Glucocorticoid-induced adrenal insufficiency: replace while we wait for evidence?

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MANAGEMENT OF ENDOCRINE DISEASE

Glucocorticoid-induced adrenal insufficiency: replace while we wait for evidence?

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Abstract

Glucocorticoids are, besides non-steroidal anti-inflammatory drugs, the most widely used anti-inflammatory medications. Prevalence studies indicate substantial use of both systemic and locally acting agents. A recognised adverse effect of glucocorticoid treatment is adrenal insufficiency, which is highly prevalent based on biochemical testing, but its clinical implications are poorly understood. Current evidence, including randomised trials and observational studies, indicates substantial variation among patients in both risk and course of glucocorticoid-induced adrenal insufficiency, but both are currently unpredictable. Oral and intra-articular formulations, as well as long-term and high-dose treatments, carry the highest risk of glucocorticoid-induced adrenal insufficiency defined by biochemical tests. However, no route of administration, treatment duration, or dose can be considered without risk. More research is needed to estimate the risk and temporal pattern of glucocorticoid-induced adrenal insufficiency, to investigate its clinical implications, and to identify predictors of risk and prognosis. Randomized trials are required to evaluate whether hydrocortisone replacement therapy mitigates risk and symptoms of glucocorticoid-induced adrenal insufficiency in patients discontinuing glucocorticoid treatment. This review aims to provide an overview of the available evidence, pointing to knowledge gaps and unmet needs.

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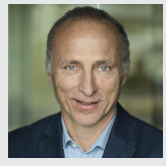

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Introduction

The potent anti-inflammatory and immunosuppressive properties of glucocorticoids are effective in managing numerous inflammatory and autoimmune conditions, as well as for symptom relief in certain cancers. This discovery led Kendall, Reichstein, and Hench to receive the Nobel Prize in Physiology or Medicine in 1950 (1). Today glucocorticoids are among the most frequently prescribed anti-inflammatory drugs, besides from non-steroidal anti-inflammatory drugs. It is recognised that glucocorticoid treatment also has many adverse effects, both on the short-term such as hyperglycaemia and neuropsychiatric symptoms and on the long-term suchlike osteoporosis and cardiovascular disease. In addition, glucocorticoid-induced adrenal insufficiency is highly prevalent based on biochemical testing. Still, the clinical implications of glucocorticoid-induced adrenal insufficiency remain poorly characterised (2, 3). While the clinical picture and severity of primary adrenal insufficiency are well-known, the degree to which these features apply to glucocorticoid-induced adrenal insufficiency remains to be documented (4, 5). The lack of evidence-based clinical guidelines on the management of glucocorticoid-induced adrenal insufficiency likely reflects a variety of factors: numerous indications for glucocorticoid therapy; multiple modes of administration; wide variation among patients in risk and course of glucocorticoid-induced adrenal insufficiency; and absence of relevant randomised trials and observational studies.

In this review of glucocorticoid-induced adrenal insufficiency, we aim to (i) provide an overview of the available evidence, (ii) identify knowledge gaps, and (iii) recommend directions for future research.

Extent of glucocorticoid use

Prevalence studies found that the prevalence of oral glucocorticoid use ranges from 0.5 to 20%, depending on settings, time period and methodology, and the prevalence of long-term use (≥3 months) is ≈1% (6, 7, 8, 9, 10, 11). The annual prevalence of glucocorticoid use in the Danish population indicates substantial use of both topical (≈0.1–10%) and systemic glucocorticoids (≈3%) (Fig. 1).

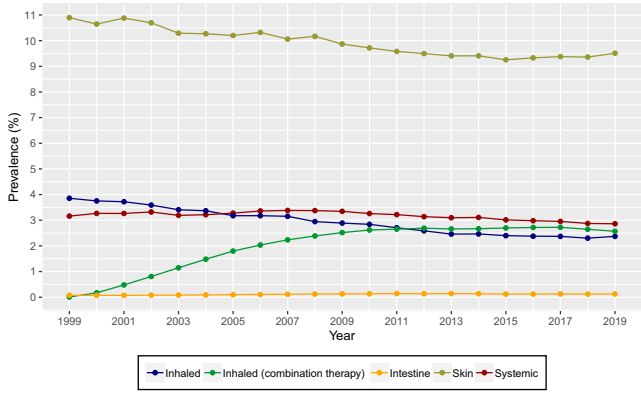

Figure 1

Annual prevalence* (%) of glucocorticoid use in the Danish population from 1999 to 2019, stratified by route of administration. *Defined as the number of people who redeemed at least one prescription for a glucocorticoid each year divided by the number of people in the population each year. Reference: medstat.dk, accessed 04/08/2020.

