ABSTRACT

Objective: Prolonged exposure to glucocorticoids lead to hypothalamic-pituitary-adrenal (HPA) axis suppression that recovers after cessation of treatment. We aimed to identify the predictive factors for HPA axis recovery after prolonged glucocorticoid use.

Methods: Retrospective review of patients who had undergone first short Synacthen test (SST) to assess HPA axis recovery after prolonged use of glucocorticoids.

Results: A total of 61% (20/33) of patients had adequate SST response at a median time of 2 years after diagnosis of adrenal insufficiency. Those who had adequate response during SST had higher ambulatory early morning cortisol ($P<.01$), shorter duration of exposure to glucocorticoids ($P=.01$), and lower final cumulative hydrocortisone replacement dose ($P=.03$). Age, gender, body mass index, indications for glucocorticoid use, and basal adrenocorticotropic hormone levels were not predictive of HPA axis recovery.

On multivariate analysis, ambulatory early morning cortisol was the only independent predictor of adequate SST response (odds ratio, 1.02; 95% confidence interval, 1.01 to 1.04; $P=.02$). Using receiver operating characteristic curve analysis, ambulatory early morning cortisol of 8.8 µg/dL predicted a positive SST response with a sensitivity of 70% and specificity of 93%.

Conclusion: Early morning ambulatory cortisol could be used to decide on timely SST in order to prevent complications from unnecessary replacement with glucocorticoids. (Endocr Pract. 2018;24:xxx-xxx)

Abbreviations: ACTH = adrenocorticotropic hormone; BMI = body mass index; CV = coefficient of variation; HPA = hypothalamic-pituitary-adrenal; SST = short Synacthen test

INTRODUCTION

Glucocorticoids have commonly been used for decades to treat a myriad of conditions that are autoimmune or inflammatory in origin (1). In Asia, glucocorticoids are also widely prescribed factitiously by traditional healers to provide symptomatic relief from many common ailments, including joint pain, rash, allergy, or even lethargy. These remedies that include Chinese traditional medicine and other homeopathic treatments have been reported to contain excess amounts of undeclared corticosteroids, namely dexamethasone, in addition to other adulterants (2-4).

Chronic use of glucocorticoids leads to undesirable metabolic complications, including weight gain, diabetes, hypertension, osteoporosis, and more importantly, steroid withdrawal symptoms and hypothalamic-pituitary-adrenal (HPA) axis suppression if the glucocorticoids are discontinued abruptly (5,6). Therefore, timely initiation of physiologic doses of glucocorticoid replacement until recovery of the adrenal function is crucial (7). Recovery of the HPA axis occurs between 1 and 3 years of cessation of...
glucocorticoids, but this time span is not well established (8,9). Although the gold-standard test to detect HPA axis recovery would be the insulin tolerance test (ITT), this test is cumbersome to perform. The short Synacthen test (SST), which is easily performed at any time of the day, has been shown to be highly correlated with the ITT and could be used as a reliable test to assess HPA axis recovery (10-12). Failure to detect recovery of the HPA axis leads to unnecessary administration of excess glucocorticoids in a person who is replete with endogenous glucocorticoids, leading to adverse cardiometabolic complications of excess glucocorticoids.

To date, there is no clear guidance for the managing clinician to predict recovery of the HPA axis in order to decide on the best timing for HPA axis testing (13,14). There are also sparse data on recovery of the HPA axis, especially after use of traditional medicines. As this is a commonly encountered cause of HPA axis suppression in our clinical practice, we decided to embark on this study to determine the predictive factors for HPA axis recovery after prolonged glucocorticoid use.

