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Diagnosis and approach to glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome

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ABSTRACT

Introduction and purpose: Primary adrenal insufficiency can result from diseases affecting the adrenal glands, while secondary adrenal insufficiency is caused by suppression of the hypothalamic-pituitary-adrenal axis. The most common cause of adrenal suppression is exogenous steroids, a condition recently termed glucocorticoid-induced adrenal insufficiency (GIAI). Glucocorticoid-induced adrenal suppression is a common adverse effect of glucocorticoid therapy, which can have severe consequences. This review provides a comprehensive overview of the diagnosis and management of glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome.

Material and methods: An extensive examination of articles published in scientific journals was carried out through online research platforms PubMed and Google Scholar. We searched articles by entering keywords in appropriate configuration: “glucocorticoid-induced adrenal insufficiency”, “glucocorticoids”, “steroids”, “adrenal crisis”, “substitution therapy”, “glucocorticoid withdrawal”.

Description of the state of knowledge: Glucocorticoids are widely used in the treatment of various inflammatory and autoimmune disorders due to their potent anti-inflammatory and immunosuppressive effects. However, chronic glucocorticoid therapy can lead to a number of adverse effects, including adrenal suppression, which can result in adrenal insufficiency.

Summary: Primary care clinicians should recognize the high prevalence of glucocorticoid-induced adrenal insufficiency in patients receiving non-oral glucocorticoid formulations. The glucocorticoid withdrawal syndrome exhibits symptoms analogous to glucocorticoid-induced adrenal insufficiency. Additional data on the morbidity and mortality linked to glucocorticoid-induced adrenal insufficiency is needed to comprehend the associated health risks, which will ultimately guide the approach to care for patients tapering long-term glucocorticoid therapy.

Keywords: glucocorticoid-induced adrenal insufficiency; glucocorticoids; steroids; adrenal crisis; substitution therapy; glucocorticoid withdrawal

Introduction and purpose:

Diseases of the adrenal glands can lead to primary adrenal insufficiency, and suppression of the hypothalamic-pituitary-adrenal axis can cause secondary adrenal insufficiency (adrenal suppression). The most common cause of secondary adrenal insufficiency is long-term treatment with high-dose glucocorticosteroids (e.g., due to rheumatic diseases), a condition recently termed glucocorticoid-induced adrenal insufficiency (GIAI).Glucocorticoids are widely used in the treatment of various inflammatory and autoimmune disorders due to their potent anti-inflammatory and immunosuppressive effects [1]. However, chronic glucocorticoid therapy can lead to a number of adverse effects, including adrenal suppression, which can result in adrenal insufficiency[1]. Glucocorticoid-induced adrenal insufficiency is a common adverse effect of glucocorticoid treatment, and healthcare providers typically anticipate its occurrence in patients receiving systemic glucocorticoids at doses equivalent to more than 5 mg of prednisone for at least 3 weeks [2]. Additionally, glucocorticoids administered through alternative routes can also lead to adrenal suppression [2]. Chronic exogenous glucocorticoid therapy inevitably suppresses the hypothalamic-pituitary-adrenal axis, and the recovery of adrenal function varies significantly among individuals. This can result in adrenal insufficiency, which is a potentially life-threatening condition that requires prompt recognition and appropriate management [3].

Types of adrenal insufficiency

The adrenal cortex produces three main categories of hormones: glucocorticoids from the zona fasciculata, mineralocorticoids from the zona glomerulosa, and androgens with their precursors from the zona reticularis. [4]

Adrenal insufficiency occurs when the adrenal cortex is unable to synthesize and secrete adequate amounts of glucocorticoids, mineralocorticoids, or both.

Primary adrenal insufficiency

Primary adrenal insufficiency results from diseases affecting the adrenal glands, such as autoimmune destruction, infections, infiltrative disorders, congenital adrenal hyperplasia, and adrenal hemorrhage or infar. The prevalence of primary adrenal insufficiency in Europe has been reported to be as high as 22.1 per 100,000 population. In the United States, the annual incidence is estimated at 4.7 per million population. [5]

Secondary adrenal insufficiency

Secondary adrenal insufficiency results from a disruption of the hypothalamic-pituitary-adrenal axis, such as pituitary adenoma, Sheehan syndrome, and exogenous glucocorticoids. Chronic exogenous glucocorticoid therapy, either oral, inhaled, topical, or injected, can lead to secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis.Adrenal insufficiency caused by suppressed corticotropin-releasing hormone is sometimes called *tertiary adrenal insufficiency*. Secondary adrenal insufficiency is more prevalent than primary adrenal insufficiency, with an estimated occurrence of up to 28 cases per 100,000 people [6]. The common causes include pituitary tumors, other tumors that have spread to the pituitary gland, and head injuries. In addition, a variety of medications that can disrupt the hypothalamic-pituitary-adrenal axis at multiple levels are also important causes of secondary adrenal insufficiency. The drugs that primary care providers most commonly encounter include immune checkpoint inhibitors, opioids, and glucocorticoids. Studies suggest that opioid use can lead to adrenal insufficiency, affecting around 15% of patients receiving opioids for at least 3 to 6 months [7]. Additionally, a report by Li et al. found that 9 out of 102 patients receiving more than 20 morphine milligram equivalents per day developed adrenal insufficiency [8].