The hypothalamic–pituitary–adrenal axis

Cortisol is an active endogenous glucocorticoid hormone produced in the zona fasciculata of the adrenal cortex (12). Plasma cortisol levels are regulated by the hypothalamic–pituitary–adrenal (HPA) axis. Cortisol secretion is stimulated by stress signals and is subject to circadian rhythmicity characterised by peak levels in the early morning and a nadir at midnight (Fig. 2) (12). In the circulatory system, cortisol is bound to cortisol-binding globulin (75–80%) and albumin (10–15%), leaving only a few per cent unbound and biologically active.

Cortisol is an essential and pervasive regulator of resting as well as stress-related homeostasis and impacts foetal development, substrate metabolism, cardiovascular function, the inflammatory and immune system, water and electrolyte homeostasis (through regulation of vasopressin), as well as the reproductive and central nervous systems (Fig. 3) (12).

Many of the actions are permissive, meaning that cortisol itself does not initiate physiological processes, but rather allows them to occur by increasing the expression and activity of enzymes and hormonal systems. Cortisol production is in the range of 10–20 mg/day and increases greatly during such stressors as infections, acute illness, trauma, surgery, hypoglycaemia, and mental stress. Cortisol exerts physiological (and adverse) effects through binding to the intracellular glucocorticoid and mineralocorticoid receptors. Binding to these receptors regulates gene transcription by either transactivation or transrepression. Due to their lipophilic structure, unbound cortisol diffuses freely through the cell membrane, but a balance between biologically active cortisol and inactive cortisone regulates intracellular bioactivity. The interconversion between cortisol and cortisone is catalysed

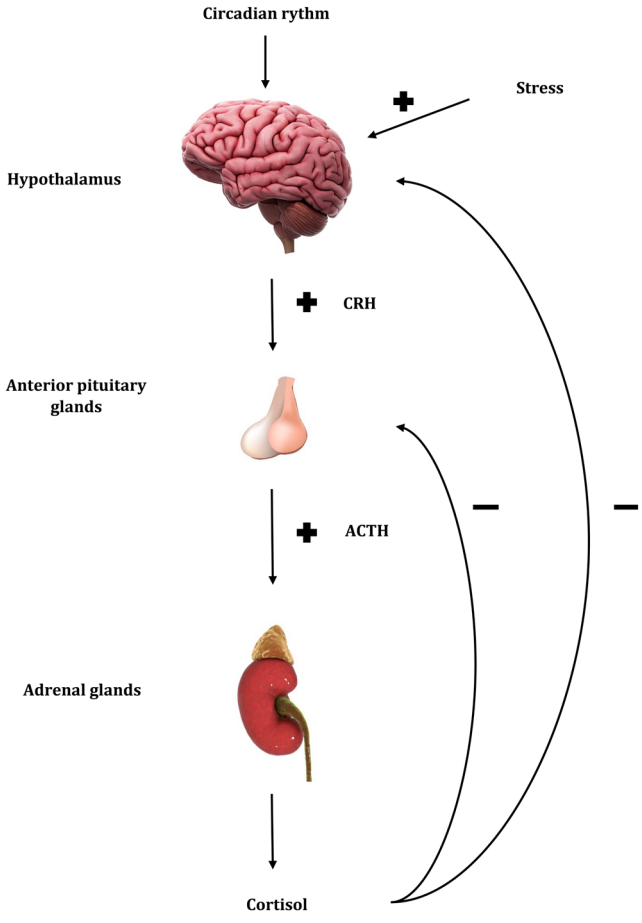

Figure 2

Overview of the hypothalamic–pituitary–adrenal (HPA) axis. When stimulated, the hypothalamic paraventricular nucleus secretes corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH promotes synthesis and release of cortisol from the adrenal glands. ACTH also exerts trophic effects on the adrenal cortex. In turn, cortisol exerts negative feedback on CRH and ACTH release through both genomic and non-genomic pathways.

by 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and 11β-HSD2 (13). Aside from effects on gene transcription, accumulating evidence suggests faster actions mediated through interactions with both lipids and proteins on the cell membrane and in the cytosol.

Glucocorticoid-induced adrenal insufficiency

Adrenal insufficiency is a biochemically defined diagnosis of hypocortisolism. Several diagnostic stimulation tests exist. Although there is no gold standard, the short Synacthen test (SST) is used most commonly in clinical practice. The cortisol cut-off value used to define an abnormal cortisol response is assay-dependent. In many modern assays, the cut-off is < 420 nmol/L (14).

