheochromocytoma, hyperaldosteronism, hyperparathyroidism. Both observational and experimental studies were included. Systematic reviews were also included. Narrative reviews were used only to identify missed references. Case reports, editorials and animal studies were excluded.

**Results**

We identified 289 potentially relevant studies from PubMed. We excluded 276 studies after title and abstract screening using predefined inclusion and exclusion criteria. The following studies were included: two for prolactin, five for GH disorders, four for endogenous hypercortisolism, one for exogenous hypercortisolism, one for catecholamine, and one for hyperparathyroidism. Two extra studies for hyperparathyroidism were identified.
Hyperprolactinaemia

Hyperprolactinaemia can be caused by a prolactin producing adenoma of the pituitary gland. Since the production of prolactin is inhibited by dopamine, also a number of conditions or disorders that influence dopamine synthesis, transport or action can lead to hyperprolactinaemia. Mild hyperprolactinaemia is often caused by drugs, especially antipsychotic therapy and oestrogen, stress or pregnancy. A direct effect of prolactin on coagulation factors has not been investigated, but pregnancy, the use of oestrogen, and antipsychotic therapy have been associated with venous thromboembolism. Wallachoski and colleagues previously described that hyperprolactinaemia is a costimulator of platelet aggregation and that patients with venous thromboembolism without a known risk factor may have higher prolactin levels compared to healthy controls and patients with a congenital risk for thrombosis6. In subsequent studies, this group showed that the prolactin-induced platelet aggregation was present in patients with ischaemic stroke and coronary artery disease4,21. GH substitution therapy11. At baseline, no significant differences in PT, aPTT and fibrinogen thromboplastin time (aPTT) and fibrinogen concentrations before and during one year of parameters in 21 adult patients with severe GHD: prothrombin time (PT), activated partial

Miljic and colleagues investigated the effects of GH administration on basic coagulation with GH. APTT values increased significantly after 12 months of treatment, but only in male

In a study of 22 patients with a recently diagnosed prolactinoma, platelet count, fibrinogen, antithrombin (AT), plasminogen activator inhibitor-1 (PAI-1), and PAI-1/tissue-plasminogen activator (tPA) ratio appeared to by higher, and tissue factor pathway inhibitor (TFPI) lower, compared to control subjects8. We conclude that results of studies on the effect of prolactin on platelets is contradictory, that evidence for an effect on coagulation factors is very limited, and that evidence for an increased venous thrombosis risk is lacking.

Growth hormone (GH) excess and deficiency in adults

Abnormal levels are associated with an increased cardiovascular and cerebrovascular mortality risk22,23. In acromegalic patients, excess of GH and insulin-like growth factor I (IGF-I) causes systemic hypertension, diabetes mellitus, sleep apnea syndrome, hypertrophic cardiomyopathy, and ischaemic coronary disease22,23. GH deficiency (GHD) in adults is responsible for higher blood pressure, dyslipidaemia, and visceral obesity22. An altered fibrinolysis has been claimed in both conditions, but without solid and definitive evidence8. Recently, 5 new studies have been published. Gomez and colleagues studied 10 patients with GHD measuring several cardiovascular parameters8. In particular, they measured fibrinogen, thrombin-antithrombin (TAT) fragments and D-dimer, which were determined by an enzyme-linked immunosorbent assay (ELISA). At baseline and 1 year after GH replacement therapy, no difference in fibrinogen and in TAT fragment concentrations among patients and controls was identified. The same group measured the same markers in 20 adult patients with GH deficiency9. Adding ten patients to their original population did not modify the results. Milijic and colleagues investigated the effects of GH administration on basic coagulation parameters in 21 adult patients with severe GHD: prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen concentrations before and during one year of GH substitution therapy10. At baseline, no significant differences in PT, aPTT and fibrinogen values between GHD and healthy subjects were observed. A significant increase in PT values, which was more pronounced in female subjects, was noted after 6 and 12 months of treatment with GH. APTT values increased significantly after 12 months of treatment, but only in male

patients. Devin and colleagues explored fibrinolysis in 12 GHD patients6. The primary outcome measures were circadian plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels with corresponding tissue-plasminogen activator (tPA) activity values, and fibrinolytic potential by venous occlusion test. Adults with GHD exhibited an unfavourable 24-h fibrinolytic profile characterised by a mean 62% reduction in PAI-1 antigen in the setting of a mean 24% reduction in t-PA activity. Fibrinolytic response was defective in patients with GHD, as demonstrated by a sustained elevation in PAI-1 activity greater than 4 IU/ml after venous occlusion. Finally, Erem and colleagues studied a total of 22 patients with active acromegaly and 22 age-matched healthy controls16. Fibrinogen, activity of factors V, VII, VIII, IX, and X, von Willebrand factor (VWF), AT, protein C, protein S, t-PA, PAI-1, TFPI and thrombin-activatable fibrinolysis inhibitor (TAFI) were measured. Compared with the control subjects, fibrinogen, AT, t-PA, and PAI-1 were increased in patients with acromegaly, whereas protein S activity and TFPI levels were significantly decreased. Plasma TAFI antigen levels did not significantly change in patients with acromegaly compared to controls. Overall, the limited sample size, the lack of an appropriate multivariate analysis, and some conflicting results do not allow for a clear conclusion on the effect of GH excess or deficiency on coagulation and fibrinolysis. The present studies suggest an effect on fibrinolysis, both for acromegaly and for GH deficiency. Altered fibrinolysis may contribute, together with other cardiovascular risk factors, to the increased cardiovascular morbidity and mortality in these patients.

