MECHANISMS IN ENDOCRINOLOGY

The spectrum of haemostatic abnormalities in glucocorticoid excess and defect

Andrea M Isidori¹,⁎, Marianna Minnetti¹,2, Emilia Sbardella¹, Chiara Graziadio¹ and Ashley B Grossman²,⁎

¹Department of Experimental Medicine, Sapienza University of Rome, Viale del Policlinico 155, Rome 00161, Italy and ²Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford, Headington, Oxford OX3 7LE, UK

*(A M Isidori and A B Grossman contributed equally to this work)

Correspondence should be addressed to A M Isidori or A B Grossman
Emails andrea.isidori@uniroma1.it or ashley.grossman@ocdem.ox.ac.uk

Abstract

Glucocorticoids (GCs) target several components of the integrated system that preserves vascular integrity and free blood flow. Cohort studies on Cushing’s syndrome (CS) have revealed increased thromboembolism, but the pathogenesis remains unclear. Lessons from epidemiological data and post-treatment normalisation time suggest a bimodal action with a rapid and reversible effect on coagulation factors and an indirect sustained effect on the vessel wall. The redundancy of the steps that are potentially involved requires a systematic comparison of data from patients with endogenous or exogenous hypercortisolism in the context of either inflammatory or non-inflammatory disorders. A predominant alteration in the intrinsic pathway that includes a remarkable rise in factor VIII and von Willebrand factor (vWF) levels and a reduction in activated partial thromboplastin time appears in the majority of studies on endogenous CS. There may also be a rise in platelets, thromboxane B2, thrombin–antithrombin complexes and fibrinogen (FBG) levels and, above all, impaired fibrinolytic capacity. The increased activation of coagulation inhibitors seems to be compensatory in order to counteract disseminated coagulation, but there remains a net change towards an increased risk of venous thromboembolism (VTE). Conversely, GC administered in the presence of inflammation lowers vWF and FBG, but fibrinolytic activity is also reduced. As a result, the overall risk of VTE is increased in long-term users. Finally, no studies have assessed haemostatic abnormalities in patients with Addison’s disease, although these may present as a consequence of bilateral adrenal haemorrhage, especially in the presence of antiphospholipid antibodies or anticoagulant treatments. The present review aimed to provide a comprehensive overview of the complex alterations produced by GCs in order to develop better screening and prevention strategies against bleeding and thrombosis.

Introduction

The haemostatic–coagulation system is the first line of defence against trauma, and it is finely tuned to prevent excessive bleeding or thrombosis (1). It is a complex but highly regulated system designed to stabilise the free flow of blood and blood constituent while also preserving the integrity of the vasculature. A broad variety of endocrine disorders have been associated with hematologic abnormalities (2) and unbalanced coagulation–fibrinolysis (3). Glucocorticoids (GCs) have potent anti-inflammatory effects and play an important role in haemostasis (4, 5). Endogenous hypercortisolism is well known to increase cardiovascular mortality (6, 7), but although hypercortisolism was initially thought to be purely a consequence of high blood pressure, diabetes and hyperlipidaemia, it has
more recently been linked to an increased risk of thrombosis. In addition, several studies have also found that patients on corticosteroid replacement therapy show increased mortality, and the authors have tentatively attributed this increased mortality to supraphysiological GC replacement therapy (8, 9, 10). Thus, now seems to be an appropriate time to review and summarise the available data on the influence of endogenous and exogenous GCs on the haemostatic-coagulation system and to consider the relevance of that system to clinical disorders and their therapy.

**Endogenous hypercortisolism**

Numerous alterations of coagulation and fibrinolysis parameters have been described in patients with endogenous Cushing’s syndrome (CS; Fig. 1) independently of its cause (11, 12, 13). However, many studies have failed to discriminate between the effects of GCs *per se* and the secondary effects of obesity and other manifestations of CS (14, 15). Furthermore, when CS is cured, cortisol levels normalise, but hypercoagulability may not completely disappear (5). However, patients with active disease after surgery clearly maintain a higher thrombotic risk than do those who are cured (16). It is therefore likely that an acute direct role of GCs may give rise to a more general, indirect chronic effect on endothelial function and atherosclerosis.

**Platelet count**

Platelets have been recognised to play a crucial role in the interface between coagulation and inflammation, and platelet adherence at the site of vascular injury is an important step in the early phase of thrombogenesis (17). In 1983, Sato *et al.* were the first to describe a significant increase in the number of platelets in patients with CS as compared to control obese patients (18) or age-matched healthy controls (19).