METHODS

Study Subjects
We reviewed all patients who had a SST at the Endocrine Unit Day Care between January 2013 and May 2017. Ethics approval was obtained from the Medical Research Ethics Committee (MREC ID no: 201610314468). Patients with established hypocortisolism from prolonged glucocorticoid use who had a SST to look for HPA axis recovery were analyzed. The diagnosis of hypocortisolism was confirmed by a peak cortisol level of <18.1 µg/dL from the SST or a very low early morning cortisol of <3 µg/dL (15-17). All patients included had documented exposure to exogenous oral glucocorticoids for a cumulative period of more than 3 months either prescribed formally or obtained from traditional healers. Patients who had the SST with known hypothalamic pituitary conditions, primary adrenal disorders, or Addison disease, pregnant or on oral contraceptives, or with incomplete records were excluded. All patients who had established hypocortisolism after exposure to glucocorticoids were managed with oral hydrocortisone. The regimen employed to taper doses of hydrocortisone replacement were hydrocortisone 20/10 mg twice a day for 1 to 3 months, as these patients are likely to experience steroid withdrawal symptoms with lower replacement doses in the acute period (18). From 3 to 6 months onwards, they are tapered to hydrocortisone 10 mg twice a day or 10/5 mg twice a day after taking into consideration clinical symptoms and changes in weight. An ambulatory AM cortisol was obtained during follow-up and used as a guide to determine possible recovery of the HPA axis. Patients were followed from diagnosis of hypocortisolism until commencement of the first SST.

Clinical Data
Data on parameters such as age, sex, body weight and height, glucocorticoid type and dose, and indication and duration of use were obtained from the electronic medical records.

Laboratory Measurements
Serum albumin levels (normal range, 32 to 48 g/L) were measured based on the method of Doumas, Watson, and Biggs with bromocresol green solution as a binding dye. Serum cortisol levels were measured by the Advia Centaur immunoassay using direct chemiluminescent technology, and plasma adrenocorticotropic hormone (ACTH) levels (normal range, 5 to 60 pg/mL) were measured by Immulite 2000 ACTH, a solid-phase, two-site, sequential chemiluminescent immunometric assay. For the cortisol assay, the intra-assay coefficients of variation (CVs) were 2.8 to 3.8%, and the interassay CVs were 1.8 to 5.4%; for the ACTH assay, the intra-assay CVs were 6.7 to 9.5%, and the interassay CVs were 6.1 to 10%. Ambulatory AM cortisol was the final early morning cortisol level obtained prior to ingestion of morning dose of hydrocortisone, at an outpatient setting, between 7 and 9 AM, within 3 months prior to the SST. Peak cortisol was defined as the highest serum cortisol level obtained during the SST at either 30 or 60 minutes.

SST
All patients included had a SST done to assess HPA axis recovery. The SST was performed in a supine position, after at least 24 hours since last oral hydrocortisone ingestion. Patients were advised to withhold the hydrocortisone the afternoon prior and the morning of the SST. Intravenous tetracosactrin (250 µg) was used, with cortisol measured at 0, 30, and 60 minutes. Adequate response or recovery was defined as a peak cortisol level of ≥18.1 µg/dL. Patients who had failed would be continued on oral hydrocortisone, and the SST would be repeated annually to re-assess recovery.

Statistical Analysis
Data are presented as mean ± SEM or median (range) where appropriate. Univariate analysis was carried out to compare the parameters between those who had adequate response versus inadequate response during first SST. Independent Student’s t test, Mann-Whitney U test, chi-square test, and Fischer’s exact test were used to compare the parameters between the two groups. Parameters that were significantly associated with a positive SST response on univariate analysis with a P value <.25 were then analyzed in a multivariate analysis using the binary logistic regression for independent predictors, with results displayed as odds ratio (95% confidence interval). A receiver operating characteristic (ROC) curve was used to determine threshold values of ambulatory cortisol that predict adequate SST.
response. All statistical analyses were conducted using the SPSS, version 22.0, and a 2-tailed $P \leq 0.05$ was considered statistically significant.

