Adverse effects of glucocorticoids: coagulopathy

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Abstract

Hypercortisolism is associated with various systemic manifestations, including central obesity, arterial hypertension, glucose intolerance/diabetes mellitus, dyslipidemia, nephrolithiasis, osteoporosis, gonadal dysfunction, susceptibility to infections, psychiatric disorders, and hypercoagulability. The activation of the hemostatic system contributes to the development of atherosclerosis and subsequent cardiovascular morbidity and mortality. Previous studies have identified an increased risk of both unprovoked and postoperative thromboembolic events in patients with endogenous and exogenous Cushing’s syndrome (CS). The risk for postoperative venous thromboembolism in endogenous CS is comparable to the risk after total hip or knee replacement under short-term prophylaxis. The mechanisms that are involved in the thromboembolic complications in hypercortisolism include endothelial dysfunction, hypercoagulability, and stasis (Virchow’s triad). It seems that at least two factors from Virchow’s triad must be present for the occurrence of a thrombotic event in these patients. Most studies have demonstrated that this hypercoagulable state is explained by increased levels of procoagulant factors, mainly factors VIII, IX, and von Willebrand factor, and also by an impaired fibrinolytic capacity, which mainly results from an elevation in plasminogen activator inhibitor 1. Consequently, there is a shortening of activated partial thromboplastin time and increased thrombin generation. For these reasons, anticoagulant prophylaxis might be considered in patients with CS whenever they have concomitant prothrombotic risk factors. However, multicenter studies are needed to determine which patients will benefit from anticoagulant therapy and the dose and time of anticoagulation.

Introduction

Patients with chronic hypercortisolism present a variety of systemic manifestations that are associated with increased cardiovascular risk, such as abdominal adiposity, arterial hypertension, insulin resistance/impaired glucose tolerance/diabetes mellitus (DM), dyslipidemia, and hypercoagulability (1, 2, 3).

The mortality rates in Cushing’s syndrome (CS) are about two times higher than those in the general population.
population, whereas the mortality from cardiovascular diseases (CVDs) is even higher (3). Myocardial infarction, cerebrovascular disease, congestive heart failure, and venous thromboembolism (VTE) appear to be the main causes of mortality (4).

Recent clinical studies have indicated various abnormalities in coagulation and fibrinolysis parameters in patients with endogenous (5, 6, 7) and exogenous hypercortisolism (8, 9, 10) that contribute to the development of thromboembolic events, atherosclerosis (11), and subsequent cardiovascular morbidity and mortality (12, 13, 14).

A literature review was undertaken from July 2013 to December 2014, and it comprised of studies that evaluated the abnormalities of coagulation and fibrinolysis parameters in patients with CS. Several studies have assessed hemostatic parameters in CS since the early 1950s (15). Nevertheless, only articles that were written in English, original studies, review articles, and current guidelines were included. Case reports, in vitro studies, and animal model experiments were excluded.

Clinical data on the association between exogenous glucocorticoids (GC) and VTE are sparse, and these studies have focused on specific populations. Although patients that receive GC therapy usually suffer from a primary disease that may have a negative influence on coagulation, endogenous CS is not associated with an underlying primary condition that is known to directly affect the risk of thrombosis. Moreover, in studies on GC use and VTE risk in the general population, no data on patient compliance regarding prescribed GC are available. Thus, endogenous CS is a suitable clinical model for investigating the pure effects of cortisol excess on hemostasis, attenuating other confounding factors. The vast majority of the studies that were included in the present review describe the association between endogenous hypercortisolism and hypercoagulability.

The aim of the present review is to report the alterations in the coagulation system in patients with endogenous and exogenous CS, to outline their potential clinical consequences, and to discuss anticoagulant prophylaxis.

**Physiology of coagulation and fibrinolysis**

**Primary hemostasis: platelet activation**

When the endothelium is damaged, the underlying collagen is exposed to circulating platelets that bind directly to collagen through collagen-specific glycoprotein (GP) Ia/IIa surface receptors. This adhesion is further strengthened by von Willebrand factor (vWF), which is released from the endothelium and from the platelets. The vWF forms additional links between the platelets, GP Ib, and collagen fibrils. These interactions also activate the platelets. Activated platelets release into the plasma ADP, serotonin, platelet activation factor (PAF), vWF, platelet factor 4, and thromboxane A2 (TXA2). These factors in turn activate additional platelets. The activated platelets change shape from spherical to stellatem and the fibrinogen cross-links with GP IIb/IIIa, which aids in the aggregation of adjacent platelets (Fig. 1) (16).