Adrenal insufficiency is categorised according to the underlying mechanism. Primary adrenal insufficiency denotes adrenal disease and is usually accompanied by deficient levels of aldosterone. Secondary adrenal insufficiency involves adrenocorticotropic hormone (ACTH) deficiency arising from pituitary or hypothalamic disorders (4, 5, 15). Some refer to tertiary adrenal insufficiency when it is caused by hypothalamic disease. The terminology has not been finalised for glucocorticoid-induced adrenal insufficiency, with some referring to the condition as iatrogenic, secondary, or tertiary adrenal insufficiency. In this review, we use the expository term 'glucocorticoid-induced adrenal insufficiency'.

Glucocorticoid treatment may cause adrenal insufficiency via feedback suppression of CRH and ACTH, eventually inducing adrenocortical hypoplasia and atrophy, and rendering the HPA axis unable to produce an adequate cortisol response to stress. Adrenal insufficiency may persist after cessation of glucocorticoid treatment. Primary adrenal insufficiency and secondary adrenal insufficiency due to structural disorders are rare (prevalence = 100–200 per million persons), but are recognised serious conditions requiring prompt diagnosis and hormone replacement therapy is considered life-saving (4, 5, 15). In contrast, glucocorticoid-induced adrenal insufficiency is much more prevalent, but with less clear clinical implications (2, 3, 16).

Occurrence

Biochemically defined glucocorticoid-induced adrenal insufficiency has been examined in numerous studies and summarised in systematic reviews and meta-analyses (2, 3, 16). Broersen *et al.*'s (2) 2015 systematic review and meta-analysis encompassed 74 studies and 3753 patients (≥12 years of age) and estimated pooled percentages of patients with glucocorticoid-induced adrenal insufficiency during or around cessation, stratified by route of administration (Fig. 4). The pooled percentages of patients with adrenal insufficiency during treatment or at cessation were ≈50% for oral use, ≈52% for intra-articular administration, ≈8% for inhaled glucocorticoids, ≈5% for topical administration, and ≈4% for intranasal administration (Fig. 4) (2). Time between last glucocorticoid dose and first test was in the range of 0–30 days, but testing was mostly performed within the first week (50/74 studies). In 22 studies, the

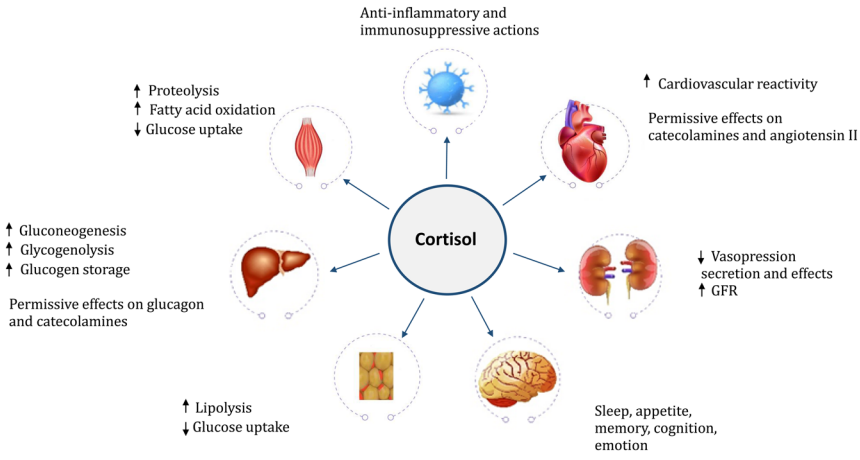

Figure 3
Physiological effects of cortisol.

authors did not report the time gap. Similar findings have been published for paediatric patients treated with systemic (16), inhaled (17, 18, 19), or topical glucocorticoids (20). In line with these studies, Joseph *et al.*'s (3) 2016 systematic review, which encompassed 73 studies and 3166 patients (≥16 years of age), reported a median percentage of 37% for glucocorticoid-induced adrenal insufficiency among systemic glucocorticoid users during or around cessation of treatment (interquartile range: 13–63%) (3).