**RESULTS**

A total of 139 patients had SST between January 2013 and May 2017. Seventy-two patients had undergone SST to assess HPA axis recovery. Of these, 39 patients were excluded, as they had known hypothalamic-pituitary dysfunction, primary adrenal failure, Addison disease, had been exposed to topical and inhalational steroids, or had incomplete records. A total of 33 patients were included in the final analysis. Of these, 20 had adequate response during SST. In the 13 patients who did not respond adequately in the first SST, 6 of them had a second SST within the study follow-up. A flow chart of patient recruitment is shown in Figure 1.

**Baseline Clinical Data**

The majority of study subjects were female (61%), with a mean age of 64 years. They were obese, with a mean body mass index (BMI) of 30.9 kg/m$^2$. The initial presentations to the endocrinologist were as follows: 5 (15%) patients presented with hypocortisolic crisis; 6 (18%) patients had hyponatremia that could not be attributed to any other cause; 7 (21%) patients were screened as part of work-up for secondary osteoporosis; 6 (18%) patients were screened for rapid-onset weight gain; 9 (27%) patients for presence of clinical features of Cushing syndrome such as thin skin or striae, easy bruising, or proximal myopathy. About half of the patients had comorbidities such as diabetes, and more than half of them had hypertension. Osteoporosis was diagnosed in one-fourth of the patients by means of bone density (dual-energy X-ray absorptiometry) T-scores of less than −2.5 in the hip or spine or the presence of an osteoporotic fracture. Twenty percent did not have a bone density done. The glucocorticoids were administered orally in all patients, and more than 80% were factitiously prescribed by traditional healers and the remainder for renal, dermatologic, and rheumatologic conditions. Patients were exposed to glucocorticoids for a median period of 2 years prior to diagnosis. Hypocortisolism from prolonged glucocorticoid use was confirmed in patients who exhibited symptoms of hypocortisolism with a low morning cortisol (<3 µg/dL) in 75% and the remaining 25% by an inadequate SST response.

All patients were replaced with oral hydrocortisone. The mean final cumulative dose prior to SST was 13.4 mg/day. The median time at testing with first SST was 23

![Flow chart of patient enrollment. HPA = hypothalamic-pituitary-adrenal; SST = short Synacthen test.](image-url)
months after initiation of hydrocortisone replacement. All patients had a normal albumin level at testing. The median ACTH and mean ambulatory AM cortisol levels prior to SST were 19 pg/mL and 9.1 µg/dL, respectively. The mean peak cortisol during SST was 19.2 µg/dL.

Comparison Between Groups With Adequate and Inadequate Response During SST

Sixty-one percent of the patients tested at a median of 2 years after replacement with hydrocortisone had adequate SST response. The median duration of exposure to glucocorticoids was significantly longer in the group that had adequate SST response: 4 years versus 1 year. The mean last cumulative dose of hydrocortisone was significantly higher in the group that had inadequate SST response: 16.0 mg/day versus 11.6 mg/day. The ambulatory early morning cortisol was significantly higher in the group that had inadequate SST response: 19.2 µg/dL versus 9.1 µg/dL. There was also a significant difference between groups for 30- and 60-minute SST: 10.3 µg/dL versus 5.32 µg/dL, respectively. The mean peak cortisol during SST was 19.2 µg/dL.

Multivariate Analysis

Parameters with a \( P < .25 \) on univariate analysis were included into the multivariate analysis to identify independent predictors of HPA axis recovery. Factors included were duration of steroid use, last cumulative hydrocortisone dose, and ambulatory early morning cortisol. Of these, only the ambulatory early morning cortisol was found to be an independent predictor of adequate SST response, with an odds ratio of 1.02 (95% confidence interval, 1.01 to 1.04; \( P = .02 \)).

ROC Curve

As ambulatory AM cortisol was independently predictive of an adequate SST, we used ROC curve analysis to determine threshold cortisol levels that could best predict HPA recovery (Fig. 2). An ambulatory cortisol level cutoff of 8.8 µg/dL was found to be predictive of an adequate SST, with a sensitivity of 70% and a specificity of 93%. The area under the curve for ambulatory AM cortisol to predict SST recovery was 0.87 (95% confidence interval, 0.75 to 0.98; \( P < .01 \)).