**Secondary hemostasis: the coagulation cascade**

Coagulation is the process by which blood forms fibrin clots. There are two important pathways that lead to fibrin formation: the extrinsic pathway and the intrinsic pathway. The extrinsic pathway is initiated after tissue factor (TF) expression, a process that occurs after vascular injury. The TF binds to factor VII in the presence of ionized calcium, which results in the activation of factor VII (VIIa). The TF-factor VIIa complex activates factor IX to factor IXa and factor X to factor Xa. Furthermore, this complex activates additional factor VII (Fig. 2) (17).

In the intrinsic pathway, contact activation stimulates the formation of factor XIa from factor XII in the presence of high-molecular-weight kininogen and kallikrein. Factor
XIIa converts factor XI into factor XIa, which activates factor IX. Factor IXa, in the presence of its cofactor VIIIa and ionized calcium, activates factor X (Fig. 3) (18).

The final common pathway initiates when the factor Xa–factor Va complex, in the presence of ionized calcium, activates factor II (prothrombin) to factor IIa (thrombin), whose primary role is the conversion of fibrinogen (factor I) to fibrin. The fibrin monomers group to form the clot, which is stabilized by factor XIIIa (Fig. 4). Thrombin is responsible for the activation of factors V, VIII, and XIII.

Factors that inhibit fibrin formation include antithrombin (AT), TF pathway inhibitor (TFPI), protein C (PC), and protein S (PS). AT is a protease inhibitor that degrades thrombin, factors IXa, Xa, and Xla, and TF-bound factor VIIa. TFPI is a protein that is produced by endothelial cells that inhibit the TF–factor VIIa complex and factors IXa and Xa. PS is a cofactor to PC, which degrades factors Va and VIIIa (Fig. 5) (19).

**Fibrinolysis**

During fibrinolysis, a fibrin clot, the product of coagulation, is broken down, and the enzyme that is responsible for this process is plasmin. Fibrinolysis is initiated when tissue plasminogen activator (tPA) and urokinase-type plasminogen activator convert plasminogen to plasmin. Plasmin, in turn, dissolves the fibrin complex. When this dissolution occurs, a number of soluble parts of fibrin are produced. These parts are called fibrin degradation products (FDP); one of these parts is called D-dimers. The FDP compete with thrombin and thus slow down clot formation by preventing the conversion of fibrinogen to fibrin.

Factors that inhibit fibrinolysis include plasminogen activator inhibitor 1 (PAI1), thrombin activable fibrinolysis inhibitor (TAFI) and α2-antiplasmin. PAI1 inhibits tPA, α2-antiplasmin inactivates plasmin, and TAFI modifies fibrin to make it more resistant to the tPA-mediated plasminogen action (Fig. 6) (20).

**Thromboembolic complications in CS: mechanisms**

Thrombosis is frequently a multifactorial disease, and all three components of the Virchow triad (vascular abnormalities and endothelial dysfunction, hypercoagulability, and stasis) may play a role in the pathogenesis of the prothrombotic state in patients with CS (21).

**Endothelial dysfunction**

CS is associated with endothelial dysfunction, which significantly predisposes to an increased risk for CVD.
Previous studies have observed decreased availability of nitric acid in patients with obesity (22), DM (23), hypertension (24), dyslipidemia (25), and insulin resistance (26), all of which are complications that are frequently associated with CS. Insulin regulates the balance between the levels of nitric acid and endothelin 1 by phosphatidylinositol 3-kinase (PI3K) and MAPK respectively. An impairment in these pathways takes place in individuals with insulin resistance, which leads to endothelial dysfunction through a lower production of nitric oxide and increased endothelin (26).

Pražny et al. (27) reported that patients with hypercortisolism have increased levels of intercellular adhesion molecule 1 and serum N-acetyl-b-glucosaminidase activity, which are markers of endothelial dysfunction. Furthermore, impaired microvascular reactivity is observed in these patients (27). Anagnostis et al. (28) reported that brachial artery flow-mediated dilatation is lower in CS patients than it is in healthy controls (29).