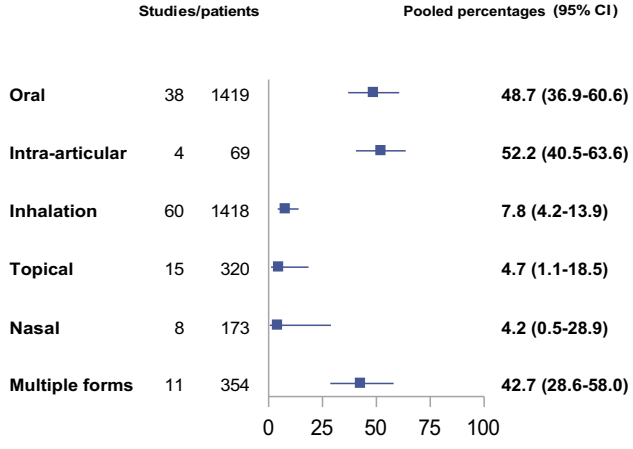

Figure 4
Pooled percentages of biochemically verified glucocorticoid-induced adrenal insufficiency during treatment or around cessation, stratified by routes of administration. Figure adapted with permission from Broersen LHA, *et al.* Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2171–280. Time between last glucocorticoid dose and first test was in the range of 0–30 days, but the test was mostly performed within the first week (50/74 studies). In 22 studies they did not report this time gap.

It is important to note that current studies are highly heterogeneous regarding patient selection, glucocorticoid treatment regimens (glucocorticoid type, administration form, dose and duration), as well as outcome assessment and choice of biochemical methods (test type, assay, and cut-off values). It is therefore difficult to make comparisons among studies. Hence, the pooled percentages in the meta-analysis by Broersen *et al.*'s (2) may be difficult to evaluate and should be interpreted with caution. Furthermore, many cohort studies or randomised trials on the subject circumvented direct reporting of effect measures as absolute risks or incidence rates, which makes it more difficult to interpret the results in the clinical context.

Recovery of the HPA axis

A key issue is time to recovery of the HPA axis following discontinuation of glucocorticoid treatment. The percentage of patients with adrenal insufficiency following oral treatment cessation declines over time, but remains up to 40% six months following cessation (21, 22, 23, 24, 25), 20% two years following cessation (26, 27, 28), and 5% three years following cessation (26). This underscores the potential long-term nature of adrenal insufficiency after glucocorticoid use.

Clinical implications

As noted earlier, the clinical implications of glucocorticoid-induced adrenal insufficiency have not been studied extensively. Supplementary Table 1 (see section on supplementary materials given at the end of this article) provides a review of thirteen case reports (including cohort studies with secondary reporting of

symptoms and signs) (24, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38), two randomised trials (39, 40), two cohort studies (27, 41) and two cross-sectional studies (42, 43) on this topic. Most were hampered by non-standardised screening for clinical outcomes or incomplete follow up in the randomised trials or cohort studies. Further, it is inherently difficult to distinguish symptoms and signs of adrenal insufficiency from the treatment indication (such as cancer) or adverse effects of concomitant treatment such as chemotherapy, and indeed the glucocorticoid treatment itself. A cohort study from UK (n = 70 638 oral glucocorticoid users) quantified dose-dependent rates of glucocorticoid-induced adrenal insufficiency diagnosed in primary or hospital care (44). Incidence rates were up to 0.86 per 1000 person-years during periods of ≥7.5 mg/day and up to 30 per 1000 person-years for periods with cumulative dose ≥3055 mg in the past year (44). The observed rates were likely lower than the true rates due to a lack of awareness of this condition among clinicians with likely underreporting as a result. Among people with glucocorticoid-induced adrenal insufficiency, the mortality rate was 51 per 1000 person years during entire follow-up. During periods of glucocorticoid treatment, people with and without adrenal insufficiency had similar mortality rates (mortality rate ratio of 1.02), but during periods of non-use mortality rate was higher among people with a prior record of adrenal insufficiency compared to those without (mortality rate ratio of 2.09). The authors speculated if this contrast was attributable to adrenal crisis during treatment discontinuation (44).

Prolonged hypocortisolemia may cause non-specific symptoms such as fatigue, anorexia, nausea, hyponatremia, weight loss, myopathy, and neuropsychiatric symptoms. Insufficient cortisol responsiveness to stress may induce an acute adrenal crisis with severe gastrointestinal symptoms, cardiovascular collapse, hypoglycaemia, seizures, and eventually coma. Little evidence is available to clarify whether the course (severity and outcome) of glucocorticoid-induced adrenal insufficiency differs from this clinical picture described earlier. Precipitating factors for an adrenal crisis include infections, other acute illnesses, trauma, surgery, starvation, or psychological distress (15). Patients receiving low-dose glucocorticoid treatment therefore may require extra glucocorticoid replacement during stress. This is a genuine concern, as glucocorticoid-induced adrenal insufficiency occurs in up to one-third of patients on low-dose oral glucocorticoid treatment (45), and awareness of the potential for adrenal insufficiency in this group may be low.