Hypercortisolism

Endogenous hypercortisolism

Cushing’s syndrome, which is characterised by lengthy and inappropriate exposure to excessive concentrations of free glucocorticoids, is an uncommon disease with an estimated incidence ranging from 0.7 to 2.4 per million inhabitants per year, depending on the population studied24. This makes alterations in the coagulation and fibrinolytic system in patients with Cushing’s syndrome extremely difficult to investigate, and even more so for clinical outcomes of venous or arterial thrombosis. However, several authors have attempted to unravel part of the puzzle, although mostly in a limited number of patients.

In a recent systematic review on this subject, we showed high levels of factor VIII, factor IX and VWF with subsequent shortening of APTT and evidence of enhanced thrombin generation in patients with Cushing’s syndrome12. Levels tended to normalise after successful treatment. Small increases in plasminogen activity, t-PA antigen, α2-antiplasmin activity, and PAI-1 activity were observed during glucocorticoid excess, but the net effect on fibrinolytic activity remained uncertain12. Erem and colleagues aimed to further elucidate ways in which endogenous glucocorticoid excess may affect fibrinolysis12. Their study was the first to investigate TAFI in 24 patients with Cushing’s syndrome using healthy gender-and-age matched controls as comparison, but failed to show any significant change. They did, however, confirm earlier observations of a glucocorticoid-induced increase in PAI-1, levels of which positively correlated with midnight serum cortisol concentration in the patients with Cushing’s syndrome. This was further supported by a recent study of Kastelan and colleagues on 33 patients with Cushing’s syndrome and 31 healthy controls. Besides a significant increase in PAI-1, they additionally found high levels of factors II, V, VIII, IX, XI and XII in patients with Cushing’s syndrome13. Finally, Casonato and colleagues showed that VWF promoter haplotypes influence
the corticosteroid-mediated increase in VWF\cite{31}. Exogenous hypercortisolism

Glucocorticoids are anti-inflammatory agents that are prescribed for a vast variety of disorders. They are reportedly used by nearly 1% of the adult population\cite{29}. Considering this widespread use of glucocorticoids, it is important to know whether the same prothrombotic effects observed during endogenous glucocorticoid excess occur in patients on glucocorticoid therapy. For this purpose, several controlled clinical trials have been initiated comparing the administration of moderate- or high-dose glucocorticoids with placebo in healthy volunteers. Most have been published prior to 2007, and have reported divergent results. In short, Jilma and colleagues found high-dose dexamethasone infusion (1.0 mg/kg twice daily for 2 days) to increase circulating VWF levels in 9 healthy males, which is in line with results in endogenous hypercortisolism\cite{32}. They additionally showed a 2-fold increase in VWF mRNA after incubation of human umbilical endothelial cells with high-dose dexamethasone. In a study of Brotman and colleagues, levels of VWF and PAI-1 were unaffected by a 5-day treatment course of dexamethasone 6 mg per day in healthy men, whereas levels of factor VII, VIII and XI significantly increased after glucocorticoid treatment\cite{33}. The absence of an effect on PAI-1 was further supported by 2 other studies using hydrocortisone\cite{32,33}. It has long been hypothesised that glucocorticoids may influence platelet activation and aggregation due to inhibition of prostaglandin synthesis with subsequent reduction of local arachidonic acid concentration on the one hand, and the demonstration of a platelet-located glucocorticoid receptor on the other hand\cite{34,35}. However, a recent study by Baranayi and colleagues failed to show an effect of glucocorticoid use on platelet activation markers\cite{36}.