### Table 1
Baseline Characteristics of the Overall Patient Cohort and Comparison of Responders Versus Nonresponders During SST

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>33</td>
<td>20 (61%)</td>
<td>13 (39%)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.0 (±1.8)</td>
<td>62.3 (±2.7)</td>
<td>66.9 (±3.1)</td>
<td>.32</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (39.4)</td>
<td>8 (40.0)</td>
<td>5 (38.5)</td>
<td>.90</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.9 (±1.1)</td>
<td>30.4 (±1.0)</td>
<td>30.0 (±2.22)</td>
<td>.56</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Type 2 diabetes mellitus</td>
<td>16 (48.5)</td>
<td>11 (55.0)</td>
<td>5 (38.5)</td>
<td>.35</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>23 (69.7)</td>
<td>15 (75.0)</td>
<td>8 (61.5)</td>
<td>.41</td>
</tr>
<tr>
<td>- Osteoporosis</td>
<td>10 (30.3)</td>
<td>6 (30.0)</td>
<td>4 (30.8)</td>
<td>.96</td>
</tr>
<tr>
<td>Indication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Traditional medicine</td>
<td>29 (87.9)</td>
<td>17 (85.0)</td>
<td>12 (92.3)</td>
<td>.53</td>
</tr>
<tr>
<td>- Dermatologic disease</td>
<td>1 (3.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Renal disease</td>
<td>1 (3.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Rheumatologic disease</td>
<td>2 (6.1)</td>
<td>1 (5.0)</td>
<td>1 (7.7)</td>
<td>.99</td>
</tr>
<tr>
<td>Duration of exogenous steroid (months)</td>
<td>24 (4-120)</td>
<td>12 (4-84)</td>
<td>48 (6-120)</td>
<td>.01</td>
</tr>
<tr>
<td>Duration between diagnosis and first SST (months)</td>
<td>23 (3-49)</td>
<td>23 (3-49)</td>
<td>13 (5-28)</td>
<td>.43</td>
</tr>
<tr>
<td>Last cumulative hydrocortisone dose (mg/day)</td>
<td>13.4 (±0.7)</td>
<td>11.6 (±0.8)</td>
<td>16.0 (±1.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Ambulatory early morning cortisol (µg/dL)</td>
<td>9.1 (±17.2)</td>
<td>10.3 (±18.8)</td>
<td>6.7 (±18.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>42.4 (±0.4)</td>
<td>42.4 (±0.5)</td>
<td>42.1 (±0.6)</td>
<td>.80</td>
</tr>
<tr>
<td>Basal plasma ACTH (pg/mL)</td>
<td>19.0 (5.0-297.0)</td>
<td>17.0 (5.0-43.0)</td>
<td>24.5 (5.0-91.0)</td>
<td>.56</td>
</tr>
<tr>
<td>30-Min cortisol (µg/dL)</td>
<td>16.9 (±29.2)</td>
<td>20.3 (±31.2)</td>
<td>11.5 (±29.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>60-Min cortisol (µg/dL)</td>
<td>19.1 (±32.3)</td>
<td>23.3 (±31.9)</td>
<td>12.6 (±28.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peak serum cortisol (µg/dL)</td>
<td>19.2 (±32.0)</td>
<td>22.1 (±22.4)</td>
<td>12.7 (±25.2)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

**Abbreviations**: ACTH = adrenocorticotropic hormone; SST = short Synacthen test.

\(^a\)Value expressed as median (range).

---

4 HPA Axis Recovery and Glucocorticoid Use, *Endocr Pract.* 2018;24(No. 1)
DISCUSSION

To our knowledge, this is the first retrospective review to assess recovery of the HPA axis after prolonged exposure to glucocorticoids that included patients exposed to traditional medicine. Unlike many Western nations, the use of traditional medicines that contain corticosteroids for symptomatic relief is common in Asia. In fact, 80% of our cohort had glucocorticoids prescribed factitiously by traditional-medical practitioners. With a median glucocorticoid exposure time of 2 years, we found that about 61% of the patients had recovered HPA axis function when tested for the first time with SST, 2 years after cessation of glucocorticoids. Is it known that serum cortisol levels are affected by serum albumin. As all of our patients were normo-albuminemic, we were able to compare the SST results.