**Platelet activation**

The serum/glucocorticoid regulated kinase 1 (SGK1) is a powerful regulator of ORAI1 protein in platelets, and ORAI1 is the key mediator of the store-operated Ca$^{2+}$ entry that is required for platelet activity. A recent study showed that SGK1 expression is stimulated by a wide variety of hormones, including GCs and mineralocorticoids (20). A previous systematic review failed to show significantly altered platelet aggregation in patients with CS, although the studies reviewed were of low quality (21). By contrast, in 2014, Karamouzis *et al.* (21) described enhanced platelet aggregation in patients with CS: thromboxane A2 (TXA2) has been shown to cause platelet release, activation and accumulation and to exert potent vasoconstrictive effects (22); TXB2, which represents a reliable indicator of TXA2 biosynthesis, was significantly higher (*P*<0.01) in patients affected by CS (21). It therefore seems likely that there is a minor, albeit significant, increase in platelet functionality in CS.

**von Willebrand factor**

von Willebrand factor (vWF) is a multimeric glycoprotein that mediates platelet adhesion at the site of vascular damage and that stabilises factor VIII (FVIII) (23). Plasma levels of vWF were found to be markedly increased in several studies (16, 24, 25, 26, 27). Chopra *et al.* (28) found that vWF was elevated in 40.9% of endogenous CS as compared to healthy volunteers. Considering that vWF concentration is related to ABO blood grouping, Manetti *et al.* (16) found that both untreated CS patients with blood group 0 (*P*=0.007) and blood group non-0 (*P*<0.0001) had higher values of vWF. CS is also characterised by the presence of unusually large vWF multimers, which are recognised to have the greatest haemostatic capacity (24). The high prevalence of specific polymorphisms in the VWF gene (promoter haplotypes) was found to be associated with higher vWF levels in patients with CS as compared to controls (29). Casonato *et al.* (24) studied the clotting profile in patients with CS before and after surgical treatment and found that plasma levels of vWF decreased after surgery and normalised within 12 months.

**Coagulation cascade**

Prothrombin time (PT) assesses the integrity of the extrinsic clotting cascade, and it is mostly maintained in patients with CS (27, 30, 31), although increased PT values as compared to healthy control subjects were recently noted in two studies (19, 32). However, a reduction in activated partial thromboplastin time (aPTT), a marker of the intrinsic system, in CS has been repeatedly described (16, 19, 24, 25, 26, 33, 34, 35). Recently, Gadelha *et al.* – using the rotation thromboelastometry (ROTEM) methodology – showed that the beginning of the clot formation is the altered step in the intrinsic pathway of CS patients (35). The most remarkable change in the intrinsic pathway is the significant increase in FVIII levels (24, 25, 26, 33, 34, 35, 36). Several coagulation markers have been found to be

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marginally increased in CS (e.g. factor II, factor V, factor IX, factor XI and factor XII) (33), but only the increase in FVIII is consistently and markedly elevated (37). Elevated FVIII levels expose to clinically relevant thrombophilia, and it has been demonstrated that high FVIII is a dose-dependent risk factor for venous thromboembolism (VTE) (38). FVIII decreases slowly after the normalisation of elevated GC levels and becomes normal 3–4 months later (39). One of the most commonly used markers of thrombin (factor II) generation is the presence of thrombin–antithrombin (TAT) complexes; increased TATs have been described in patients with CS in two studies (16, 27). Fibrinogen (FBG, factor I) is an inflammatory marker that contributes to thrombotic risk (40). Increased FBG levels have been found in most (16, 19, 26, 31, 34, 41), but not all (25), studies on CS. Patients with untreated CS had higher values of D-dimer (35), although D-dimer concentrations were not significantly different between patients before and after surgery (16).

**Coagulation regulators: protein C, protein S and ATIII**

Uncontrolled blood coagulation is potentially dangerous, and redundant regulatory mechanisms are present at each level of the pathway. The protein C anticoagulant inhibits the procoagulant agents FVIIIa and factor V, whereas protein S supports the anticoagulant activity of activated protein C in the degradation of factor Va and FVIIa (42). Unexpectedly, Kastelan et al. (33) showed that both protein C and protein S were significantly higher in CS.