Despite these conflicting results, glucocorticoid use has been reported to increase the risk of cardiovascular events, with the highest risk observed in the group with the highest average daily dose\cite{37,38}. Moreover, glucocorticoid use has been identified as a risk factor for the development of venous thromboembolism in several epidemiological studies\cite{39,40}. Evidence against a possible prothrombotic effect of exogenous glucocorticoids comes from 3 out of 4 identified randomised controlled trials that investigated, either as primary or as secondary outcome, the number of venous thromboembolic during glucocorticoid treatment compared to placebo, and found no difference between groups\cite{41-44}. It may therefore well be that these epidemiological data more represent an association with the underlying condition necessitating glucocorticoid treatment, e.g. inflammatory disease, than with glucocorticoids itself. However, several in vitro studies have suggested glucocorticoids to synergistically act with inflammation to induce a prothrombotic state\cite{45-46}. This may especially be true for alterations in PAI-1, on the gene of which a glucocorticoid-responsive element with enhancer-like properties has been located\cite{47,48}. In conclusion, although it is not unlikely that exogenous glucocorticoids shift the haemostatic balance towards a prothrombotic state, either alone or in synergy with inflammation, the present literature is ambiguous. Future studies are needed to correctly assess the risk-benefit of glucocorticoids when regarding thrombotic disease.

Hypocortisolism

To the best of our knowledge, no studies exist on coagulation and fibrinolytic parameters in patients with primary adrenal insufficiency, also known as Addison’s disease. However, the mortality rate in patients with Addison’s disease is 2-fold increased (RR 2.19, 95% CI 1.91-2.51), with cardiovascular disease being the major determinant\cite{49}. A number of patients do receive replacement therapy with supraphysiological doses of glucocorticoids, which may increase cardiovascular mortality. Conversely, inadequate glucocorticoid replacement in response to stress and concurrent illness may provide another explanation. Interestingly, the glucocorticoid receptor haplotype 3, which is related to relative cortisol resistance and therefore a more active pro-inflammatory system, has recently been associated with a more than 2-fold increased risk of myocardial infarction (hazard ratio 2.1, 95% CI 1.13-2.07), and an almost 3-fold increased risk of coronary heart disease (hazard ratio 2.6, 95% CI 1.40-4.81)\cite{50}.

Pheochromocytoma

Besides case reports of an association between pheochromocytoma and thromboembolism, recent literature is scarce in elucidating the relationship between an excess of catecholamines and haemostasis\cite{51}. In the past, several data have shown an influence of the sympathetic nervous system and increased catecholamine levels on haemostasis, with in vivo evidence of mild activation of both the coagulation and fibrinolytic system\cite{52}. However, it is uncertain whether this is relevant for patients\cite{53}. There are several reasons for this. Pheochromocytoma is a rare disease, which makes it difficult to detect an increased frequency of thromboembolism, and some of the thromboses described in case reports may also be explained by vascular compression or malignant transformation\cite{54}. But it has also been suggested that overactivity of the sympathetic nervous system is a physiological mechanism that protects the organism from deleterious bleeding in a ‘fight or flight’ situation\cite{55}. Recently, Eggers hypothesised...
that factor XII is a potential link between catecholamine excess and hypercoagulability\(^\text{\textsuperscript{65}}\). The hypothesis is that epinephrine activates platelets by binding to alpha-2A adrenergic receptors. Subsequently, activated platelets convert prebound factor XII to its active form, which then initiates the intrinsic coagulation cascade. Neither tissue factor nor preformed thrombin is required.

**Primary hyperaldosteronism**

Primary aldosteronism is usually secondary to Conn’s adenoma or bilateral adrenal hyperplasia. It is a rare condition, but in hypertensive patients it is detected in 0.5% to 2% of the patients\(^\text{\textsuperscript{56}}\). Low plasma renin is concomitant with elevated aldosterone levels\(^\text{\textsuperscript{56}}\). The effect of primary aldosteronism on the coagulation system has not been systematically investigated. An association with venous thromboembolism has not been claimed. However, clinicians should be aware that an increased risk of cardiovascular events has recently been shown in patients with primary aldosteronism in comparison to patients with essential hypertension\(^\text{\textsuperscript{69}}\). Indeed, past literature suggests a role of the renin-angiotensin-aldosterone system (RAAS) in the regulation of fibrinolytic activity. Angiotensin II, and probably aldosterone, stimulates PAI-1 expression, whereas angiotensin-converting-enzyme inhibition decreases PAI-1 both \textit{in vitro} and \textit{in vivo}\(^\text{\textsuperscript{60-62}}\). Recent studies have been focused on the possible pathophysiological interaction between RAAS and haemostasis, the genetic determinants of this interaction, and on the effect of antihypertensive drugs on coagulation and fibrinolytic markers. RAAS may modify the haemostatic balance through additive mechanisms, such as an increased tissue factor expression in the atherosclerotic plaque stimulated by angiotensin II and an upregulation of the protein-C receptor in the vascular endothelium by aldosterone\(^\text{\textsuperscript{60-62}}\). T-PA and PAI-1 levels are determined by gender and genetic factors involved in the fibrinolytic, RAAS and bradykinin system, in particular, the bradykinin B2 gene, the polymorphisms from the bradykinin receptor (BDKRB2) gene, the angiotensin II type 1 receptor A1166C, and the bradykinin receptor B2 58CT polymorphism\(^\text{\textsuperscript{56-60}}\).

