

A Guide on Iatrogenic Cushing's Syndrome and Steroid-related Adverse Events

Key Points

- Glucocorticoids are important steroid hormones with widespread effects on the body, including the immune system, cardiovascular system and metabolic functions. The production of endogenous glucocorticoids is tightly regulated by the hypothalamic-pituitary-adrenal (HPA) axis
- Synthetic glucocorticoids are commonly used in therapeutic drugs and illegally used in adulterated complementary health products (CHPs) for their anti-inflammatory properties. Long-term unmonitored use of these products may lead to suppression of the HPA axis
- It is important for healthcare professionals to recognise signs and symptoms of glucocorticoid excess in patients, and those at risk of HPA axis suppression secondary to exogenous glucocorticoids
- A checklist for the reporting of suspected steroid-related adverse events (AEs) to HSA is provided

What effects may exogenous glucocorticoids have on the body?

Cortisol secretion is regulated by negative feedback via the hypothalamic-pituitary-adrenal (HPA) axis.¹ Corticotropin-releasing hormone (CRH) is released by the hypothalamus in response to diurnal rhythm and stressors. CRH stimulates the production of adrenocorticotropic hormone (ACTH) from the pituitary gland, which in turn stimulates production and secretion of cortisol by the adrenal glands. Cortisol, once released into the circulation, exerts a negative feedback by inhibiting secretion of CRH and ACTH (Figure 1A).

Exogenous glucocorticoids, similar to endogenously produced cortisol, may have diverse effects on metabolism, skin and soft tissues, skeletal system, cardiovascular system, immune system, central nervous system etc. Depending on the potency and duration of glucocorticoids administered, patients may develop features of Cushing's syndrome. Exogenous glucocorticoids also exert inhibitory effects on the hypothalamus and pituitary gland (Figure 1B). The degree of this negative feedback effect depends on dose, potency, half-life and duration of glucocorticoid exposure. Prolonged negative feedback leads to HPA axis suppression and adrenal atrophy. The resultant adrenal insufficiency following cessation of glucocorticoid therapy may persist for months to years. Both Cushing's syndrome and adrenal insufficiency are associated with increased morbidity and mortality. Prompt recognition is vital.

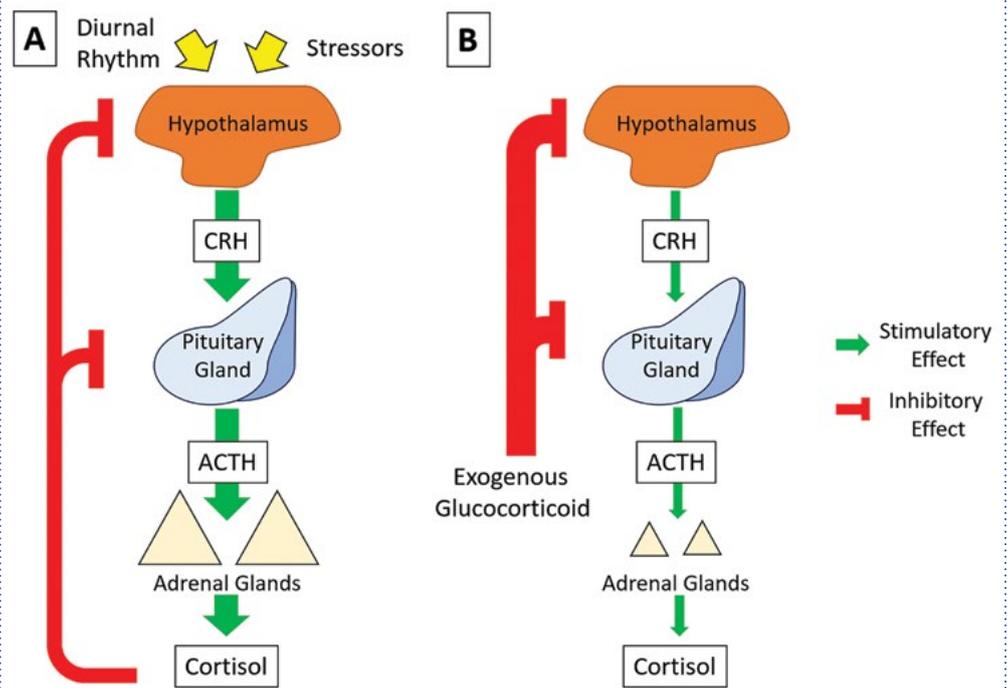


Figure 1. Regulation of cortisol secretion in normal physiology (A) and in presence of exogenous glucocorticoid (B). Adapted from source: William's Textbook of Endocrinology¹

When to suspect exposure to exogenous glucocorticoids?