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**Figure 1**

Effects of endogenous hypercortisolism (blue circles with white arrows) on coagulation cascade, platelets, regulators and fibrinolysis. aPTT, Activated partial thromboplastin time; FVIII, Factor VIII; FVIIIa, Activated factor VIII; PAI1, Plasminogen activator Inhibitor-1; PT, Prothrombin time; TAFI, Thrombin-activatable fibrinolysis inhibitor; TXA2, Thromboxane A2; tPA, Tissue Plasminogen Activator; vWF, Von Willebrand factor.
Koutroumpi et al. (32) compared 33 patients with CS to a group of 28 patients that were matched for the features of the metabolic syndrome and to 31 healthy volunteers, and they found that protein C and protein S were both significantly higher in CS as compared to either groups. Even in patients with subclinical CS, higher levels of protein C activity and free protein S have been described (43). However, not all studies have confirmed differences in the activity of protein C and protein S (16, 19), which suggests that alternative mechanisms could be involved. AT is a serine protease inhibitor (serpin) that plays an important role in the regulation of coagulation as the major inhibitor of thrombin (factor IIa) and factor Xa (44). Many authors have described increased AT levels in CS patients (16, 19, 32, 33). These changes in anticoagulant factors are difficult to explain in terms of the generalised alteration in procoagulant activity just noted, but they may in part constitute a compensatory response to the prothrombotic processes (32, 33, 38, 43). This should be taken into account in the treatment strategy.

Fibrinolysis

Fibrinolysis is the process that prevents blood clots from growing, which thus limits the haemostatic process and aids in recovery from thrombosis (45). CS is correlated with increased levels of the natural fibrinolytic inhibitors (plasminogen activator inhibitor type 1 (PAI1), thrombin-activatable fibrinolysis inhibitor (TAI1) and α2-antiplasmin) (34). This defective fibrinolytic potential could contribute to the hypercoagulability of CS. PAI1 is the main inhibitor of the fibrinolytic system, and a significant increase in PAI1 activity has been described in many studies (16, 19, 25, 26, 33, 34). However, a systematic review suggests that both inhibitors and stimulators of fibrinolysis (i.e., plasminogen activity) were found to be increased in patients with CS (30), and it is thus difficult to differentiate between changes that are causal and those that are compensatory.

Bleeding risk

The ‘bleeding time’ is mostly unchanged in patients with CS (30). Hypercortisolism is associated with bruising and poor wound healing, although these manifestations are most probably a result of alterations in the synthesis of key skin components rather than a specific coagulation disorder (46). Between 1994 and 2008, 114 patients with adrenal CS and subclinical CS were studied during and after laparoscopic adrenalectomy: only one single patient developed post-operative bleeding. This finding was concordant with the incidence of bleeding in patients that underwent laparoscopic adrenalectomy for causes other than adrenal CS (47). Pituitary tumour apoplexy is a rare clinical syndrome that often occurs spontaneously as a result of haemorrhage and/or infarction into a pituitary macroadenoma; CD arises in most cases within a microadenoma, and it is thus not unexpected that pituitary apoplexy in CD is rare (48).

Venous thromboembolism

In general, chronic GC excess can influence all three factors of the Virchow triad: endothelial dysfunction, haemodynamic changes and hypercoagulability (12). In a systematic review, Van Zaane et al. showed that VTE events were the cause of death in 0–1.9% of patients with CS. There was a 1.9–2.5% risk not provoked by surgery, whereas the risk of post-operative VTE varied between 0 and 5.6% (30). The risk of VTE in patients with CD is comparable to the risk that follows major orthopaedic surgery (5).

Antithrombotic prophylaxis in CS

Boscaro et al. retrospectively analysed post-operative thromboembolic events in patients with CS that were evaluated in the period from 1982 to 2000. Before anticoagulant prophylaxis was routinely used in their centre, they had a 10% mortality resulting from VTE events and 10% vascular morbidity (26). They reported that since post-operative antithrombotic prophylaxis (unfractionated heparin at doses of 15 000–22 500 U/day for at least 2 weeks and warfarin for at least 4 months) had become their standard of care, morbidity and mortality resulting from VTE events fell to 6 and 0.4% respectively (26). Furthermore, Trementino et al. (13) have suggested the routine use of antithrombotic prophylaxis even during inferior petrosal sinus sampling as well as during the immediate post-operative period after transphenoidal or adrenal surgery.