The recovery of adrenal function begins to take place about 1 year after cessation of glucocorticoid therapy (19). In our study, the median time to axis recovery was 2 years but occurred as early as 3 months. The median time between cessation of glucocorticoids to testing was longer in the group with recovery, although not statistically significant. A previous study by Jamilloux et al (20) examining a homogenous cohort of patients with giant cell arteritis showed that recovery occurred by 3 years after cessation of glucocorticoids in almost 85% of patients, similar to our findings. However, adrenal function remained impaired in some patients in our cohort even up to 4 years after discontinuing glucocorticoids. It is uncertain if there are patients who will remain adrenal insufficient even years after cessation of glucocorticoids, as reported in up to 5% in the prior study (20). There is also a suspicion that patients who were given steroids factitiously may have had re-exposure during the course of follow-up, causing continued HPA axis suppression. However, none of the patients in our cohort had admitted to this.

The only independent predictor of HPA axis recovery after exposure to glucocorticoids was the ambulatory early morning cortisol. It has been standard practice at our center to screen these patients with an ambulatory morning cortisol every 3 to 6 months during follow-up in order to estimate the accurate timing for SST. This study is the first study to validate the ambulatory cortisol cut-off values that could predict adequate SST in our local population. A threshold of 8.8 µg/dL was found to predict adequate SST response, with a sensitivity of 70% and specificity of 93%. Similar results have been reported by Yo et al (21) in an Australian cohort that identified an ambulatory cortisol of 8.5 µg/dL to predict recovery, with a sensitivity of 84% and specificity of 71%. The findings indicate that the ambulatory early morning cortisol would be the most appropriate screening test to decide on best timing of SST. There is a strong correlation between basal morning cortisol and the response to dynamic tests, as previously demonstrated (8,22). A meta-analysis of 12 studies by Kazlauskante et al (23) indicated a wide range of ambulatory cortisol levels between 6 and 13 µg/dL that would require further confirmatory dynamic testing by SST, with a value above 13 µg/dL to have a >90% chance of adequate SST. The cut-off value of 8.8 µg/dL from our study falls within this range, and in clinical practice, it would be prudent to start testing with SST at this cut-off in order to prevent unnecessary glucocorticoid replacement in patients who have previously been exposed to prolonged periods of high-dose steroids.

All of our patients were replaced with oral hydrocortisone and advised to withhold hydrocortisone replacement for 24 hours prior to SST — on the day of SST and the afternoon prior — in order to avoid assay interference (6,24). Using the current cut-off ambulatory cortisol, 54% of the total SST would not have been indicated in our cohort, and this would translate to resource savings that include not only carrying out of the procedure but also travel costs incurred by patients. In addition, the ambulatory cortisol threshold ensures timely testing of HPA axis recovery in order to avoid unnecessary hydrocortisone replacement that could lead to unfavourable metabolic consequences from excess glucocorticoids.

The dose of glucocorticoid exposure is likely to affect recovery of SST. In our cohort, the majority had HPA axis suppression from factitiously prescribed traditional medicine. These factitious steroids were in the form of oral preparations in all patients. The indications varied among joint aches, back pain, lethargy, skin disorders, and allergies. We admit that the study is limited by the fact that not all patients had the factitious steroid analyzed for content and dose; however, in 6 of the patients who had submitted the substance, the National Pharmaceutical Control Agency...
of Malaysia confirmed the presence of dexamethasone as the main constituent, with addition of chlorpheniramine of unknown dose. All of the patients had similar forms of this factitious steroid that were prescribed by Chinese traditional healers. In our country, there is no clear legislation that regulates prescription of these medications, which are popular among the public, and many people are therefore unaware of their actual content. The median duration of exposure to glucocorticoids was significantly longer in the group that failed the SST (4 years) versus the group that passed (1 year), most likely because longer exposure leads to more profound adrenal suppression that requires longer to recover (9,25).