Diagnostic accuracy of the insulin tolerance test and the short Synacthen test

Several stimulation tests exist to confirm the diagnosis of glucocorticoid-induced adrenal insufficiency, including the insulin tolerance test (ITT) and the short Synachten test (SST).

- The ITT evaluates the HPA axis at the central level (hypothalamic and pituitary level) and is considered the gold standard for diagnosing secondary adrenal insufficiency. However, it is rarely used in routine clinical practice, as it is labour-intensive, unpleasant for the patients and contraindicated in patients with a history of cardiovascular disease or seizures. As well, the ITT may not be reliable, as levels of induced hypoglycaemia can differ.
- The SST, the most widely used test, evaluates the HPA axis at the adrenal gland level. It was originally devised for diagnosing primary adrenal insufficiency. The test is performed by measuring cortisol before and 30 min after intravenous administration of 250 µg of synthetic ACTH (Synachten). A plasma cortisol value above the cut-off value 30 min post-Synacthen administration indicates an adequate adrenal response. The cortisol cut-off value is assay-dependent; a value of 420 nmol/L is used in many modern assays (14). The liquid chromatography-tandem mass spectrometry (LC-MS/MS) is considered most specific for measure of plasma cortisol levels, as LC-MS/MS avoids cross-reactivity with other steroids (14). In clinical settings, plasma cortisol is, however, often measured with immunoassays. The cortisol cut-off value of 420 nmol/L is decided based on the 2.5 percentile of plasma cortisol in healthy adults measured by LC-MS/MS. Clinicians should mind that this choice of cut-off value is a matter of sensitivity and specificity (higher cut-off values provide a higher sensitivity but lower specificity). Values close to the normal range should, therefore, be interpreted in combination with the clinical context. A central consideration is that we currently lack gold standard to define glucocorticoid-induced adrenal insufficiency, partly due to the complexity of the condition as well as its many unknown aspects.

Measuring morning cortisol/ACTH may provide a pragmatic alternative, but sufficient evidence is lacking and the SST is still considered superior.

Ideally, the diagnostic accuracy of any biochemical test should be validated before use in clinical practice. The SST was developed for Addison's disease (primary adrenal insufficiency) (46) and the diagnostic accuracy of the test

in relation to glucocorticoid-induced adrenal insufficiency remains unknown. A meta-analysis that investigated the diagnostic accuracy of the SST in secondary adrenal insufficiency (due to pituitary disorders) documented relative high specificity (0.93) and low sensitivity (0.64). The study excluded patients on glucocorticoid treatment partly due to a lack of a gold standard against which to validate the SST (47).

Several concerns are salient in use of the SST to diagnose glucocorticoid-induced adrenal insufficiency. First, the diagnostic accuracy of the test is unknown. Second, as the test evaluates the HPA axis at the adrenal gland level, it may yield a false normal response in the early stage of any non-primary adrenal insufficiency. Third, the cortisol cut-off value to rule out or rule in adrenal insufficiency remains a pragmatic choice of sensitivity and specificity levels. Fourth, in many patients the clinical picture is of limited value for the diagnosis, given the overlap in clinical symptoms with the concomitant treatment and underlying diseases.

The association between the Synacthen test and clinical outcomes

The association between the Synacthen test and clinical outcomes is unknown and several questions remain unanswered. We discuss two questions:

– *First, does an insufficient cortisol response to a stimulation test correlate with symptoms and clinical outcomes of adrenal insufficiency?*

As mentioned, the SST was originally developed to diagnose primary adrenal insufficiency (46) and subsequently was used to diagnose secondary adrenal failure, typically in patients with pituitary disease (48). The clinical picture of severe primary adrenal insufficiency has stood the test of time and the life-saving effects of hydrocortisone replacement are self-evident (49, 50). The clinical picture of secondary adrenal insufficiency is often less severe, since some residual adrenal function may remain, including intact aldosterone production. It is uniformly accepted that affected patients should be offered hydrocortisone replacement if they respond insufficiently to the SST (51). It is tempting to extrapolate this clinical experience to patients with glucocorticoid-induced adrenal insufficiency. However, given its high prevalence, specific pathogenesis, and often dynamic nature of this condition, one could ask if not the time has come to test this assumption in the context of a prospective trial? This is an important questions, as hydrocortisone replacement may also be associated with adverse effects due to overtreatment.