To date, there have been no prospective placebo-controlled trials to evaluate the effects of thrombo prophylaxis in patients with CD.

Conclusions regarding endogenous hypercortisolism

There is now ample evidence that CS leads to a prothrombotic state mainly as a result of an increase in vWF and FVIII, along with a decrease in fibrinolytic factors.
Glucocorticoids in haemostasis

Those who do not develop a Cushingoid appearance (51). A greater incidence of cardiovascular events as compared to features of iatrogenic CS have also been shown to exhibit (11). Patients that receive systemic GT and develop clinical of GCs may induce the development of an iatrogenic CS. Because of the widespread use of GT, an increased risk of thrombosis may be carried by up-regulating procoagulants, down-regulating anticoagulants and suppressing fibrinolysis (52), and one might thus anticipate a lower number such events. On the other hand, the thrombotic risks in GT-treated patients may reflect the severity of the underlying diseases for which GT is prescribed (53). Because of the widespread use of GT, an increased risk of thrombosis may carry profound clinical and socioeconomic implications. Features of exogenous hypercortisolism are depicted in Fig. 2 using a diagram that is similar to the one used for endogenous CS, which allows for a direct comparison. In addition, peculiar changes that occurred when steroids were used in the context of inflammatory disorders have been reported.

Exogenous hypercortisolism

Glucocorticoid therapy (GT) is frequently used for a wide range of autoimmune, inflammatory and neoplastic disorders, and oral GCs are used by ~1% of the adult population in the UK (49). Prolonged or high-dose GT has multiple side effects (50), and the chronic administration of GCs may induce the development of an iatrogenic CS (11). Patients that receive systemic GT and develop clinical features of iatrogenic CS have also been shown to exhibit a greater incidence of cardiovascular events as compared to those who do not develop a Cushingoid appearance (51). However, inflammation has been shown to modulate thrombotic responses by up-regulating procoagulants, down-regulating anticoagulants and suppressing fibrinolysis (52), and one might thus anticipate a lower number of such events. On the other hand, the thrombotic risks in GT-treated patients may reflect the severity of the underlying diseases for which GT is prescribed (53). Because of the widespread use of GT, an increased risk of thrombosis may carry profound clinical and socioeconomic implications. Features of exogenous hypercortisolism are depicted in Fig. 2 using a diagram that is similar to the one used for endogenous CS, which allows for a direct comparison. In addition, peculiar changes that occurred when steroids were used in the context of inflammatory disorders have been reported.

Platelet count

The GC receptor has been described in human platelets (50). Furthermore, megakaryocytes express steroid receptors, which may constitute an autocrine loop in the formation of proplatelets, the cytoplasmatic protrusions within which nascent platelets are assembled (54). High-dose dexamethasone (DEX) has been shown to increase platelet counts in healthy men by a maximum of 18% above baseline (55). According to one study, platelet count was decreased in patients with polymyalgia rheumatica after several years of prednisolone treatment (56). Most physicians routinely use systemic corticosteroids, such as oral prednisone, for the treatment of thrombotic thrombocytopenic purpura (TTP), and around 60–80% of patients respond with an elevation in platelet count. Several mechanisms have been described for the action of corticosteroids in TTP, including a reduction in autoantibody production, a stabilisation of platelets and endothelial cell membranes and a suppression of reticulo-endothelial phagocytic activity (57, 58, 59, 60, 61). However, this is clearly quite a different situation to that wherein patients with normal platelet numbers and function are subject to GT.

Platelet activation

Several studies have reported contradictory results concerning the effect of GC treatment on platelet function. Most of the discrepancies between the studies can be attributed to the dose amount and the steroid used as well as the experimental design. Ex vivo measured platelet aggregation is dose-dependently inhibited by DEX treatment (62). Van Giezen et al. (63) investigated the effect of oral DEX administration in rats and found that the primary effect on haemostasis was an inhibition of arterial thrombosis via lowered platelet aggregation; the latter effect, however, was lost at higher doses of steroids because of decreased fibrinolytic activity. Conventional clinical doses of prednisone (80 mg given orally for 2 days) and the administration of DEX (15 mg for 4 days) do not appear to impair platelet function in healthy subjects (64, 65). P-selectin is an adhesion molecule that is stored within platelet α-granules. P-selectin is important in the recruitment and aggregation of platelets at injured sites, and elevated baseline levels are associated with increased cardiovascular risk (66). A double-blind, randomised, placebo-controlled study showed that soluble P-selectin rose 48 h after the infusion of a therapeutic dose of DEX (0.04 and 1.0 mg/kg b.i.d. on 2 days) in healthy men (P=0.017) (55), whereas another study on healthy subjects randomised to hydrocortisone (HCT) (daily dose 40 mg) or placebo on 7 consecutive days found no HCT-related changes in platelet activation or P-selectin (67).