Hypercoagulability

Thromboembolic complications are observed in CS with elevations in the plasma levels of the procoagulant factors that apparently contribute to thrombosis (14, 30). Cortisol induces an increase in vWF; however, this increase depends on genetic characteristics present in the vWF gene promoter. Haplotype 1 (-3268C/-2709T/-2661G/-2527A), which cosegregates with short GT repeats (15–19, GT), and confers a greater risk of vWF up-regulation by cortisol than does haplotype 2 (-3268C/-2709T/-2661G/-2527A), which cosegregates with long repeats (GT ≥20, GT). Therefore, in CS, the presence of haplotype 1 is associated with an increased risk of developing high vWF levels and a consequent hypercoagulable condition, whereas haplotype 2 correlates more frequently with normal vWF levels and thus protects against thrombotic complications (31).

Casonato et al. (5) reported that patients with CS not only had higher plasma levels of vWF, but they also exhibit unusually large vWF multimers, which may be evidence of endothelial dysfunction. The authors found an increase in the plasma levels of large vWF multimers in the immediate postoperative period, and the persistence of this increase was sporadically observed in cured patients (5).

Most of the studies that have evaluated the procoagulant factors in patients with hypercortisolism have found a decrease in PTT values (5, 6, 7, 14, 32, 33, 34, 35, 36, 37, 38) and an increase in the plasma levels of...
factors II (14, 34, 39), V (14, 34, 39), VIII (5, 7, 14, 30, 32, 34, 36, 37, 38, 39, 40), and IX (7, 14, 34, 39) (Table 1). The PTT is shortened, probably because of an increase in FVIII. The levels of FVIII may be influenced by the high levels of vWF, because the latter reduces the degradation of FVIII (41). In one systematic review, the authors observed that even after remission of hypercortisolism, vWF, VIII, and IX factors remained high (42).

With respect to endogenous anticoagulants, two studies found an increase in PS, PC, and AT plasma levels (14, 38). Moreover, an increase in the elements involved in the fibrinolytic pathway, such as plasminogen and tPA, was described (6, 7). This elevation in endogenous anticoagulants is probably secondary to the high levels of procoagulant factors, which represent a protective mechanism against hypercoagulability in these patients. However, an increase in factors that inhibit fibrinolysis, such as PAI1 (6, 14, 32, 34, 35, 36, 38), TAFI (36) and α2-antiplasmin (36, 43), was also reported, which demonstrates that the fibrinolytic pathway is also impaired in hypercortisolism.

The majority of the studies included in the present review were cross-sectional analyses of coagulation parameters in patients with CS vs healthy subjects, and they did not evaluate the presence of common comorbidities associated with CS, like arterial hypertension, DM, and smoking, which could lead to a hypercoagulable state (7, 30, 39, 44). It is also known that individuals with blood type O have lower values of vWF as compared to individuals with the blood types that are not O (45). However, only two studies matched the patients with CS and controls for ABO blood type (36, 37).

Recently, our group studied hemostatic and thromboelastometric parameters in 30 patients with active CS and in 30 control subjects matched for age, sex, BMI, DM, arterial hypertension, ABO blood group, and smoking (37). Rotation thromboelastometry was used to evaluate the intrinsic, extrinsic, and fibrinogen pathways. We demonstrated that only the beginning of clot formation (the intrinsic pathway) is altered, and we found increased plasma levels of FVIII, vWF, and D-dimer and decreased activated partial thromboplastin time in patients with active CS. In addition, we observed an increased clot formation speed and higher clot strength in obese CS patients as compared to non-obese CS patients (37).

**Stasis**

Venous thrombi frequently occur at regions of slow blood flow, such as large venous sinuses in the calf, the valve cusp pockets of the deep veins of the calf or thigh, or the parts of the veins that are exposed to external compression. The concentration of endogenous anticoagulants varies among vascular beds, and the major difference is determined by the ratio of the endothelial cell surface to the blood volume. The efficacy of natural anticoagulants is increased inside the microcirculation as compared to larger vessels. During stasis, blood increases its residence time in the large vessels, which increases the propensity for developing clots (46). Moreover, in CS patients, previous studies found increased hematocrit, and this alteration can lead to hyperviscosity, which results in reduced blood flow and predisposes to thromboembolic complications (21).

**Clinical events that are related to the disturbance of coagulation and fibrinolysis in CS**

We reviewed the occurrence of clinical events related to hypercoagulability in endogenous hypercortisolism in a total of 13 studies with 1356 patients with CS (1080 cases of Cushing’s disease (CD), 234 cases of adrenal adenoma or hyperplasia, 21 cases of adrenal carcinoma, and 21 cases of ectopic CS). Of these patients, 8.9% had VTE, and 53% of...
Table 1 Alterations in coagulation and fibrinolysis in Cushing’s syndrome.