– *Second, does a normal stimulated cortisol response test rule out related clinical symptoms and outcomes?*

Even among patients without biochemical adrenal insufficiency following cessation of glucocorticoid treatment, some exhibit withdrawal symptoms (52). The withdrawal syndrome is likely related to high glucocorticoid doses. It typically manifests with unspecific symptoms such as anorexia and weight loss, nausea and vomiting, headache and lethargy, fever, myalgia and arthralgia, skin desquamation, and postural hypotension (52). These symptoms resemble adrenal insufficiency. The syndrome is considered to be a consequence of tolerance development and dependence. During the period of glucocorticoid treatment, the body adjusts to a new equilibrium, which is disrupted after discontinuation (52). As with glucocorticoid-induced adrenal insufficiency, the clinical impact of the glucocorticoid withdrawal syndrome is unknown.

Predictors of glucocorticoid-induced adrenal insufficiency and recovery

Given the widespread use of glucocorticoids and the substantial individual variation in susceptibility to glucocorticoid-induced adrenal insufficiency, it is critical to identify valid predictors of diagnosis, recovery, and clinical adverse outcomes. The purpose of such predictors would be to stratify patients into relevant risk categories. Currently, the risk and course of glucocorticoid-induced adrenal insufficiency are unpredictable, as discussed subsequently.

Treatment regimens

Glucocorticoid treatment regimens (generic glucocorticoid type, dose, duration, and route of administration) are highly heterogeneous and may affect the risk of glucocorticoid-induced adrenal insufficiency and HPA axis recovery time.

Route of administration

As stated previously, treatment with oral and intra-articular glucocorticoids carries the highest risk of glucocorticoid-induced adrenal insufficiency, but no routes of administration can be considered completely safe from this risk (2).

Generic types of glucocorticoids

The generic types of glucocorticoids have different pharmacokinetic and pharmacodynamic properties. As displayed in Table 1, 5 mg of oral prednisolone is

considered equivalent to 20 mg of hydrocortisone, 4 mg of methylprednisolone and 0.75 mg of beta- or dexamethasone in concern to anti-inflammatory potency (53). Furthermore, systemic glucocorticoids are categorised into short-acting (hydrocortisone), intermediate-acting (prednisolone, prednisone, methylprednisolone), and long-acting (dexamethasone, betamethasone) based on their biological half-life (53). As biological half-life is a direct reflection of time of ACTH-suppression, long-acting formulations may increase the risk of glucocorticoid-induced adrenal insufficiency compared to for example, short-acting glucocorticoids (given same equivalent dose and duration of treatment). Two randomised controlled trials that compared high-dose prednisolone vs dexamethasone treatment in children with acute lymphoblastic leukaemia found no difference in the incidence of glucocorticoid-induced adrenal insufficiency (40, 54). A cohort study observed earlier recovery in children treated with prednisolone vs dexamethasone (25).

Dose and duration

The effect of dose and duration on risk of glucocorticoid-induced adrenal insufficiency remains controversial. The meta-analysis conducted by Broersen *et al*. showed that high-dose and long-term glucocorticoid treatment produced a higher risk of glucocorticoid-induced adrenal insufficiency. However, no treatment dose or duration is completely without risk (Fig. 5) (2). The systematic review by Joseph *et al*. found no obvious pattern after stratifying by average daily dose, duration, or cumulative dose of systemic glucocorticoids (3).

When evaluating the risk of glucocorticoid-induced adrenal insufficiency by treatment regimen, it is important to recognise that factors such as dose, treatment duration, and route of administration are intercorrelated. As an example, intra-articular treatments are high-dose depot formulations with unavoidable systemic absorption. This likely explains the high percentage of associated glucocorticoid-induced adrenal insufficiency. In contrast, topically applied glucocorticoids are low-dose formulations with low bioavailability, which is likely to underlie the relatively low percentage of associated glucocorticoid-induced adrenal insufficiency. In addition, the systematic reviews by Broersen *et al*. (2), Joseph *et al*. (3), as well as the majority of studies included in those reviews reported average daily glucocorticoid dose during the entire treatment periods and not just prior to cessation.

Test results

Test results could be a valuable clinical tool to predict HPA axis recovery time. One study is available that assessed use of the SST to predict adrenal recovery (55). The study included a subgroup of 110 patients with glucocorticoid-induced adrenal insufficiency. In this subgroup, Δ cortisol (30 min cortisol after Synacthen – basal cortisol) divided into >100 nmol/L and ≤100 nmol/L was predictive of adrenal recovery. The area under the curve of the receiver operating curve (AUC) was 0.77 and the median recovery time was 262 days in patients with Δ cortisol >100 nmol/L, compared to 974 days for patients with Δ cortisol ≤100 nmol/L (55). However, the study was prone to selection bias, as it stipulated a future second SST at the time of study inclusion (55).