von Willebrand factor

vWF levels were increased in in vitro studies when GCs were used in healthy volunteers, whereas a decrease in vWF levels has been described when GCs are used in the context of inflammation (Fig. 2). Two in vitro studies
showed that GCs may increase the release of VWF and mRNA expression of VWF from cultured human umbilical vein endothelial cells (68, 69). A positive correlation was found between plasma cortisol and vWF levels, with a $1 \mu g/ml$ rise in plasma cortisol causing a $2.52$ IU/dl increase in vWF (28). In contrast, a recent systematic review found that in patients with inflammatory disease (e.g. giant cell arteritis), GCs lowered vWF levels (70, 71, 72, 73). An acute high-dose of GC has been associated with a rapid activation of endothelial nitric oxide (NO) synthase via a direct non-genomic effect, which in turn enhances NO release (74). NO exerts a negative feedback on vWF secretion (75). Two studies investigated the effect of 1–3 mg DEX twice daily for 5–6 days in healthy males and found no differences in vWF levels (76, 77). On the contrary, therapeutic doses of DEX (0.04 or 1.0 mg/kg for 2 days) given parenterally to healthy men were shown to increase levels of vWF after 24 and 48 h ($P=0.011$) (55).

**Coagulation cascade**

A recent study demonstrated that DEX prophylaxis in paediatric patients that underwent cardiopulmonary bypass for heart surgery was associated with decreased aPTT ($P=0.025$) (78). A rise in several coagulation factors was shown in a trial that randomised 24 healthy volunteers to receive either 3 mg DEX twice daily or placebo for 5 days. The authors found increased levels of FVIII; PAI1, Plasminogen activator Inhibitor-1; PT, Prothrombin time; TAFI, Thrombin-activatable fibrinolysis inhibitor; TXA2, Thromboxane A2; tPA, Tissue Plasminogen Activator; vWF, Von Willebrand factor.
factor VII, FVIII, factor XI and FBG (77). Rat liver cells in vitro have been shown to respond to DEX by increasing the synthesis of FBG mRNA, whereas no induction of the FBG-polypeptide mRNA was observed in vivo at various times after the injection of different doses of GCs into the livers of rats (79). When GCs are used in the setting of increased inflammatory activity, they significantly decreased FBG (56, 71, 78, 80). This biphasic response is explained by the dose-dependency of GC anti-inflammatory effects on the acute phase response (including FBG) (70) (Fig. 2).

Coagulation regulators: protein C, protein S and ATIII
All of the regulators have been described as being increased in patients with systemic lupus erythematosus under chronic prednisone treatment (81) and in patients with other autoimmune diseases (82). A recent study proposed that GC modulation of ATIII could represent a low-cost alternative to exogenous ATIII supplementation in several non-specific conditions when endogenous AT activity is decreased (e.g. in the early post-operative period following major surgery) (83).

Fibrinolysis
The use of GT in an inflammatory context has been shown to induce alterations in fibrinolysis, which causes a significant rise in PAI1, the main inhibitor of the fibrinolytic system, whereas this has not been described in healthy volunteers using GCs. GC responsive elements have been found in the promoter regions of the Tafi and Pai1 genes in rat hepatoma cells (84, 85). Moreover, DEX has been shown to enhance PA11 expression in cultured human adipose tissue (86). Van Zaane et al. suggested that when GCs are used in the context of inflammation, they inhibit fibrinolytic activity, mainly because of increased PAI1 activity and levels. In addition, during inflammation, GCs inhibit the surgery-induced increase in tPA (70). Darmon et al. (87) showed that moderate hypercortisolism equivalent to that observed in response to mild stress induces an elevation in circulating PAI1 levels that is significantly greater in obese subjects than in lean subjects. In a controlled clinical trial performed in healthy subjects that received oral metyrapone followed by i.v. saline plus low- or high-dose HCT, short-term variations in plasma GC levels did not alter the systemic fibrinolytic balance or endothelial function (88); this was confirmed in two studies that showed no significant changes in the PAI1, tPA or D-dimer levels of healthy men treated with 3 mg DEX vs placebo for 5 days or with 1 mg DEX vs placebo for 6 days (76, 77).