Patients with exposure to exogenous glucocorticoid may not actively report this for various reasons. For instance, patients may not be aware of the contents of the products they have taken, especially when glucocorticoids are not declared as ingredients on the labels of adulterated CHPs. Furthermore, parenteral forms of glucocorticoids such as intra-articular injections are often overlooked in medication-history taking. It is hence important for clinicians to be vigilant and keep a look out for patients with manifestations of chronic glucocorticoid exposure – namely iatrogenic Cushing's syndrome from the direct effects of glucocorticoids, and adrenal insufficiency from HPA axis suppression.

Table 1. Clinical features of Cushing's syndrome and adrenal insufficiency resulting from steroid exposure.^{2,3}

Cushing's Syndrome

History

Changes in mood – depression, irritability
 Fatigue
 Weight gain
 Back pain
 Changes in appetite
 Decreased concentration
 Decreased libido
 Positive history of steroid exposure

Examination

Discriminative signs

- Easy bruising
- Facial plethora
- Proximal myopathy
- Violaceous striae (> 1cm wide)
- In children: weight gain with decreasing growth velocity

Less discriminatory signs

- Soft tissue changes - dorsocervical fat pad (buffalo back), supraclavicular fullness, facial fullness (moon face), peripheral oedema
- Skin changes – thin skin, acne, poor skin healing
- Obesity
- In children: short stature, abnormal puberty

Associated conditions

Cardiovascular disorder
 Hypertension
 Osteoporosis
 Type 2 diabetes
 Hypokalaemia
 Unusual infections

Adrenal Insufficiency

History

Fatigue
 Weight loss
 Postural dizziness
 Anorexia
 Abdominal discomfort
 Positive history of steroid exposure

Examination

Hypotension/ Postural hypotension
 In children – failure to thrive

Associated conditions

Hyponatraemia

The severity of the Cushingoid features depends on the potency of the preparations used, its dose, the route and duration of its administration, and concomitant use of medications that prolong the half-life of glucocorticoids. Patients who develop clinical features of Cushing's syndrome are at a higher risk of adrenal insufficiency. In reality, however, there is great heterogeneity in the susceptibility of individuals to development of adrenal insufficiency.

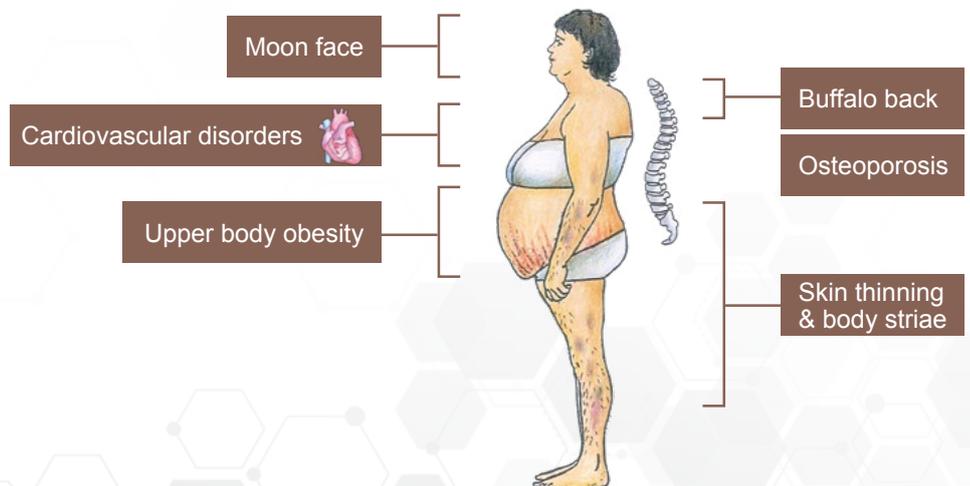


Figure 2. Some clinical features of Cushing's Syndrome

Table 2. Examples of Glucocorticoids

Type of Drug	
Therapeutic drugs containing glucocorticoids	
Oral	Topical
<ul style="list-style-type: none"> • Dexamethasone • Methylprednisolone • Betamethasone • Prednisolone • Hydrocortisone 	<ul style="list-style-type: none"> • Clobetasol propionate • Betamethasone dipropionate
Inhaled	Intra-articular
<ul style="list-style-type: none"> • Budesonide • Fluticasone 	<ul style="list-style-type: none"> • Triamcinolone
Therapeutic drugs containing steroids with glucocorticoid activity (at high doses)	
Megestrol acetate	