TABLE 1 Common causes of secondary adrenal insufficiency

Pituitary tumors
Nonpituitary tumors **Meningioma** **Craniopharyngioma** **Sellar or suprasellar metastases (lung, colon, and breast cancer)**
Pituitary infiltration ***Granulomatosis with polyangiitis Sarcoidosis*** ***Amyloidosis*** ***Hemochromatosis*** ***Lymphoma***
Autoimmune

Pituitary apoplexy
Head trauma
Drug-induced central adrenal insufficiency
Rare congenital causes

Glucocorticoid-induced adrenal insufficiency (GIAI)

As mentioned earlier, the most common cause of secondary adrenal insufficiency is long-term treatment with high-dose glucocorticoids. The use of glucocorticoids, whether oral, inhaled, topical, or injected, can suppress the hypothalamic-pituitary-adrenal axis, which is essential for the normal stress response. Excessive glucocorticoids, whether produced within the body due to adrenal gland abnormalities or obtained from external sources, interact with receptors in the hypothalamus and pituitary gland, causing negative feedback on the release of adrenocorticotropic hormone. This chronic suppression of adrenocorticotropic hormone leads to the atrophy of the zona fasciculata, the region of the adrenal cortex that produces cortisol, while leaving the zona glomerulosa, which makes mineralocorticoids, unaffected. This results in impaired cortisol secretion but maintains normal mineralocorticoid production [9]. When glucocorticoids are discontinued, there is a resurgence of ACTH stimulation on the adrenal cortex. In most cases, the adrenal cortex is able to recover and restore adequate cortisol production. However, the full biochemical and clinical recovery of the hypothalamic-pituitary-adrenal axis can vary significantly in duration [10]. Glucocorticoid therapy at immunosuppressive or anti-inflammatory doses far exceeds the body's natural cortisol production, inevitably leading to suppression of the hypothalamic-pituitary-adrenal axis. As glucocorticoids are tapered from these supraphysiologic levels, patients may experience glucocorticoid withdrawal syndrome, which presents with clinical signs and symptoms akin to adrenal insufficiency. However, symptoms due to adrenal insufficiency are much more likely to develop when overall total daily glucocorticoid dose is below physiologic levels, or levels required for an adequate stress response. In contrast, symptoms of adrenal insufficiency are far more likely to occur when the total daily glucocorticoid dose is below the physiological levels needed for an adequate stress response.

Risk factors of GIAI

A meta-analysis of the risk of developing biochemical glucocorticoid-induced adrenal insufficiency stratified by glucocorticoid route of administration showed pooled percen- tages of 4.2% (95% CI 0.5-28.9) for nasal administration, 48.7% (95% CI 36.9-60.6) for oral use, and 52.2% (95% CI 40.5-63.6) for intra-articular administration [11]. The risk also varied when stratified for the underlying disease and increased with higher dose (low dose 2.4% (95% CI 0.6-9.3) to high dose 21.5% (95% CI 12.0-35.5)) and longer treatment duration (1.4% (95% CI 0.3-7.4) (<28 days) to 27.4% (95% CI 17.7-39.8) (>1 year)) in patients with asthma [11]. Studies have shown that rheumatoid arthritis patients taking high doses of glucocorticoids have an increased risk of overall mortality, with the risk escalating as the current daily and total cumulative doses rise.

Conversely, this association was not observed when the daily glucocorticoid dose was equivalent to less than 5 mg of prednisone. The estimates from these studies should be interpreted cautiously due to potential confounding factors, such as the underlying disease and its severity [12]. High-dose glucocorticoid pulse therapy (eg, intravenous methylprednisolone 250-500 mg weekly for 6-12 weeks) and single-day dosing schedules are less likely to induce glucocorticoid-induced adrenal insufficiency compared to bedtime dosing and frequent dosing regimens [13] [14][15]. Glucocorticoid-induced adrenal insufficiency following brief courses of glucocorticoids (7-14 days) is rarely reported [16]. Using glucocorticoids along with medications that inhibit the hepatic cytochrome P450 3A4 enzyme can increase the levels of the active metabolites of glucocorticoids, consequently raising the risk of glucocorticoid-induced adrenal insufficiency [17]. This occurs with all glucocorticoid formulations that are metabolized by the cytochrome P450 3A4 enzyme, regardless of the route of administration [18] [19]. The risk of developing adrenal insufficiency and experiencing adrenal crisis rises with the accumulation of various factors during glucocorticoid treatment and tapering, including the potency of the glucocorticoid, the route of administration, the dosage, and the duration of treatment.