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aPTT, activated partial thromboplastin time; PT, prothrombin time; vWF, von Willebrand factor; FII, factor II; FV, factor V; FVII, factor VII; FXII, factor XII; FX, factor X; FXI, factor XI; FXI, factor XI; PC, protein C; PS, protein S; AT, antithrombin; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; PAI1, plasminogen activator inhibitor 1; TAFI, thrombin activatable fibrinolysis inhibitor; n, number of patients; NS, not significant. Blank means not evaluated.
Few studies have reported an association between exogenous GC and VTE. A recent case–control study (52) was performed with 38 765 VTE patients (53.7% women; median age 67 years) and 387 650 control individuals from the general population to evaluate the risk of VTE among GC users. They found 6696 cases of VTE (17%) related to GC in patients with risk factors for thrombosis, such as surgery, major trauma or fracture, and cancer, and 3177 cases (8.1%) in patients without risk factors. The authors considered different routes of administration of GC and subdivided the subjects into three groups according to when the patients had filled their most recent GC prescription: 90 days or less, 91–365 days, and more than 365 days before the date when VTE was diagnosed. Among the VTE cases, 61.2% had deep vein thrombosis, 38.8% had pulmonary embolism (PE), and 57.7% had unprovoked VTE. Patients who used oral GC showed a greater risk as compared to individuals who used the injectable form, and the risk was greater for prednisolone-equivalent cumulative doses from 1000 to 2000 mg. For systemic GC, the risk of VTE was higher among individuals who had a GC prescription for 90 days or less as compared to those who used GC 91–365 days before the date when VTE had been diagnosed. An association with VTE was not observed in patients who used GC for more than 365 days before the thrombosis. For inhaled GC, only individuals with first-ever prescription redemption within 90 days before VTE were associated with an increased VTE risk. Another study in 3550 VTE cases showed that the relative risk for VTE was 4.7 for 0–30 days of use of GC, but the risk decreased to 2.0 for more than 1 year of use (53).

**Prophylaxis for thromboembolism in patients with CS**

Of the 22 studies (5, 6, 7, 9, 14, 15, 30, 32, 33, 34, 35, 36, 37, 38, 39, 40, 44, 47, 48, 49, 50, 51) that evaluated hypercoagulability in CS, few of them assessed the risk of thromboembolism in patients who received thromboprophylaxis (32, 38, 51). Prophylactic treatment appeared to be safe, seeing as no case of bleeding was reported in patients during anticoagulant treatment (54).

Boscaro et al. (32) examined 307 patients with CS (203 patients with CD) and divided them into two groups: 75 patients who did not receive thromboprophylaxis after surgery and 232 patients who received unfractionated heparin (doses of 15 000–22 500 U/day for at least 2 weeks) and warfarin for at least 4 months. During follow-up, 15 patients (20%) in the first group and 14 (6%) in the second group showed thromboembolic complications, and most
### Table 2: Thromboembolic events in Cushing's syndrome.

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<td>9</td>
<td>11</td>
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<tr>
<td>Rees et al. 2002 (48)</td>
<td>54</td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
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<tr>
<td>Sudhakar et al. 2004 (49)</td>
<td>22</td>
<td></td>
<td>1</td>
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<tr>
<td>Kastelan et al. 2009 (14)</td>
<td>33</td>
<td>↑ FII, FV, FVIII, FIX, FXI, PC, PS, PAI1, plasminogen, AT ↓ aPTT</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
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<tr>
<td>Manetti et al. 2010 (50)</td>
<td>40</td>
<td>↑ FIX, PAI1, fibrinogen, AT, D-dimer, vWF, α2-antiplasmin ↓ aPTT</td>
<td>2</td>
<td>1</td>
<td></td>
<td>1</td>
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<td></td>
<td></td>
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<td>2</td>
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<tr>
<td>Stuijver et al. 2011 (51)</td>
<td>473</td>
<td>↑ FVIII, fibrinogen, PS, α2-antiplasmin, PAI1, TAF1</td>
<td>16</td>
<td>15</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Van der Pas et al. 2012 (36)</td>
<td>17</td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Koutroumpi et al. 2013 (40)</td>
<td>58</td>
<td>↑ vWF, FVIII</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Barbot et al. 2014 (38)</td>
<td>78</td>
<td>↑ PT, FVIII, vWF, AT, PC, PS, PAI1 ↓ aPTT</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>1356</td>
<td></td>
<td>65 (49%)</td>
<td>49 (36%)</td>
<td>4 (3%)</td>
<td>16 (12%)</td>
</tr>
</tbody>
</table>