Bleeding risk
Some studies have suggested a possible association between DEX and an increased risk of post-operative haemorrhage; however, a meta-analysis excluded an association between DEX administration and post-operative bleeding in children that underwent tonsillectomy or adeno-tonsillectomy (89). In their systematic review, Sauerland et al. (90) found that a perioperative single shot of high-dose methylprednisolone was not associated with increased gastrointestinal bleeding.

VTE events
Cosgriff et al. first suggested a state of hypercoagulability in patients that were treated with cortisone (91, 92). Isolated cases of cerebral VTE after i.v. steroid pulse therapy have been reported in patients with multiple sclerosis (93). A large prospective cohort study in 6550 UK patients with VTE using the General Practice Research Database showed a threefold increased risk of VTE in current users of oral GCs as compared to non-users (94). A Danish population-based case–control study found that systemic GC increased VTE risk among present (incidence rate ratio (IRR) = 2.31), new (IRR = 3.06), continuing (IRR = 2.02) and recent (IRR = 1.18) steroid users but not among former users (IRR = 0.94). Oral GCs are associated with a higher risk of VTE than the injectable form is, possibly because some injections are used for intra-articular treatment, which has lower bioavailability (95). Finally, an association between oral GCs and a fourfold increased risk of pulmonary embolism, especially during the first month of exposure, was reported in a case–control study using a Dutch population-based pharmacy registry (96). Thus, there appears to be little doubt that patients with exogenous hypercortisolism have a higher risk of VTE, and that risk is as high as that for patients with endogenous CS.

Conclusions regarding exogenous hypercortisolism
Although there are variable changes in thrombotic factors after the acute short-term administration of GCs, longer-term use is complicated by the effects on the underlying disease process as well as by specific changes that result from the GCs. However, there appears to be solid agreement that long-term use is associated with a
significant increase in VTE. Yet, dedicated guidelines for preventing VTE in long-term GC use are lacking.

**Hypocortisolism**

Adrenal insufficiency (AI) is the clinical manifestation of insufficient GC production or action. The cardinal symptoms of AI, as first described by Thomas Addison in 1855, include weakness, fatigue, abdominal pain, weight loss, anorexia, orthostatic hypotension and salt craving; characteristic hyperpigmentation of the skin occurs with primary adrenal failure. Signs or symptoms related to coagulation disorders are not commonly described in AI (97), despite the fact that increased mortality from cardiovascular disorders has been reported. AI is not usually complicated by thrombotic or bleeding episodes; however, neither in vitro nor in vivo studies have been performed to explore these aspects (98). To date, no studies that describe platelet count or function, vWF, coagulation cascade, regulators or fibrinolysis have been performed. What does seem clear is that various coagulation disorders may lead to AI, and these will be the focus of the present section.

**Primary AI**

Primary AI results from disease that is intrinsic to the adrenal cortex. Not infrequently, primary AI is a consequence of bilateral adrenal haemorrhage that results from antiphospholipid antibody syndrome (APLS), anticoagulant use, disseminated intravascular coagulation (97, 99) and immune-mediated heparin-induced thrombocytopenia (HIT) (100).

APLS, also variously known as Hughes syndrome, is a systemic, autoimmune, acquired disorder characterised by the association of pregnancy morbidities and/or VTE and/or arterial thrombosis with the detection of autoantibodies to phospholipids (101). Addison’s disease has been reported in only 0.4% of patients with confirmed APLS; conversely, APLS is diagnosed in <0.5% of all patients with Addison’s disease. (102). Furthermore, 10–26% of APLS patients can have adrenal failure in catastrophic form. Adrenal vein thrombosis, adrenal haemorrhage and autoimmune mechanisms have been proposed to be pathogenic factors for AI (103). The main hypothesis suggests that the primary event is bilateral adrenal vein thrombosis, which results in bilateral haemorrhagic infarction of the adrenal glands. Another theory presumes that bilateral spontaneous (without thrombosis) adrenal haemorrhage is the main event (103). Primary APLS presenting as AI is very rare, but it should always be considered in a young female patient that presents with abdominal pain and haemodynamic instability (104) or in any patient with adrenocortical failure of unclear pathogenesis (105).