Biomarkers and genotypes

Currently, no biomarkers exist to predict diagnosis or clinical course of glucocorticoid-induced adrenal insufficiency, but potential candidates include the 24-hour urine steroid metabolome, soluble CD16,

Table 1 Pharmacokinetic and pharmacodynamic properties of selected oral glucocorticoids.

Systemic glucocorticoid	AE dose* (mg)	Relative GC activity	Relative MC activity	Half-life** (h)
Short-acting				
Hydrocortisone	20	1	1	8–12
Intermediate-acting				
Prednisolone	5	4	0.8	12–36
Prednisone	5	4	0.8	12–36
Methylprednisolone	4	5	Minimal	12–36
Long-acting				
Dexamethasone	0.75	30	Minimal	36–54
Betamethasone	0.75	30	Minimal	36–54

*Equivalent anti-inflammatory dose is for oral or intravenous administration. **The biologic effective half-life is based on the duration of ACTH suppression.
AE, approximate equivalent; GC, glucocorticoid; MC, mineralocorticoid.

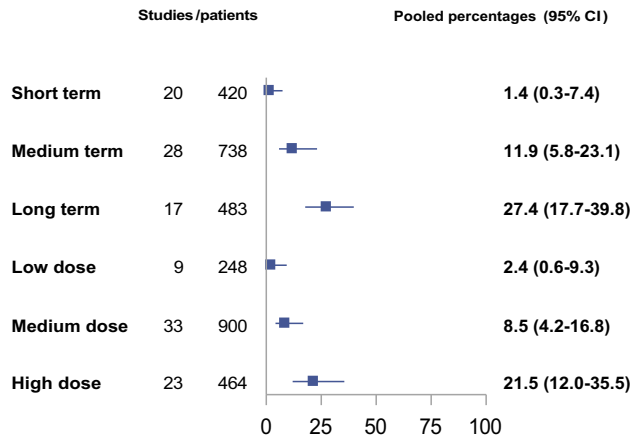

Figure 5

Pooled percentages of biochemically verified glucocorticoid-induced adrenal insufficiency during treatment or around cessation, stratified by treatment dose and duration. Figure adapted with permission from Broersen LHA *et al.* Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2171–280. Treatment duration was categorised as follows: short-term: <1 month; medium-term: 1 month - 1 year; long-term: >1 year. Treatment dose was categorised according to recommended doses, with the doses between the lower and upper bounds of the recommendation coded as medium-dose, doses below the lower bound as low-dose, and doses above the upper bound as high-dose. For categorisation, average dose and duration were used. For exact scheme of dose ranges, please see Supplementary Table 2. Analysis was performed for asthma patients only, as opposed to the entire population of glucocorticoid users, to provide a homogeneous patient population.

ADAM17 (disintegrin and metalloproteinase domain-containing 17) or CDF15, among others (56, 57, 58). Steroid biosynthesis and metabolism are mirrored by the 24-hour urine steroid metabolome. Metabolome profiling, therefore, provides unique fingerprints associated with disorders of steroid biosynthesis and metabolism and may be used for diagnostic and prognostic prediction (56). Further, concentrations of soluble CD16 and ADAM17 are increased in patients with adrenal insufficiency compared with healthy controls (57). CD16 is normally expressed at the surface of natural killer cells, neutrophils, monocytes, and macrophages, but shredding may occur in states of glucocorticoid deficiency, hence leading to an increase in soluble CD16. ADAM17 is the main metalloproteinase responsible for CD16 shredding. Last, glucocorticoid deficiency is associated with elevated levels of GDF15, a stress-induced hormone acting in the brain to induce an aversive response towards food intake (58).

Despite the individual variation in susceptibility to glucocorticoid-induced adrenal insufficiency, research focusing on genotype as predictive or etiological factors is limited. Biologically plausible gene candidates could relate to all components of the HPA axis and glucocorticoid signalling pathways. A recent genome-wide association study found that genetic variation in the platelet-derived growth factor D (PDGFD) gene locus was associated with adrenal suppression in children and adults treated with inhaled glucocorticoids for asthma or COPD (59). PDGFD is highly expressed in the adrenal glands and the PDGFD signalling pathway is important for the development of steroid-producing cells and steroidogenesis (60, 61). Other plausible gene loci include those coding for the glucocorticoid receptor or the enzyme 11β-HSD. The response to glucocorticoids varies considerably among individuals and this may also affect susceptibility to glucocorticoid-induced adrenal insufficiency, as demonstrated by the low-dose dexamethasone suppression test (62). At present, polymorphisms in the gene loci encoding the glucocorticoid receptor as well as 11β-HSD are leading candidate genes to account for the large variation in glucocorticoid response (63). Gene-environment studies on this subject are needed to disentangle etiological pathways.