aPTT, activated partial thromboplastin time; PT, prothrombin time; vWF, von Willebrand factor; FII, factor II; FV, factor V; FVIII, factor VIII; FIX, factor IX; FXI, factor XI; FXII, factor XII; PC, protein C; PS, protein S; AT, antithrombin; PAI1, plasminogen activator inhibitor 1; TAFI, thrombin activatable fibrinolysis inhibitor; PE, pulmonary embolism; DVT, deep vein thrombosis; AT, arterial thrombosis; n, number of patients.

<sup>a</sup>One patient: PE + AT.

<sup>b</sup>VTE, venous thromboembolism.
of these complications occurred within 3 months after the surgical procedure. Of these patients, eight patients from group 1 (10.7%) and one patient from group 2 (0.4%) died. The authors concluded that after the introduction of postoperative antithrombotic prophylaxis (group 2), the morbidity and mortality resulting from thromboembolic events dropped to 6% and 0.4% respectively.

Stuilver et al. (51) studied 473 patients with CS (353 patients with CD) and compared them to patients who were surgically treated for nonfunctioning pituitary adenoma, which allowed them to distinguish between the risk of VTE associated with cortisol overexposure and the risk resulting from the surgical procedure itself. The patients who had undergone surgery received thromboprophylaxis based on the recommendations that were used for surgical procedures at a low risk of VTE: dalteparin 2500 U/day or nadroparin 2850 U/day from the day of surgery or 1 day before surgery until mobilization or discharge (calparin or i.v. unfractionated heparin was used in 12 surgeries). Nineteen VTE events occurred before treatment, 12 occurred after surgery, and five occurred during cortisol-lowering treatment. None of the VTE events were fatal. In four out of 12 patients with postoperative VTE, the event occurred while they patient was receiving thromboprophylaxis, and most of the events occurred between 1 week and 2 months after surgery. The risk for postoperative VTE in patients with CS was 3.4% as compared to 0% for controls, and the risk was comparable with the risk after total hip or knee replacement under short-term prophylaxis (7–10 days). Based on these results, the authors recommended that thromboprophylaxis should be considered before starting treatment and mainly when additional risk factors for VTE are present. In patients with adrenocorticotrophin-dependent CS who undergo pituitary surgery, thromboprophylaxis should be extended to 10–35 days after surgery, which is comparable to surgical procedures for patients at a high risk for VTE.

Recently, Barbot et al. (38) studied 78 patients with CD who underwent pituitary transsphenoidal surgery, and they divided the patients into two groups: group A (34 patients) received fractionated heparin (nadroparin 3800 U/day or enoxaparin 4000 U/day) from the day after surgery until discharge or for a maximum of 14 days after surgery plus GC replacement therapy, and group B (44 patients) was treated with fractionated heparin (enoxaparin 4000–8000 U/day) for 30 days, starting 24 h after the surgical procedure, plus graduated elastic compression stockings, early ambulation, and no early GC replacement. Three cases of VTE were recorded in group A (all occurring within 30 days after surgery), and none were observed in group B. The authors concluded that the prevention of postoperative VTE with low-molecular-weight heparins for long-term, early mobilization and the use of graduated compression stockings are the best management practices in patients with CD, seeing as fatal PE can occur without warning signs. Furthermore, the occurrence of more cases of VTE in groups who received GC replacement before the assessment of the success of the surgical procedure raises the question of whether patients with persistent disease who receive GC unnecessarily may be at an even greater risk of VTE.

In conclusion, in order for thrombotic events in patients with CS to occur, the presence of at least two components from Virchow’s triad (vascular abnormalities and endothelial dysfunction, hypercoagulability, and stasis) seems to be necessary. Studies recommend that thromboprophylaxis with low-molecular-weight heparin or low-dose unfractionated heparin should be used routinely in patients with CS who undergo transsphenoidal or adrenal surgery (open or laparoscopic) (42, 50). However, there is no consensus about the dose or duration of use of prophylactic anticoagulant therapy. Moreover, it is not clear whether thromboprophylaxis should be undertaken in patients with CS, either postoperatively or throughout the active disease. Multicenter prospective studies are needed to answer these important questions and to thereby reduce the morbidity and mortality associated with this disease.

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

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