Glucocorticoid withdrawal syndrome

Prolonged exposure to excessive endogenous hormone levels or exogenous administration often leads to tolerance, followed by physiological and psychological dependence [2]. In this context, slowly reducing the dose or suddenly stopping the glucocorticoids can cause glucocorticoid withdrawal syndrome, even when patients are still taking excessive amounts of the medication. It is important for all patients starting a glucocorticoid taper to be made aware of the potential for glucocorticoid withdrawal syndrome. The symptoms of glucocorticoid withdrawal often closely resemble those of adrenal insufficiency and most patients experiencing glucocorticoid withdrawal syndrome also have accompanying adrenal insufficiency [20]. Anticipating and preparing for these potential symptoms can increase patient awareness and reduce the need for urgent medical intervention. Glucocorticoid withdrawal syndrome presents with a range of nonspecific symptoms, stemming from multiple underlying mechanisms. Chronic suppression of corticotropin-releasing hormone after discontinuing or tapering glucocorticoids leads to adrenal insufficiency, adrenal crisis, mood changes, excessive sleepiness, and fatigue [21]. Prolonged suppression of proopiomelanocortin-related peptides causes muscle and joint pain, fever, and headache. Depression of central noradrenergic and dopaminergic systems manifests as nonspecific withdrawal symptoms, accompanied by reduced appetite, nausea, vomiting, and weight loss. The loss of glucocorticoid's inhibitory effect on calcium absorption results in elevated blood calcium and phosphate levels [2]. Prolonged use of excessive glucocorticoid levels, whether from the body or external sources, can suppress the hypothalamic-pituitary-adrenal axis, leading to adrenal insufficiency. Concurrently, dependence on high-dose glucocorticoids can cause withdrawal symptoms when tapering or stopping these medications. While adrenal insufficiency and glucocorticoid withdrawal syndrome have overlapping clinical presentations, they are distinct conditions that coexist until the hypothalamic-pituitary-adrenal axis recovers. In cases of severe glucocorticoid withdrawal syndrome, clinicians may temporarily increase the glucocorticoid dose to the most recently tolerated level, and extend the duration of the glucocorticoid taper [22].

Research indicates that glucocorticoid withdrawal syndrome is frequently observed in 40-67% of patients who are gradually reducing glucocorticoid therapy after undergoing curative adrenalectomy for adrenal Cushing's syndrome [23]. Patients who underwent curative surgery for endogenous hypercortisolism experienced a correlation between their baseline clinical severity and the severity of glucocorticoid withdrawal. Additionally, their withdrawal symptoms became more severe once their total daily glucocorticoid dose dropped below the equivalent of 30 to 35 mg of hydrocortisone [24].

Recommendations regarding taper of systemic glucocorticoid therapy, diagnosis and approach to glucocorticoid-induced adrenal insufficiency