Anticoagulant-associated adrenal haemorrhage is an infrequent complication of anticoagulant therapy, but it can be successfully treated if it is recognised (106). HIT is characterised by the development of platelet-activating IgG antibodies against the platelet factor 4–heparin complex, which predisposes to VTE or arterial thromboembolism or heparin skin necrosis (107). HIT occurs in up to 1% of patients that receive unfractionated heparin for post-operative antithrombotic prophylaxis (108). The mechanism of HIT-induced adrenal haemorrhage begins with adrenal vein thrombosis triggered by platelet activation, endothelial injury and coagulation system activation (100).

Soran et al. reported a case of bilateral adrenal haemorrhage secondary to thrombosis in a patient who was later found to have a heterozygous factor V Leiden defect. Anticoagulation may cause bilateral adrenal haemorrhage, with subsequent permanent damage of both adrenals that results in acute Addisonian crisis (109). Derex et al. (110) reported a case of spontaneous intracerebral haemorrhage that occurred in a young woman with undiagnosed Addison’s disease; the authors concluded that primary AI should be considered as a rare potential cause of non-hypertensive intracerebral haemorrhage.

**Secondary AI**

One of the possible causes of hypopituitarism is Sheehan’s syndrome, which is a result of ischaemic pituitary necrosis caused by severe postpartum haemorrhage. Several patients with Sheehan’s syndrome have demonstrated acquired FVIII and vWF deficiency, thrombocytopenia, shorter PT and aPTT and higher FBG levels (111). The incidence of hypopituitarism after aneurysmal subarachnoid haemorrhage is unclear because of conflicting reports in the literature (112, 113).

In 2002, Setian et al. (114) described a 9-year-old boy with hypopituitarism and factor V, FVIII and vWF deficiency, but no other case reports have been described. Peacey et al. (115) found that an increased dose of HCT for 2 weeks did not significantly affect PAI1, tPA or FBR levels in patients with hypopituitarism.

**Overall conclusions**

Several defects in the coagulation–fibrinolytic system have been described among patients affected by GC disorders.
A remarkable rise in FVIII and vWF levels and a reduction in aPTT have been confirmed in many studies as has a rise in the number of platelets, TXB2 levels, TAT complex level and FBG levels. In many studies, increased activity of the endogenous coagulation inhibitors has been described, probably as a compensating mechanism in the face of increased haemostasis. Impaired fibrinolytic capacity, which is reflected especially by elevated plasma concentration of PAI1, has also been described (Supplementary Table 1, see section on supplementary data given at the end of this article). The changes lead to a very significant increase in VTE. Haemostatic abnormalities seem to persist after treatment in CS patients, and this suggests that increased risk in thrombosis might be a result of the persistence of abdominal obesity, diabetes, hypertension and dyslipidaemia. CS should be included in the checklist of VTE risk factors, and it is important to recognise that patients with CS are at high risk of VTE, especially perioperatively. Based on these data, antithrombotic prophylaxis in CS patients that undergo adrenal and transphenoidal surgery is highly recommended.

Concerning GC treatment, during active inflammation, GCs decrease vWF and FBG levels, which apparently reduces the risk of thrombosis, but they also reduce fibrinolytic activity, which increases PAI1 levels. There is an increased risk of VTE in current GC users as compared to non-users, but GCs are prescribed to treat conditions that involve inflammation, which by itself makes patients more prone to VTE. People treated with GCs who develop iatrogenic CS should be targeted for early screening and management of thrombosis risk factors. In healthy men, in the absence of other influencing factors, the alterations in coagulation balance depend on the dose and type of GCs administered (Supplementary Table 1). Additional studies should evaluate the clinical relevance of introducing coagulation-based tests in patients before and during short-term and long-term GC treatment.

Primary AI does not seem to present a major challenge to the haemostatic system, although proper studies are required to test this. By contrast, AI may present as a consequence of bilateral adrenal haemorrhage, especially in patients with APLS or who are therapeutically anticoagulated. In summary, GCs could affect nearly every player that is involved in haemostasis, and for all subjects with prolonged hypercortisolaemia, but most importantly for patients with CS, a consensus on the type, dose and duration of anticoagulation is urgently needed in order to prevent major VTE and a potentially avoidable lethal outcome.
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