Illegal Complementary Health Products containing glucocorticoids

A local study reviewed commonly used herbs and concluded that most herbs do not naturally contain glucocorticoids.⁴ The main cause of concern surrounding use of CHPs comes from illegal products adulterated with exogenous glucocorticoids. These products may be used by elderly patients for their analgesic and anti-inflammatory effects.



When to suspect iatrogenic Cushing’s syndrome and steroid-induced adrenal insufficiency?

Iatrogenic Cushing’s syndrome. Once iatrogenic Cushing’s syndrome is suspected, its subsequent confirmation is generally straightforward. Most steroid-adulterated products contain dexamethasone, which is not readily detected using commercially available cortisol assays. A common biochemical finding of patients with iatrogenic Cushing’s syndrome is a suppressed endogenous early morning cortisol level. This, combined with clinical features of glucocorticoid excess, would be suggestive of iatrogenic Cushing’s syndrome.⁵

Adrenal Insufficiency. Adrenal insufficiency due to HPA axis suppression from exogenous glucocorticoids is characterised by inappropriately low early morning cortisol level and a corresponding low ACTH level. It is important to ensure that patient is not actively taking the suspected steroid-containing drug at the time of blood sampling, as even a single low dose of dexamethasone (1mg) is sufficient to suppress the entire HPA axis briefly. If the early morning cortisol is indeterminate, an ACTH stimulation test may be considered.²

How should a steroid-related AE be managed?

When there is a suspicion that a patient suffers from AEs of exogenous glucocorticoids, apart from prompt reporting of the case to HSA, it is important to consider management plans that addresses the two key areas:

Table 3. AE Management Plans

Key areas	Management Plan
Consequences of glucocorticoid excess	Consider screening patients for complications such as diabetes mellitus and osteoporosis, and treating as appropriate. ⁵
Consequences of HPA axis suppression	For patients at risk of developing adrenal insufficiency, consider assessing HPA axis function and gradual withdrawal of glucocorticoid until recovery of HPA axis (if glucocorticoid is not required for therapeutic purposes). Patients on replacement glucocorticoids should be counselled on sick day management and steroid dose adaptation. ⁵

Given the increasing trend of consumers turning to the use of alternative treatments, HSA encourages healthcare professionals to ask their patients about the use of such health products, including CHPs during medication history-taking. This information may be useful for detection and assessment of steroid-related AEs due to the use of adulterated products, marketed as CHPs.



How to report suspected AEs to HSA?

You may submit the yellow Adverse Drug Reaction (ADR) reporting form (downloadable from HSA website at www.hsa.gov.sg/adr) to the Vigilance and Compliance Branch of HSA via the following channels:

 **Email** : HSA_productsafety@hsa.gov.sg

 **Phone** : (65) 6866 1111

 **Electronic reporting:**
http://www.hsa.gov.sg/ae_online

 **Mail:**
Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way
#11-03, Helios
Singapore 138667

 **Fax** : (65) 6478 9069

Checklist on important information in an AE report:

-  Pre-existing conditions of the patient
-  Relevant laboratory reports (e.g. cortisol level, Synacthen test, if available)
-  Other differential diagnoses that were ruled out
-  Indication for using the CHP(s) / steroid-related therapeutic drugs
-  Dose, dose frequency and the start/stop dates of the suspected CHP(s)/steroid-related therapeutic drugs
-  Photos of all sides of the CHP(s)
-  Source of the CHP(s) (Name, address and contact particulars of the vendor)

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References

1. Williams R. Williams textbook of endocrinology. 13th edition. Melmed S, Polonsky KS, Larsen PR, Kronenberg H, editors. Philadelphia, PA: Elsevier; 2016. 1916 p.
2. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2008 May;93(5):1526–40.
3. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016 Feb;101(2):364–89.
4. Fung FY, Linn YC. Steroids in traditional Chinese medicine: what is the evidence? *Singapore Med J.* 2017 Mar;58(3):115–20.
5. Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. *Endocrinol Metab Clin North Am.* 2005 Jun;34(2):371–84, ix.



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