Patients on long-term glucocorticoid therapy should only attempt to taper their dose if the underlying condition that required glucocorticoids is now controlled and the medications are no longer needed. In such cases, the glucocorticoids should be gradually reduced until the patient reaches a physiologic daily dose equivalent. Generally, the glucocorticoid taper can proceed more quickly and with larger dose reductions when the total daily glucocorticoid dose is high. However, as the total daily dose approaches the physiologic equivalent, the taper should be slower and involve smaller decrements [22]. When tapering glucocorticoid therapy, it is important to evaluate the patient's risk of adrenal insufficiency and potential for disease flare. Additionally, clinicians should consider the patient's underlying medical conditions and any concomitant medications that may affect glucocorticoid metabolism and overall exposure. When glucocorticoids are reduced to physiologic replacement levels, the European Society of Endocrinology proposes two possible methods for discontinuing glucocorticoid treatment. However, there is a lack of studies demonstrating the superiority of these approaches in terms of clinical outcomes or cost-effectiveness. Patients can slowly reduce their glucocorticoid dose while being carefully monitored for indications of adrenal insufficiency. If the patient shows signs and symptoms of adrenal insufficiency, the glucocorticoid regimen should be restarted and maintained until the hypothalamic-pituitary-adrenal axis has recovered. However, if the patient does not experience any symptoms, the tapering can continue until the glucocorticoid is discontinued. Another option is for patients to undergo morning serum cortisol testing to evaluate HPA axis recovery (measured between 8:00 and 9:00 AM, after holding glucocorticoid dose for at least 24 hours). If adrenal insufficiency is confirmed, the exogenous glucocorticoid dosage should not be lowered below the minimum physiologic replacement range. This ensures adequate replacement for the adrenal insufficiency while still providing a stimulus for HPA axis recovery [25]. Patients should be retested and further significant dose reduction should only occur once there is evidence of HPA axis recovery. Patients with very low morning cortisol levels (as a guide: < 150 nmol/L are very likely to have persistent adrenal insufficiency. In such cases, dynamic testing is unlikely to be useful. Patients demonstrating significantly reduced morning cortisol levels (5µg/dL) are highly likely to have persistent adrenal insufficiency [26]. In these circumstances, dynamic testing may not be an effective approach. These patients should continue with physiologic daily dose equivalent glucocorticoid replacement aiming for the lowest safe dose and undergo repeat morning cortisol testing until recovery occurs. Patients with severely reduced morning cortisol levels should maintain a physiologic daily glucocorticoid replacement dose, using the lowest effective amount. They should undergo repeated cortisol testing until their adrenal function has recovered.

For patients with higher serum cortisol levels, but still below 300 nmol/L, the HPA axis may be able to recover. In these situations, the most practical and cost-effective approach is for the patients to continue taking a physiologic daily dose of glucocorticoid replacement, and have their morning serum cortisol checked regularly until their recovery is confirmed. Research indicates that in patients with suspected primary or secondary adrenal insufficiency, a morning cortisol level of 354 nmol/L or higher was found to reliably predict normal adrenal function [27]. Additionally, observations from the treatment of endogenous Cushing's syndrome suggest that in patients recovering from excess endogenous cortisol, a morning cortisol level of at least 276 nmol/L was associated with the absence of reported glucocorticoid withdrawal symptoms or adrenal crisis [23]. Patients with a history of glucocorticoid treatment/exposure presenting with manifestations of Cushing syndrome should be assumed to have a fully suppressed HPA axis and managed accordingly. Exogenous Cushing syndrome can occur with any glucocorticoid formulation and can take several months to resolve after the glucocorticoid daily dose is decreased to physiological range [28]. Morning cortisol measurement can differentiate those with adrenal insufficiency (suppressed cortisol level) or identify those with recovering adrenal axis, but persistence of cushingoid features. Individuals with a history of glucocorticoid exposure who present with signs of Cushing's syndrome should be presumed to have a fully suppressed hypothalamic-pituitary-adrenal axis, requiring appropriate management. Exogenous Cushing's syndrome can develop with any glucocorticoid formulation and may take several months to resolve once the daily glucocorticoid dose is lowered to physiological levels [28]. Measuring morning cortisol levels can help distinguish those with adrenal insufficiency or identify patients whose adrenal axis is recovering, even if cushingoid features persist.

Expecting HPAA recovery in patients with GIAI

Existing research on HPAA recovery after successful treatment of endogenous Cushing's syndrome may provide insights into GIAI [23]. Factors associated with slower HPAA recovery include higher glucocorticoid doses, female gender, lower body mass index, and persistent Cushing's features. In contrast, faster recovery is seen in patients treated with high-dose oral glucocorticoids for less than a month [29]. For those treated for over 12 months, HPAA normalization can take 6 to 12 months [30]. Additional studies are needed to further validate these observations in the GIAI population.

Summary

Primary care clinicians should be aware of the high incidence of glucocorticoid-induced adrenal insufficiency in patients receiving non-oral glucocorticoid formulations. Glucocorticoid withdrawal syndrome, stemming from dependence on supraphysiologic doses, presents symptoms similar to GIAI. Comprehensive biomedical and psychosocial research is needed to enhance our understanding of glucocorticoid withdrawal, with the goal of identifying reliable clinical biomarkers. This would assist healthcare providers in better distinguishing between glucocorticoid withdrawal and glucocorticoid-induced adrenal insufficiency.Clinicians are urged to taper glucocorticoids when feasible and assess for hypothalamic-pituitary-adrenal axis recovery. If patients experience glucocorticoid withdrawal symptoms during tapering, clinicians may consider modestly increasing the glucocorticoid dose and attempting a slower taper.

Additional data regarding the morbidity and mortality associated with glucocorticoid-induced adrenal insufficiency is required to understand the associated health risks, which will ultimately define the approach to care for patients tapering long-term glucocorticoid therapy.

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