Clinical practice – a call for evidence

Glucocorticoid treatment is by far the most common cause of adrenal insufficiency, but there are no evidence-based clinical guidelines to support clinical management or prevention.

Currently, monitoring *of* glucocorticoid-induced adrenal insufficiency during and following cessation of treatment is unsystematic, sporadic, and reliant on individual clinicians' knowledge and awareness. From a patient-safety and cost-effectiveness perspective, evidence-based clinical guidelines need to be developed, to provide effective, uniform, and economical monitoring.

To reduce the adverse effects of glucocorticoids, such as glucocorticoid-induced adrenal insufficiency, most available clinical guidelines recommend using the lowest possible effective glucocorticoid dose and then tapering treatment. Nevertheless, up to one-third of patients receiving low-dose oral glucocorticoid treatment have biochemically verified adrenal insufficiency (45). These

patients may be particularly vulnerable to adrenal crisis during stress as their glucocorticoid treatment dose does not cover the extra need for glucocorticoid during stressful periods. In patients treated with supraphysiologic doses of glucocorticoids, glucocorticoid dose below which patients need additional stress doses are not well known. Randomised placebo-controlled trials thus are needed to investigate the benefit of hydrocortisone replacement therapy in patients with moderate or borderline glucocorticoid-induced adrenal insufficiency as assessed by the SST. Further, it remains to be investigated which patients may benefit from day to day replacement and which only need replacement during stress. Evidence is also needed about the efficacy and safety of tapering regimens, as despite tapering up to 40% of former oral glucocorticoid users have persistent HPA axis suppression at 6 months post-cessation and 5% at 3 years post-cessation (23, 26). In addition, resolution is needed for conflicting evidence on strategies to mitigate the risk and clinical consequences of glucocorticoid-induced adrenal insufficiency. Some suggest the need for a low threshold to test patients following withdrawal, and others advise switching to hydrocortisone during tapering or withdrawal. Neither of these strategies are evidence-based, pointing to the need for randomised trials on this subject. The physiological rationale for converting from other generic glucocorticoids to hydrocortisone during tapering is that time of ACTH-suppression (biological half-life) is shortest for hydrocortisone compared to the other systemic glucocorticoids. Theoretically, hydrocortisone, therefore, carries lowest risk of adrenal insufficiency and may also shorten time to recovery of the HPA axis (given the same equivalent dose), but no evidence on this exist. Further, switching to hydrocortisone eases monitoring of tapering for example in relation to the interpretation of biochemical measures. Strategies for management and prevention may further vary by administration forms and if concomitant administration forms are used. It also remains to be clarified to which extent biochemically diagnosed adrenal insufficiency translates into clinically relevant morbidity.

Conclusion and future perspectives

Glucocorticoid-induced adrenal insufficiency is prevalent based on biochemical testing and potentially life-threatening. Nonetheless, substantial individual variation is likely to present and needs to be investigated further. More research is needed to refine the diagnosis and to support evidence-based clinical decision-making. Necessary steps are (i) studies on risk and prognosis and how the biochemical diagnosis translates into morbidity, (ii) studies comparing the effect of different tapering strategies, (iii) randomised controlled trials to evaluate whether hydrocortisone replacement therapy mitigates the clinical consequences during and following discontinuation of glucocorticoid treatment, and (iv) research that identifies biomarkers useful for diagnosis, assessing prognosis, and the effect of replacement therapy.

Highlights

Current knowledge and unsolved questions

- The continued widespread use of glucocorticoids (annual prevalence ≈ 3% for oral use) underscores the need for evidence-based clinical guidelines on managing glucocorticoid-induced adrenal insufficiency, which may be present in ≈ 50% of patients after oral treatment.
- Predictors of glucocorticoid-induced adrenal insufficiency include prolonged high-dose treatment, as well as oral and intra-articular administration, but it may also occur after topical or short-term treatment.
- Glucocorticoid-induced adrenal insufficiency is potentially life-threatening. However, the full spectrum of clinical implications has not yet been elucidated.

Future research directions

Cohort studies and randomised trials should be designed to:

- Estimate the risk and temporal pattern of glucocorticoid-induced adrenal insufficiency, investigate its clinical implications, and identify markers of risk and prognosis, with the goal of improving patient management.
- Investigate the correlation between biochemical tests, novel biomarkers, and patient outcomes.
- Study the efficacy and safety of withdrawal regimens with respect to glucocorticoid-induced adrenal insufficiency.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-20-1199.

Declaration of interest

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