Our cohort of patients with exogenous steroid-induced hypocortisolism mainly consisted of middle-aged women who were obese and postmenopausal, likely because these women would be more prone to take factitious steroids for lethargy, osteoarthritis, or aches and pains common in the postmenopausal period. Also, we observed that there are social and peer influences within this age group and gender that likely predispose them to take exogenous steroids. As obese individuals are more likely to be suspected of having exogenous Cushing syndrome, this would explain the BMI distribution within this study cohort. More than half had cardiometabolic complications associated with steroid use; 70% (23/33) had hypertension, and about half, 48.5% (16/33), had diabetes. The study also underscores the need for screening for hypocortisolism, including a detailed history to indicate consumption of traditional medications or other glucocorticoids and physical examination to identify features of Cushing syndrome. Patients who present with signs and symptoms of hypocortisolism, whether in crisis or not, hyponatremia in which no other cause is found, and early onset or secondary osteoporosis as seen in our cohort, should be screened for hypocortisolism.

There was no difference in terms of baseline demographics amongst patients who had HPA axis recovery and those without. The last cumulative dose of hydrocortisone could guide us to the precise timing of SST. Patients who had adequate response on SST had a lower mean dose of hydrocortisone of 11.6 mg/day compared with the group that had an inadequate response (16.0 mg/day). Patients who were able to taper hydrocortisone doses to lower doses exhibited recovery of adrenal function and therefore had higher likelihood of adequate SST response.

Interestingly, the morning pre-SST levels of ACTH in the group that had inadequate response to SST tended to be higher. This could be explained by the recovery process that occurs in the HPA axis, for which ACTH and corticotropin-releasing hormone as trophic hormones recover earlier to then stimulate the adrenals to produce adequate glucocorticoids. This is in keeping with the observation by Graber et al (26). However, some advocate the use of repeated ACTH testing at different time intervals to accurately determine ACTH response. As this study was retrospective, this was not done, as it was not routine clinical practice, and this could explain the ACTH-cortisol dissociation in our cohort. The values of cortisol during the SST show that in the adequate SST group, both 30- and 60-minute cortisol values were not discrepant but instead significantly higher than in the inadequate-response group. The peak cortisol levels were 2-fold higher in the group with an adequate response. The analysis of cortisol levels during SST provides information to say that there is a clear delineation between groups with and without adequate cortisol response. There are also data to advocate the use of 1 µg Synacthen to detect subtle adrenal suppression, particularly in secondary adrenal insufficiency, but this was not routine practice at our center (27). Despite this, all our patients who were discontinued from hydrocortisone replacement by assessment of the standard 250 µg Synacthen had no withdrawal symptoms or acute crisis during follow-up.

The study is limited by its retrospective design and small sample size. Although there was no standardized protocol to determine the timing of SST, the study reflects real-life clinical practice, in which the timing for testing was based on the treating physician’s decision. With timely SST, unnecessary exposure to hydrocortisone that could lead to adverse metabolic outcomes in patients who had recovered adrenal function could be avoided. Of importance, the study validates ambulatory cortisol as a guide to prevent premature testing with SST that leads to additional costs incurred with the procedure.

CONCLUSION

Recovery of the HPA axis after prolonged exposure to glucocorticoids occurred in about 61% within 2 years after cessation of treatment. An ambulatory morning cortisol is the only independent predictor of adrenal function recovery. An ambulatory cortisol cut-off value of 8.8 µg/dL could be used as a guide to decide on timely SST.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES


25. Harrison BDW, Rees LH, Cayton RM, Nabarro JD. Recovery of hypothalamic-pituitary-adrenal function in asthmatics whose oral steroids have been stopped or reduced. *Clin Endocrinol (Oxf).* 1982;17:109-118.