Antihypertensive drugs have a different profile on the coagulation and fibrinolytic system. Angiotensin-converting-enzyme inhibitors have generally been shown to improve the fibrinolytic balance by reducing plasma PAI-1 levels, calcium channel blockers have been reported to increase t-PA activity, and angiotensin receptor blockers seem to be neutral in their effects\(^\text{\textsuperscript{60}}\). Scarcce and conflicting data exist regarding the effects of diuretics and beta-blockers on the fibrinolytic system\(^\text{\textsuperscript{61;62}}\). Among recent studies, we only report one study in detail for its potential clinical relevance. Verhamme and colleagues explored the role of spironolactone in a population-based case-control study of 523 cases with gastric or duodenal ulcer or upper gastrointestinal bleeding and 5230 matched controls\(^\text{\textsuperscript{65}}\). Current use of spironolactone was associated with a 2.7-fold (95% confidence interval 1.2 to 6.0) increased risk of a gastrointestinal event\(^\text{\textsuperscript{65}}\).

**Hyperparathyroidism**

Data on cardiovascular manifestations of primary hyperparathyroidism (PHPT) are inconsistent\(^\text{\textsuperscript{64}}\). However, several recent data suggest an increased cardiovascular morbidity and mortality in PHPT patients\(^\text{\textsuperscript{66-68}}\). Hypertension may be an explanation, but also plasma parathyroid hormone (PTH) levels predict cardiovascular mortality\(^\text{\textsuperscript{69}}\).

Data on haemostasis are scant. A previous study in secondary hyperparathyroidism (SHPT) due to chronic renal failure suggests that PTH does not cause uremic platelet defects\(^\text{\textsuperscript{60}}\). The same lack of effect on platelet function was observed in a small group of PHT patients\(^\text{\textsuperscript{62}}\). Recently, three small case-control studies were published on the influence of PTH on markers of coagulation and fibrinolysis\(^\text{\textsuperscript{60-62}}\). Chertok-Shacham and colleagues showed that levels of PAI-1 were significantly higher among 35 patients with PHPT than among 25 controls\(^\text{\textsuperscript{62}}\). Levels of fibrinogen and D-dimer were similar in patients and controls. Across all subjects PAI-1 was significantly correlated with PTH levels. Erem and colleagues studied 24 PHPT patients and 20 age-matched healthy controls for several coagulation and fibrinolytic markers\(^\text{\textsuperscript{60}}\). They tested fibrinogen, activity levels of factors V, VII, VIII, IX and X, VWF, AT, protein C, protein S, t-PA, PAI-1, TFPI, and TAFI. They showed that FVII, FX activities, and D-Dimer levels were significantly increased in patients with PHPT (p<0.05). T-PA, PAI-1, and PAI-1/t-PA ratios were significantly increased in patients with PHPT (p<0.05), whereas TFPI levels were significantly decreased (p<0.05). Plasma TAFI antigen levels were not significantly different between patients with PHPT and controls.

Unfortunately, due to several methodological drawbacks of the cited studies, no firm conclusion can be drawn. Moreover, no data are available on the clinical impact of these findings.

**Conclusions**

The main effect of the discussed pituitary, adrenal, and parathyroid hormones on the coagulation and fibrinolytic system and its potential clinical implications are summarised in Table 1. As we state in the table, the only endocrine disorder in this review that is clearly associated with an increased risk of VTE, is endogenous Cushing’s syndrome after pituitary or adrenal surgery. The risk of VTE in these patients is comparable to major joint replacement orthopaedic surgery. Whether this justifies routine thromboprophylaxis in patients with Cushing’s syndrome remains to be elucidated.

This update of the literature confirms that pituitary, adrenal, and parathyroid hormones probably influence the haemostatic system, as each described hormone modifies several parameters of coagulation and fibrinolysis\(^\text{\textsuperscript{71;74}}\). However, important methodological drawbacks drastically reduce the strength of evidence and do not allow us to draw definitive conclusions. Well-designed clinical studies are still necessary for a better definition of the interaction between hormones and the haemostatic system. In particular, whether these hormonal alterations are associated with an increased risk of thrombosis.

In the meantime, until definitive evidence becomes available, we should remember that both cardiovascular events and VTE are best understood as “multicausal” diseases in which more than one genetic or environmental condition coincides to produce clinically apparent thrombosis\(^\text{\textsuperscript{72}}\). For this reason, also weak thromboembolic risk factors may be clinically relevant, especially if treatable such as endocrine disorders.
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<tr>
<th>Endocrine disorder</th>
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<td>Primary hyperparathyroidism</td>
<td>Probable mild hypercoagulable state</td>
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VTE indicates venous thromboembolism; and GH, growth hormone.

References

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